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THURSDAY, SEPTEMBER 9, 1976

THE NATIONAL ARCHIVES OF THE UNITED STATES * 1934 *

highlights

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The six-month trial period ended August 6. The program is being continued on a voluntary basis (see OFR notice, 41 FR 32914, August 6, 1976). The following agencies have agreed to remain in the program:

Monday	Tuesday	Wednesday	Thursday	Friday
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DOT/OHMO	CSC		DOT/OHMO	CSC
DOT/OPSO	LABOR		DOT/OPSO	LABOR

Documents normally scheduled on a day that will be a Federal holiday will be published the next work day following the holiday.

Comments on this program are still invited. Comments should be submitted to the Day-of-the-Week Program Coordinator, National Archives and Records Service, General Services Administration, Washington, D.C. 20408.

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USDA/APHIS—Meat and poultry inspection; sanitary requirements for vehicles. 23699; 6–11–76

List of Public Laws

This is a continuing numerical listing of public bills which have become law, together with the law number, the title, the date of approval, and the U.S. Statutes citation. The list is kept current in the FEDERAL REGISTER and copies of the laws may be obtained from the U.S. Government Printing Office.

S. 3435..... Pub. Law 94–394
To increase an authorization of appropriations for the Privacy Protection Study Commission, and to remove the fiscal year expenditure limitation
(Sept. 3, 1976; 90 Stat. 1198)

H.R. 3052..... Pub. Law 94–396
To amend section 512(b)(5) of the Internal Revenue Code of 1954 with respect to the tax treatment of the gain on the lapse of options to buy or sell securities
(Sept. 3, 1976; 90 Stat. 1201)

H.R. 13679..... Pub. Law 94–395
To provide assistance to the Government of Guam, to guarantee certain obligations of the Guam Power Authority, and for other purposes
(Sept. 3, 1976; 90 Stat. 1199)

presidential documents

Title 3—The President

PROCLAMATION 4454

United Nations Day, 1976

By the President of the United States of America

A Proclamation

On October 24 we will observe the 31st anniversary of the United Nations Charter, adopted in 1945 by governments determined to prevent a repetition of world war, to encourage the development of human rights and justice, and to remove the underlying causes of conflict by promoting economic and social progress for all nations.

The United States has played a leading role in encouraging the Organization to fulfill the promise of the Charter. We, and the rest of mankind, have benefited greatly from the vital contributions made by the Organization, particularly the Security Council, to the maintenance of world peace—the most striking reminder being the current peacekeeping role of the United Nations in the Middle East.

The United Nations has also been a forum for other areas of international concern: conferences to work out laws to govern the use of the oceans, to promote arms control, and to focus world attention on such problems as human rights, health, education, and hunger; new programs to promote trade and economic developments; and other activities designed to solve many of the new problems associated with independence in today's world.

NOW, THEREFORE, I, GERALD R. FORD, President of the United States of America, do hereby designate Sunday, October 24, 1976, as United Nations Day. I urge the citizens of this Nation to observe that day with community programs that will promote the United Nations and its affiliated agencies.

I have appointed Edgar Speer to be United States National Chairman for United Nations Day and, through him, I call upon State and local officials to encourage citizens' groups and all agencies of communication to engage in appropriate observances of United Nations Day in cooperation with the United Nations Association of the United States of America and other interested organizations.

IN WITNESS WHEREOF, I have hereunto set my hand this seventh day of September in the year of our Lord nineteen hundred seventy-six, and of the Independence of the United States of America the two hundred and first.

Gerald R. Ford

[FR Doc.76-26493 Filed 9-7-76; 12:36 pm]

PROCLAMATION 4455

Columbus Day, 1976

By the President of the United States of America

A Proclamation

In this our Bicentennial year, we owe special tribute to the great Italian explorer whose historic voyage to the new world opened the way to the founding of these United States.

Sustained by the vision and financial support of Queen Isabella I of Spain, Christopher Columbus established the first permanent European settlement in the Americas, paving the way for the generations of immigrants from all over the world who came to build a new nation. This great achievement marked the beginning of a new era in the history of mankind.

As the heirs to the spirit and determination of Christopher Columbus, we are proud to honor his memory and unshakable courage and faith which made his epic journey a reality nearly five centuries ago.

In tribute to the achievement of Columbus, the Congress of the United States, by joint resolution approved April 30, 1934 (48 Stat. 657, 36 U.S.C. 146), as modified by the Act of June 28, 1968 (82 Stat. 250, 5 U.S.C. 6103(a) and note), requested the President to proclaim the second Monday in October of each year as Columbus Day.

NOW, THEREFORE, I, GERALD R. FORD, President of the United States of America, do hereby designate Monday, October 11, 1976, as Columbus Day; and I invite the people of this Nation to observe that day in schools, churches and other suitable places with appropriate ceremonies in honor of the great explorer.

I also direct that the flag of the United States be displayed on all public buildings on the appointed day in memory of Christopher Columbus.

IN WITNESS WHEREOF, I have hereunto set my hand this seventh day of September, in the year of our Lord nineteen hundred seventy-six, and of the Independence of the United States of America the two hundred and first.

Gerald R. Ford

[FR Doc.76-26573 Filed 9-7-76;4:36 pm]

PROCLAMATION 4456

National Forest Products Week, 1976

By the President of the United States of America

A Proclamation

In the Nation's first century, Americans viewed their forests primarily as a source of survival and economic growth. In our second century, we continue to depend upon our forest resources for fuel, timber and sustenance, but we recognized the limits of our natural resource heritage and initiated action to conserve and manage our forests for future generations.

Fortunately, as we begin our third century, we have developed important tools to balance the needs of a growing population, our desire for an ever-improving standard of living, and concern for environmental quality.

Forestry research continues to make progress in achieving maximum efficient utilization of forest resources. In addition, strong Federal, State, and local forestry programs have been established to foster sound management of publicly owned forest lands and to encourage private forest landowners, through education, technical assistance, and grants, to practice sound forestry management on their lands. This cooperation among Federal, State, and private sectors is essential if we are to continue to provide the forest products our people require.

In order to emphasize America's reliance on forest resources and products, and to recognize their contribution in providing this Nation with consumer products, transportation systems, jobs and capital for economic growth, the Congress, by joint resolution of September 13, 1960 (74 Stat. 898; 36 U.S.C. 163), has designated the seven-day period beginning the third Sunday of October in each year as National Forest Products Week and has requested the President to issue annually a proclamation calling for its appropriate observance.

NOW, THEREFORE, I, GERALD R. FORD, President of the United States of America, do hereby call upon the people of the United States to observe the week beginning Sunday, October 17, 1976, as National Forest Products Week, with activities and ceremonies designed to invite public attention to the forest resources with which we are blessed and from which we have benefited, both materially and spiritually.

IN WITNESS WHEREOF, I have hereunto set my hand this eighth day of September, in the year of our Lord nineteen hundred seventy-six, and of the Independence of the United States of America the two hundred and first.

Gerald R. Ford

[FR Doc.76-26637 Filed 9-8-76;11:33 am]

Executive Order 11936 • September 8, 1976

The President's Commission on Olympic Sports

By virtue of the authority vested in me as President of the United States, Section 4(c) of Executive Order No. 11868 of June 19, 1975, is hereby amended to read as follows:

"Sec. 4(c) The second report shall be an analysis of the organizational and developmental problems in each Olympic sport. This shall be submitted no later than January 15, 1977, and contain an analysis of the financial and facilities requirements of each sport and recommend ways to provide needed funds.".

Gerald R. Ford

THE WHITE HOUSE,
September 8, 1976.

[FR Doc.76-26638 Filed 9-8-76;11:34 am]

rules and regulations

This section of the FEDERAL REGISTER contains regulatory documents having general applicability and legal effect most of which are keyed to and codified in the Code of Federal Regulations, which is published under 50 titles pursuant to 44 U.S.C. 1510.

The Code of Federal Regulations is sold by the Superintendent of Documents. Prices of new books are listed in the first FEDERAL REGISTER issue of each month.

Title 7—Agriculture

CHAPTER IX—AGRICULTURAL MARKETING SERVICE (MARKETING AGREEMENTS AND ORDERS; FRUITS, VEGETABLES, NUTS), DEPARTMENT OF AGRICULTURE

[Valencia Orange Reg. 544]

PART 908—VALENCIA ORANGES GROWN IN ARIZONA AND DESIGNATED PART OF CALIFORNIA

Limitation of Handling

PREAMBLE

This regulation fixes the quantity of California-Arizona Valencia oranges that may be shipped to fresh market during the weekly regulation period Sept. 10–16, 1976. It is issued pursuant to the Agricultural Marketing Agreement Act of 1937, as amended, and Marketing Order No. 908. The quantity of Valencia oranges so fixed was arrived at after consideration of the total available supply of Valencia oranges, the quantity of Valencia oranges currently available for market, the fresh market demand for Valencia oranges Valencia orange prices, and the relationship of season average returns to the parity price for Valencia oranges.

§ 908.844 Valencia Orange Regulation 544.

(a) *Findings.* (1) Pursuant to the marketing agreement, as amended, and Order No. 908, as amended (7 CFR Part 908), regulating the handling of Valencia oranges grown in Arizona and designated part of California, effective under the applicable provisions of the Agricultural Marketing Agreement Act of 1937, as amended (7 U.S.C. 601–674), and upon the basis of the recommendations and information submitted by the Valencia Orange Administrative Committee, established under the said amended marketing agreement and order, and upon other available information, it is hereby found that the limitation of handling of such Valencia oranges, as hereinafter provided, will tend to effectuate the declared policy of the act.

(2) The need for this regulation to limit the respective quantities of Valencia oranges that may be marketed from District 1, District 2, and District 3 during the ensuing week stems from the production and marketing situation confronting the Valencia orange industry.

(i) The committee has submitted its recommendation with respect to the quantities Valencia oranges that should be marketed during the next succeeding week. Such recommendation, designed to provide equity of marketing opportunity to handlers in all districts, resulted from consideration of the factors enumerated in the order. The committee further reports that the fresh market demand for Valencia oranges is stronger. Prices f.o.b. for the week ending September 2 were $3.54 per carton on 582 cars as compared with $3.53 per carton on 538 cars during the prior week. Track and rolling supplies at 341 cars were up 78 cars from last week.

(ii) Having considered the recommendation and information submitted by the committee, and other available information, the Secretary finds that the respective quantities of Valencia oranges which may be handled should be fixed as hereinafter set forth.

(3) It is hereby further found that it is impracticable and contrary to the public interest to give preliminary notice, engage in public rule-making procedure, and postpone the effective date of this regulation until 30 days after publication hereof in the FEDERAL REGISTER (5 U.S.C. 553) because the time intervening between the date when information upon which this regulation is based became available and the time when this regulation must become effective in order to effectuate the declared policy of the act is insufficient, and a reasonable time is permitted, under the circumstances, for preparation for such effective time; and good cause exists for making the provisions hereof effective as hereinafter set forth. The committee held an open meeting during the current week, after giving due notice thereof, to consider supply and market conditions for Valencia oranges and the need for regulation; interested persons were accorded an opportunity to submit information and views at this meeting; the recommendation and supporting information for regulation during the period specified herein were promptly submitted to the Department after such meeting was held; the provisions of this regulation, including its effective time, are identical with the aforesaid recommendation of the committee, and information concerning such provisions and effective time has been disseminated among handlers of such Valencia oranges; it is necessary, in order to effectuate the declared policy of the act, to make this regulation effective during the period herein specified and compliance with this regulation will not require any special preparation on the part of persons subject hereto which cannot be completed on or before the effective date hereof. Such committee meeting was held on September 7, 1976.

(b) *Order.* (1) The respective quantities of Valencia oranges grown in Arizona and designated part of California which may be handled during the period September 10, 1976, through September 16, 1976, are hereby fixed as follows:

(i) District 1: 315,000 cartons;
(ii) District 2: 385,000 cartons;
(iii) District 3: Unlimited."

(2) As used in this section, "handled", "District 1", "District 2", "District 3", and "carton" have the same meaning as when used in said amended marketing agreement and order.

(Secs. 1–19, 48 Stat. 31, as amended; 7 U.S.C. 601–674)

Dated: September 8, 1976.

CHARLES R. BRADER,
Deputy Director, Fruit and Vegetable Division, Agricultural Marketing Service.

[FR Doc.76-26654 Filed 9-8-76;8:48 am]

PART 910—LEMONS GROWN IN THE STATES OF CALIFORNIA AND ARIZONA

Expenses and Rate of Assessment

This document authorizes expenses of $378,000 for the Lemon Administrative Committee, under Marketing Order No. 910, for the 1976–77 fiscal year and fixes a rate of assessment of $0.0315 per carton of lemons handled in such period to be paid to the committee by each first handler as his pro rata share of such expenses.

On August 11, 1976, notice of proposed rulemaking was published in the FEDERAL REGISTER (41 FR 33922) regarding proposed expenses and the proposed rate of assessment, pursuant to the marketing agreement, as amended, and Order No. 910, as amended (7 CFR Part 910), regulating the handling of lemons grown in the States of California and Arizona. This notice allowed interested persons until August 31, 1976, during which they could submit data, views, or arguments pertaining to these proposals. None were submitted. This regulatory program is effective under the Agricultural Marketing Agreement Act of 1937, as amended (7 U.S.C. 601–674). After consideration of all relevant matters presented, including the proposals set forth in such notice, which were submitted by the Lemon Administrative Committee (established pursuant to said marketing agreement and order), it is hereby found and determined that:

§ 910.214 Expenses and rate of assessment.

(a) *Expenses.* Expenses that are reasonable and likely to be incurred by the Lemon Administrative Committee during the period August 1, 1976, through July 31, 1977, will amount to $378,000.

(b) *Rate of assessment.* The rate of assessment for said period payable by each handler in accordance with § 910.41, is fixed at $0.0315 per assessable carton of lemons.

It is hereby further found that good cause exists for not postponing the effective date hereof until 30 days after publication in the FEDERAL REGISTER (5 U.S.C. 553) in that (1) shipments of the current crop of lemons grown in the designated production area are now being made; (2) the relevant provisions of said marketing agreement and this part require that the rate of assessment herein fixed shall be applicable to all assessable lemons handled during the aforesaid period, and (3) such period began on August 1, 1976, and said rate of assessment will automatically apply to all such lemons beginning with such date.

(Secs. 1–19, 48 Stat. 31, as amended; 7 U.S.C. 601–674)

Dated: September 2, 1976.

CHARLES R. BRADER,
Deputy Director, Fruit and Vegetable Division, Agricultural Marketing Service.

[FR Doc.76-26312 Filed 9-8-76;8:45 am]

CHAPTER XIV—COMMODITY CREDIT CORPORATION, DEPARTMENT OF AGRICULTURE

SUBCHAPTER B—LOANS, PURCHASES, AND OTHER OPERATIONS

[CCC Grain Price Support Reg., 1976 Crop Rice Supplement Amdt. 1]

PART 1421—GRAINS AND SIMILARLY HANDLED COMMODITIES

Subpart—1976 Crop Rice Loan and Purchase Program

RICE: CHANGES IN RATES

The regulations issued by the Commodity Credit Corporation (CCC) and published on June 14, 1976, at 41 FR 23930, which set forth specific requirements with respect to loans and purchases for the 1976 crop of rice, are hereby amended to increase the loan rates for rice. This increase reflects the change in the index of prices paid by farmers for production items, interest, taxes, and wage rates during the period beginning on the date of enactment and ending July 31, 1976, as required by the Rice Production Act of 1975 (Pub. L. 94–214, 90 Stat. 181, approved February 16, 1976). It is impracticable and contrary to the public interest to give notice of proposed rulemaking with respect to this amendment because 1976 crop rice is currently being harvested and it is essential that the rates provided for in this subpart be put into effect with respect to such rice on the earliest possible date.

Paragraphs (a) and (c) of § 1421.328 are hereby revised to increase the loan rates for farm-storage and warehouse-storage rice. Accordingly, 7 CFR, 1421.328 (a) and (c) are revised to read as follows:

§ 1421.328 Loan and purchase rates.

(a) *Farm storage loans.* The loan rate for farm-storage rice shall be $6.19 per hundredweight for any class. The settlement rate shall be the applicable basic rate specified in paragraph (c) of this section, adjusted in accordance with the provision of this section and §§ 1421.310 and 1421.22.

* * * * *

(c) *Basic rates.* The basic rate per 100 pounds of rice shall be computed as follows: Multiply the milling yield (in pounds per hundredweight) of whole kernels by the applicable loan rate for whole kernels (as shown in the table below according to class) and round the result to the nearest hundredth. Similarly, multiply the difference between the total milling yield and the whole kernels milling yield (in pounds per hundredweight) by the applicable loan rate for broken rice and round the result to the nearest hundredth. Add the results (as rounded) of these two computations to obtain the basic loan or purchase rate per 100 pounds of rice and express such rate in dollars and cents.

Loan rates for whole kernels and broken rice

[Cents per pound]

Rough rice class	Whole kernels	Broken rice
Grains:		
Long	10.75	4.75
Medium	9.25	4.75
Short	9.25	4.75

(Secs. 4 and 5, 62 Stat. 1070, as amended (15 U.S.C. 714b and c); secs. 101, 401, 63 Stat. 1051, as amended (7 U.S.C. 1441 note and 1421).)

Effective date: This amendment takes effect on September 9, 1976.

Signed at Washington, D.C., on September 2, 1976.

KENNETH E. FRICK,
Executive Vice President, Commodity Credit Corporation.

[FR Doc.76-26370 Filed 9-8-76;8:45 am]

CHAPTER XVIII—FARMERS HOME ADMINISTRATION, DEPARTMENT OF AGRICULTURE

SUBCHAPTER A—GENERAL REGULATIONS

[FmHA Instruction 410.1]

PART 1801—RECEIVING AND PROCESSING APPLICATIONS

Subpart A—Receiving and Processing Applications

Section 1801.2 of Subpart A, Part 1801 of Chapter XVIII, Title 7, Code of Federal Regulations (36 FR 15737, Redesignated at 38 FR 4772; 41 FR 14860; 41 FR 26676) is amended. This amendment is required to comply with the revised Real Estate Settlement Procedures Act and the Department of Housing and Urban Development's Regulations.

This amendment is not published for proposed rulemaking because its effect is to provide for FmHA compliance with the Real Estate Settlement Procedures Act and regulations issued by the Department of Housing and Urban Development.

Sections 1801.2(l) and 1801.2(l) (1) and (2) are amended to make references to the information booklet entitled "Settlement Costs," and to Form FmHA 440–58, "Estimate of Settlement Costs" which replaces Exhibit A to Subpart I of Part 1901 if this chapter, entitled, "Attachment to Special Information Booklet".

As amended, § 1801.2 reads as follows:

§ 1801.2 Receiving applications.

* * * * *

(l) For all loans and credit sales secured by a first mortgage and involving the purchase of an existing 1 to 4 family unit or purchase of a building site and construction of 1 to 4 family residential units, the booklet entitled "Settlement Costs" will be hand-delivered to the applicant when the completed application is received or mailed to the applicant within three (3) business days after receipt of the application in the County Office.

(1) Form FmHA 440–58, "Estimate of Settlement Costs" will be completed by the County Supervisor and mailed or delivered to the applicant with the booklet.

(2) A record of the date and method of delivery of the booklet and Form FmHA 440–58 will be kept in the running record section of the applicant/borrower County Office case folder.

* * * * *

(7 U.S.C. 1989; 42 U.S.C. 1480; 5 U.S.C. 301; Sec. 10 Pub. L. 93–357, 88 Stat. 392; delegation of authority by the Sec. of Agri., 7 CFR 2.23; delegation of authority by the Asst. Sec. for Rural Development, 7 CFR 2.70.)

Effective date: This amendment is effective September 9, 1976.

Dated: August 27, 1976.

JOSEPH R. HANSON,
Acting Administrator, Farmers Home Administration.

[FR Doc.76-26371 Filed 9-8-76;8:45 am]

SUBCHAPTER B—LOANS AND GRANTS PRIMARILY FOR REAL ESTATE PURPOSES

[FmHA Instruction 443.1]

PART 1821—FARM PURCHASE AND DEVELOPMENT LOANS TO INDIVIDUALS

Subpart A—Farm Ownership Loan Policies, Procedures, and Authorizations

Sections 1821.4(a), 1821.7(b), and 1821.11(a) of Subpart A of Part 1821, Title 7, Code of Federal Regulations (38 FR 27055) are revised. Section 1821.4(a) is revised to include in the definition of a farm a residence physically separate from the farm acreage if it is ordinarily treated as part of the farm in the community. The revision to § 1821.7(b) removes the material in the "note" following paragraph (b)(3) of this section and incorporates its contents into § 1821.11(a). As revised, § 1821.11(a) will allow use of buildings owned by the applicant and not located on the farm; specify the requirements of farm dwellings financed with rural housing funds; and allow use of a mobile home as a dwelling when the mobile home is already owned by the applicant. By relieving certain restrictions, these revisions make the farm ownership program available to more present and future farmers. The revision is designed to meet the current

needs of these farmers, as evidenced by the many applications already received for loans under the amended requirements contained herein. Delay in the processing of these applications caused by a delay in the effective date of this revision, would be contrary to the public interest. Notice and public procedure are therefore unnecessary. However, it is the policy of this Department that rules relating to public property, loans, grants, benefits, or contracts shall be published for comment notwithstanding the exemption in 5 U.S.C. 553 with respect to such rules. In accordance with the spirit of that policy, interested persons may submit written comments, suggestions or arguments to the Office of the Chief, Directives Management Branch, Farmers Home Administration, U.S. Department of Agriculture, Room 6316, South Building, Washington, DC 20250, on or before October 12, 1976. Material thus submitted will be evaluated and acted upon in the same manner as if this document were a proposal. All written submissions made pursuant to this notice will be made available for public inspection at the Office of the Chief, Directives Management Branch, during regular business hours (8:15 a.m.–4:45 p.m.). Section 1821.4(a) and 1821.11(a) of Subpart A of Part 1821 as revised, however, will remain effective until they are further revised or amended.

As revised, § 1821.4(a) reads as follows:

§ 1821.4 Definitions.

(a) *Farm.* The term "farm" includes a tract or tracts of land, improvements, and other appurtenances considered to be farm property, and owned or to be acquired by the applicant, used or to be used in the production of crops or livestock including the production of fish under controlled conditions. The term "farm" also includes any such land and improvements and facilities used in a nonfarm enterprise. It will also include a residence which, although physically separate from the farm acreage, is ordinarily treated as part of the farm in the local community.

* * * * *

Section 1821.11(a) is revised to read as follows:

§ 1821.11 Special Requirements.

(a) *Dwellings and other essential buildings.* (1) Buildings adequate for the planned operation of the farm, including any nonfarm enterprise, must be available for the applicant's use after the loan is made. The necessary buildings ordinarily will be located on the applicant's farm. However, if an applicant already owns an adequate, decent, safe, and sanitary dwelling suitable for the family's needs, which is located close enough to the farm so the farm may be operated successfully, it will not be necessary to provide a dwelling on the farm. A real estate lien will be taken on such dwelling. In an unusual case, an exception to the requirement that the farm include a suitable dwelling may be made when the applicant has a long-term lease on acceptable rented buildings that are adjacent to or near the farm, or the applicant occupies suitable buildings of relatives that he will eventually inherit or be permitted to purchase.

(2) When provision of a dwelling is planned and an applicant is eligible for an RH loan, an RH loan will be processed simultaneously with the FO docket. Dwellings will meet the requirements for RH loans required in Subpart A of Part 1822 of this chapter.

(3) If the farm does not have an adequate dwelling and the applicant owns a suitable mobile home which he uses or plans to use as his residence, the applicant will not be required to build a dwelling.

* * * * *

(7 U.S.C. 1989, 42 U.S.C. 1480, delegation of authority by the Secretary of Agriculture, 7 CFR 2.23, delegation of authority by the Assistant Secretary for Rural Development, 7 CFR 2.70.)

Effective date: These revisions are effective September 9, 1976.

Dated: September 1, 1976.

JOSEPH R. HANSON,
Acting Administrator,
Farmers Home Administration.

[FR Doc.76-26372 Filed 9-8-76;8:45 am]

SUBCHAPTER H—GENERAL

PART 1901—PROGRAM-RELATED INSTRUCTIONS

Subpart I—Truth in Lending—Real Estate Settlement Procedures

Section 1901.406 of Subpart I, Part 1901 of Chapter XVIII, Title 7, Code of Federal Regulations (41 FR 16159; 41 FR 26677) is amended. This amendment changes a reference made from the "Special Information Booklet" to "Settlement Costs" booklet and provides for a form to replace Exhibit A of this subpart. This amendment is necessary to comply with the revised Real Estate Settlement Procedures Act and the Department of Housing and Urban Development's Regulation X.

Specifically, this amendment makes the following changes:

1. Section 1901.406(c)(1) is amended to make reference to the information booklet entitled "Settlement Costs."

2. Section 1901.406(c)(1) (i) and (ii) are amended to make reference to Form FmHA 440–58, "Estimate of Settlement Costs" which is given to applicants. This form replaces Exhibit A, "Attachment to Special Information Booklet" which is deleted.

This amendment is not published for Proposed Rulemaking because its effect is to provide for FmHA compliance with the Real Estate Settlement Procedures Act and regulations issued by the Department of Housing and Urban Development.

§ 1901.406 Real estate settlement procedures.

* * * * *

(c) *Actions required.* (1) the information booklet entitled, "Settlement Costs," will either be given to the applicant at the time the completed application is received or mailed to the applicant no later than three (3) business days after receipt of the application in the County Office.

(i) Form FmHA 440–58 "Estimate of Settlement Costs" is to be used to provide a "good faith" statement of estimated closing costs. Form FmHA 440–58 will be completed by the County Supervisor and mailed or delivered to the applicant with the Settlement Costs booklet.

(ii) Form FmHA 440–58 does not replace Truth-In-Lending forms. Appropriate forms listed in § 1901.401 will continue to be used.

* * * * *

(7 U.S.C. 1989; 42 U.S.C. 1480; 40; delegation of authority by the Sec. of Agri., 7 CFR 2.23; delegation of authority by the Asst. Sec. for Rural Development, 7 CFR 2.70.)

Effective date: This amendment is effective on September 9, 1976.

Dated: August 27, 1976.

JOSEPH R. HANSON,
Acting Administrator,
Farmers Home Administration.

[FR Doc.76-26373 Filed 9-8-76;8:45 am]

PART 1901—PROGRAM-RELATED INSTRUCTIONS

Subpart J—Grant-In-Aid Information

INTER-GOVERNMENTAL COOPERATION ACT—SECTION 201—TREASURY CIRCULAR—1082

There is hereby established under Chapter XVIII, Title 7, Subchapter H, "General—Part 1901, Program-Related Instructions," a new Subpart J, "Grant-In-Aid Information," (§§ 1901.451, 1901.500) in the Code of Federal Regulations. This new Subpart J provides guidelines to be followed by the Farmers Home Administration (FmHA) in order to comply with Section 201 of the Intergovernmental Cooperation Act of 1968, as set forth in Department of Treasury Circular Number 1082.

Inasmuch as FmHA is complying with the existing Intergovernmental Cooperation Act of 1968 and grants for Federal assistance provided by Pub. L. 90–448, 92–419, and 88–560, notice and public procedure thereon are unnecessary.

Accordingly, new Subpart J of Part 1901 is set forth below.

Subpart J—Grant-In-Aid Information

Sec.
1901.451 Purpose.
1901.452 Policy.
1901.453 Authorities and responsibilities.
1901.454 [Reserved]
1901.455 Preparation of Standard Form 424.
1901.456 Function of SCIRA.
1901.457–1901.500 [Reserved]
Exhibit A—Directory of State Clearinghouses and State Central Information Reception Agencies (For A–95/TC–1082 use).
Exhibit B—Standard Form 424, "Federal Assistance."

AUTHORITY: 7 U.S.C. 1989; 42 U.S.C. 1480; 42 U.S.C. 2942; 5 U.S.C. 301; Sec. 10 Pub. L. 93–357, 88 Stat. 392; delegation of authority by the Sec. of Agri., 7 CFR 2.23; delegation of

authority by the Asst. Sec. for Rural Development, 7 CFR 2.70; delegations of authority by Dir., OEO 29 FR 14764, 33 FR 9850.

§ 1901.451 Purpose.

This subpart outlines the procedures that the Farmers Home Administration (FmHA) must follow to comply with section 201 of the Intergovernmental Cooperation Act of 1968 as set forth in the Department of Treasury Circular Number 1082. (This section required that Federal agencies administering grant-in-aid programs to State Governments or their political subdivision must supply to the Governor and the legislature of any State, on the request of either the Governor or the legislature, information on the amounts and purposes of all grants under the program in that State.)

§ 1901.452 Policy.

FmHA will provide the required information to the State Central Information Reception Agency (SCIRA) (an agency designated by the Governor of a State, in consultation with the legislature, to serve as the central reception point in a State for Federal grant-in-aid information) about the following grants approved on or after July 1, 1970:

(a) Grants for self-help technical assistance under Pub. L. 90–448.

(b) Grants for facilitating the development of private business enterprises under Pub. L. 92–419 (Industrial Development Grants).

(c) Grants for development of water and waste disposal facilities under Pub. L. 92–419.

(d) Grants to provide low rent housing for domestic farm labor under Pub. L. 88–560.

§ 1901.453 Authorities and responsibilities.

The State Director, for the grants listed in § 1901.452, will:

(a) Notify SCIRA using section III of Standard Form 424, "Federal Assistance," within 7 days after approval of an initial or subsequent grant or after a change in the amount or purpose of a grant. One copy of CF 424 will be sent to SCIRA and clearinghouse. However, additional copies may be supplied on request.

(b) Keep current the name and address of the SCIRA. See Exhibit A, "Directory of State Clearinghouses and State Central Information Reception Agencies (for A–95/TC–1082 use).

§ 1901.454 [Reserved]

§ 1901.455 Preparation of Standard Form 424.

This form will be obtained from the Finance Office, St. Louis, Missouri. See Exhibit B for guidance in completing Standard Form 424 for grants listed in § 1901.452. The date of the application (on Form AD–624, "Application for Federal Assistance (Construction Projects)" for Water and Waste Disposal and Industrial Development grants, and on Form AD–625, "Application for Federal Assistant (Short Form)" for Technical Assistance grants) will be used as the "application received" date in Item 25 of Standard Form 424. In addition to copies of SCIRA and clearinghouse, a copy will be sent to the National Office (and to the US Department of Agriculture, Office of Management and Finance, 14th and Independence Avenue, SW., Washington, D.C. 20250.)

§ 1901.456 Function of the SCIRA.

In each State, this Agency will:

(a) Distribute information about FmHA grants available to the State and its political subdivisions provided by the State Director to the Governor, State legislature, and other agencies of the State that the Governor may designate.

(b) Make the information available to regional and metropolitan agencies and to local governments of the State.

§§ 1901.457–1901.500 [Reserved]

EXHIBIT A—DIRECTORY OF STATE CLEARINGHOUSES AND STATE CENTRAL INFORMATION RECEPTION AGENCIES (FOR A–95/TC–1082 USE)

The following addresses should be sent Federal assistance action notices in compliance with Circular A–95 for Clearinghouse, and in compliance with Circular TC–1082 for State Central Information Reception.

Agencies (SCIRAS). Note that in 44 States the address of the State Clearinghouse and the SCIRA is the same. A single notification will suffice when both A–95 and TC–1082 compliance (at State level) is required. Appropriate areawide clearinghouse addresses must also be informed as applicable under A–95. Please note, the State Clearinghouse and the SCIRA are different addressees in the States of Vermont, New Jersey, Illinois, Colorado, Nevada, and Hawaii. The list will be updated periodically, at least on an annual basis.

Alabama:
Alabama Development Office, State Office Building, Montgomery, Alabama 36104.

Alaska:
Planning and Research Div., Office of the Governor, Pouch AD, State Capitol, Juneau, Alaska 99801.

Arizona:
Dept. of Economic Planning and Development, Arizona State Clearinghouse, 1624 West Adams Street, Phoenix, Arizona 85007.

Arkansas:
Department of Planning, 400 Train Station Square, Little Rock, Arkansas 72201, Fred Kleinhauer (501) 371–2311.

California:
Office of the Governor, Office of Planning and Research, 1400 Tenth Street, Sacramento, California 95814.

Colorado (2):
(1) State Clearinghouse: Division of Planning, Department of Local Affairs, 1845 Sherman Street, Denver, Colorado 80203.
(2) SCIRA: Office of State Planning & Budgeting, 617 State Services Building, Denver, Colorado 80203, Gary Heats (916) 445–0613.

Connecticut:
Office of Intergovernmental Programs, 340 Capitol Avenue, Hartford, Connecticut 06115.

Delaware:
State Planning Office, Thomas Collins Building, 530 S. Dupont Highway, Dover, Delaware 19901.

Florida:
Bureau of Intergovernmental Relations, Division of State Planning, 660 Apalachee Parkway, Tallahassee, Florida 32304.

Georgia:
Office of Planning and Budget, Attention: Clearinghouse, 270 Washington Street, SW., Atlanta, Georgia 30334.

Hawaii (2):
(1) State Clearinghouse: Department of Planning and Economic Development, P.O. Box 2359, Honolulu, Hawaii 96804.
(2) SCIRA: State of Hawaii, Department of Budget and Finance, P.O. Box 150, Honolulu, Hawaii 96810.

Idaho:
Division of Budget, Policy Planning and Coordination, State House, Boise, Idaho 83720.

Illinois (2):
(1) State Clearinghouse: State Clearinghouse, Bureau of the Budget, 103 State House, Springfield, Illinois 62706.
(2) State of Illinois, Commission on Intergovernmental Cooperation, 217 S. First Street, Springfield Illinois 62706.

Indiana:
Indiana State Budget Agency, 212 State House, Indianapolis, Indiana 46204.

Iowa:
Office of Planning and Programming, 523 East 12th Street, Des Moines, Iowa 50310.

Kansas:
Division of Planning and Research, Department of Administration, State Office Building, Topeka, Kansas 66612.

Kentucky:
State Clearinghouse, Office for Local Government, Capitol Annex, Room 327, Frankfort, Kentucky 40601.

Louisiana:
Office of Intergovernmental Relations, P.O. Box 44455, Baton Rouge, Louisiana 70804.

Maine:
Executive Department, Maine State Clearinghouse, 184 State Street, Augusta, Maine 04333, Allen G. Pease (207) 289–3261.

Maryland:
Department of State Planning, 301 W. Preston Street, Baltimore, Maryland 21202.

Massachusetts:
Office of State Planning, John McCormack Building, 1 Ashburton Place, Boston, Massachusetts 02108.

Michigan:
Department of Management and Budget, Office of Intergovernmental Relations, Federal Aid Management Division, Lewis Cass Building, Lansing, Michigan 48913.

Minnesota:
State Clearinghouse, State Planning Agency, Capitol Square Building, Room 101, St. Paul, Minnesota 55101.

Mississippi:
Coordinator Federal-State Programs, Office of the Governor, 400 Watkins Building, 510 George Street, Jackson, Mississippi 39201.

Missouri:
Office of Administration, State Planning and Analysis Div., P.O. Box 809, State Capitol Building, Jefferson City, Missouri 65101, Terry Rehma (314) 751–4834.

Montana:
Research and Information Systems Division, Department of Community Affairs, 1424 9th Avenue, Helena, Montana 59601.

Nebraska:
Office of Planning and Programming, Box 94601, State Capitol, Lincoln, Nebraska 68509.

Nevada (2):
(1) State Clearinghouse: State Planning Coordinator, State Capitol Building, Carson City, Nevada 89701.
(2) SCIRA: State Department of Administration, Blasdale Building, Room 205, Carson City, Nevada 89701.

New Hampshire:
Coordinator of Federal Funds, State House, Concord, New Hampshire 03301.

New Jersey (2):
(1) State Clearinghouse: Bureau of State and Regional Planning, Department of Community Affairs, 329 W. State Street, P.O. Box 2768, Trenton, New Jersey 08625.
(2) SCIRA: Department of Treasury, Bureau of the Budget, State House, Trenton, New Jersey 08625.

New Mexico:
State Planning Office, State Capitol, Sante Fe, New Mexico 87501.

New York:
State Division of the Budget, State Capitol, Albany, New York 12224.

North Carolina:
Office of Intergovernmental Relation, 116 W. Jones Street, Raleigh, North Carolina 27603.

North Dakota:
State Planning Agency, State Capitol, Bismarck, North Dakota 58501.

Ohio:
Office of Governor, State Clearinghouse, State Office Tower, 30 E. Broad Street, Columbus, Ohio 43215, Nancy Hippert (614) 466-2673.

Oklahoma:
State Grant-in-Aid Clearinghouse, 5500 N. Western, Oklahoma City, Oklahoma 73118.

Oregon:
Federal Aid Coordinator, Intergovernmental Relations Division, 240 Cottage Street, Salem, Oregon 97310.

Pennsylvania:
State Clearinghouse, Intergovernmental Relations Division, Governor's Office of Budget, P.O. Box 1323, Harrisburg, Pennsylvania 17120.

Rhode Island:
Statewide Planning Program, Dept. of Administration, Room 201, 265 Melrose Street, Providence, Rhode Island 02907.

South Carolina:
State Clearinghouse, Division of Administration, 1205 Pendleton Street, Columbia, South Carolina 29201.

South Dakota:
State Planning Bureau, State Capitol, Pierre, South Dakota 57501.

Tennessee:
Office of Urban and Federal Affairs, Suite 108, Parkway Towers, 404 Robertson Parkway, Nashville, Tennessee 37319.

Texas:
Division of Planning Coordination, Office of Governor, Capitol Station, P.O. Box 12428, Austin, Texas 78711.

Utah:
State Planning Coordinator, 118 State Capitol Building, Salt Lake City, Utah 84114.

Vermont (2):
(1) State Clearinghouse: State Planning Office, Pavilion Office Building, Montpelier, Vermont 05602.
(2) SCIRA: Department of Budget and Management, Pavilion Office Building, Montpelier, Vermont 05602.

Virginia:
Division of State Planning and Community Affairs, 1010 Madison Building, Richmond, Virginia 23219, Charles A. Christophensen.

Washington:
Office of Governor, Program Planning and Fiscal Management, House Office Building, Olympia, Washington 98504.

West Virginia:
Grant Information Department, Office of Federal-State Relations, State Capitol Building, Charleston, West Virginia 25305.

Wisconsin:
State Clearinghouse/Central Information Reception Agency, Department of Administration, Room B-158, State Office Building, 1 West Wilson Street, Madison, Wisconsin 53702.

Wyoming:
State Planning Coordinator, Office of the Governor, Capitol Building, Cheyenne, Wyoming 82002.

District of Columbia:
Office of Budget and Management Systems, District Building, 14th and E Street, NW., Washington, D.C. 20004.

Puerto Rico:
Planning Board, P.O. Box 9447, Santurce, Puerto Rico 00908.

Virgin Islands:
Office of the Governor, P.O. Box 599, St. Thomas, Virgin Islands 00801.

Guam:
Governor of Guam, Agana, Guam 96910.

Samoa:
Planning and Budget Office, Government of American Samoa, Pago Pago, American Samoa 96799.

- Exhibit-8

OMB Approval No. 29-R0218

FEDERAL ASSISTANCE

SECTION I—APPLICANT/RECIPIENT DATA

1. TYPE OF ACTION (Mark appropriate box) ☐ PREAPPLICATION ☐ APPLICATION ☐ NOTIFICATION OF INTENT (Opt.) ☐ REPORT OF FEDERAL ACTION
2. APPLICANT'S APPLICATION — a. NUMBER; b. DATE (Year month day) 19
3. STATE APPLICATION IDENTIFIER — a. NUMBER; b. DATE ASSIGNED (Year month day) 19
Leave Blank
4. LEGAL APPLICANT/RECIPIENT — a. Applicant Name; b. Organization Unit; c. Street/P.O. Box; d. City; e. County; f. State; g. ZIP Code; h. Contact Person (Name & telephone No.)
5. FEDERAL EMPLOYER IDENTIFICATION NO.
6. PROGRAM (From Federal Catalog) — a. NUMBER; b. TITLE
7. TITLE AND DESCRIPTION OF APPLICANT'S PROJECT
8. TYPE OF APPLICANT/RECIPIENT — A-State; B-Interstate; C-Substate District; D-County; E-City; F-School District; G-Special Purpose District; H-Community Action Agency; I-Higher Educational Institution; J-Indian Tribe; K-Other (Specify): Enter appropriate letter
9. TYPE OF ASSISTANCE — A-Basic Grant; B-Supplemental Grant; C-Loan; D-Insurance; E-Other. Enter appropriate letter(s)
10. AREA OF PROJECT IMPACT (Names of cities, counties, States, etc.)
11. ESTIMATED NUMBER OF PERSONS BENEFITING
12. TYPE OF APPLICATION — A-New; B-Renewal; C-Revision; D-Continuation; E-Augmentation. Enter appropriate letter
13. PROPOSED FUNDING — a. FEDERAL $ .00; b. APPLICANT .00; c. STATE .00; d. LOCAL .00; e. OTHER .00; f. TOTAL $ .00
14. CONGRESSIONAL DISTRICTS OF: a. APPLICANT; b. PROJECT
15. TYPE OF CHANGE (For 11c or 12c) — A-Increase Dollars; B-Decrease Dollars; C-Increase Duration; D-Decrease Duration; E-Cancellation; F-Other (Specify): Enter appropriate letter(s)
16. PROJECT START DATE (Year month day) 19
17. PROJECT DURATION Months
18. ESTIMATED DATE TO BE SUBMITTED TO FEDERAL AGENCY (Year month day) 19
19. EXISTING FEDERAL IDENTIFICATION NUMBER
20. FEDERAL AGENCY TO RECEIVE REQUEST (Name, City, State, ZIP code)
21. REMARKS ADDED ☐ Yes ☐ No

SECTION II—CERTIFICATION

22. THE APPLICANT CERTIFIES THAT ▶ a. To the best of my knowledge and belief, data in this preapplication/application are true and correct, the document has been duly authorized by the governing body of the applicant and the applicant will comply with the attached assurances if the assistance is approved. b. If required by OMB Circular A-95 this application was submitted, pursuant to instructions therein, to appropriate clearinghouses and all responses are attached: (1) (2) (3) — No response ☐ ☐ ☐; Response attached ☐ ☐ ☐
23. CERTIFYING REPRESENTATIVE — a. TYPED NAME AND TITLE; b. SIGNATURE; c. DATE SIGNED (Year month day) 19

SECTION III—FEDERAL AGENCY ACTION

24. AGENCY NAME
25. APPLICATION RECEIVED (Year month day) 19
26. ORGANIZATIONAL UNIT
27. ADMINISTRATIVE OFFICE
28. FEDERAL APPLICATION IDENTIFICATION
29. ADDRESS
30. FEDERAL GRANT IDENTIFICATION
31. ACTION TAKEN — ☐ a. AWARDED; ☐ b. REJECTED; ☐ c. RETURNED FOR AMENDMENT; ☐ d. DEFERRED; ☐ e. WITHDRAWN
32. FUNDING — a. FEDERAL $ .00; b. APPLICANT .00; c. STATE .00; d. LOCAL .00; e. OTHER .00; f. TOTAL $ .00
33. ACTION DATE ▶ (Year month day) 19
34. STARTING DATE (Year month day) 19
35. CONTACT FOR ADDITIONAL INFORMATION (Name and telephone number)
36. ENDING DATE (Year month day) 19
37. REMARKS ADDED ☐ Yes ☐ No
38. FEDERAL AGENCY A-95 ACTION — a. In taking above action, any comments received from clearinghouses were considered. If agency response is due under provisions of Part I, OMB Circular A-95, it has been or is being made. b. FEDERAL AGENCY A-95 OFFICIAL (Name and telephone no.)

424-101 STANDARD FORM 424 PAGE 1 (10-75)

GENERAL INSTRUCTIONS

This is a multi-purpose standard form. First, it will be used by applicants as a required facesheet for pre-applications and applications submitted in accordance with Federal Management Circular 74–7. Second, it will be used by Federal agencies to report to Clearinghouses on major actions taken on applications reviewed by clearinghouses in accordance with OMB Circular A–95. Third, it will be used by Federal agencies to notify States of grants-in-aid awarded in accordance with Treasury Circular 1082. Fourth, it may be used, on an optional basis, as a notification of intent from applicants to clearinghouses, as an early initial notice that Federal assistance is to be applied for (clearinghouse procedures will govern).

APPLICANT PROCEDURES FOR SECTION I

Applicant will complete all items in Section I. If an item is not applicable, write "NA". If additional space is needed, insert an asterisk "*", and use the remarks section on the back of the form. An explanation follows for each item:

Item

1. Mark appropriate box. Pre-application and application guidance is in FMC 74–7 and Federal agency program instructions. Notification of intent guidance is in Circular A–95 and procedures from clearinghouse. Applicant will not use "Report of Federal Action" box.

2a. Applicant's own control number, if desired.

2b. Date Section I is prepared.

3a. Number assigned by State clearinghouse, or if delegated by State, by areawide clearinghouse. All requests to Federal agencies *must* contain this identifier if the program is covered by Circular A–95 and required by applicable State/areawide clearinghouse procedures. If in doubt, consult your clearinghouse.

3b. Date applicant notified of clearinghouse identifier.

4a–4h. Legal name of applicant/recipient, name of primary organizational unit which will undertake the assistance activity, complete address of applicant, and name and telephone number of person who can provide further information about this request.

5. Employer identification number of applicant as assigned by Internal Revenue Service.

6a. Use Catalog of Federal Domestic Assistance number assigned to program under which assistance is requested. If more than one program (e.g., joint-funding) write "multiple" and explain in remarks. If unknown, cite Public Law or U.S. Code.

6b. Program title from Federal Catalog. Abbreviate if necessary.

7. Brief title and appropriate description of project. For notification of intent, continue in remarks section if necessary to convey proper description.

8. Mostly self-explanatory. "City" includes town, township or other municipality.

9. Check the type(s) of assistance requested. The definitions of the terms are:

A. Basic Grant. An original request for Federal funds. This would not include any contribution provided under a supplemental grant.

B. Supplemental Grant. A request to increase a basic grant in certain cases where the eligible applicant cannot supply the required matching share of the basic Federal program (e.g., grants awarded by the Appalachian Regional Commission to provide the applicant a matching share).

C. Loan. Self explanatory.

Item

D. Insurance. Self explanatory.

E. Other. Explain on remarks page.

10. Governmental unit where significant and meaningful impact could be observed. List only largest unit or units affected, such as State, county, or city. If entire unit affected, list it rather than subunits.

11. Estimated number of persons directly benefiting from project.

12. Use appropriate code letter. Definitions are:

A. New. A submittal for the first time for a new project.

B. Renewal. An extension for an additional funding/budget period for a project having no projected completion date, but for which Federal support must be renewed each year.

C. Revision. A modification to project nature or scope which may result in funding change (increase or decrease).

D. Continuation. An extension for an additional funding/budget period for a project the agency initially agreed to fund for a definite number of years.

E. Augmentation. A requirement for additional funds for a project previously awarded funds in the same funding/budget period. Project nature and scope unchanged.

13. Amount requested or to be contributed during the first funding/budget period by each contributor. Value of in-kind contributions will be included. If the action is a change in dollar amount of an existing grant (a revision or augmentation), indicate only the amount of the change. For decreases enclose the amount in parentheses. If both basic and supplemental amounts are included, breakout in remarks. For multiple program funding, use totals and show program breakouts in remarks. Item definitions: 13a, amount requested from Federal Government; 13b, amount applicant will contribute; 13c, amount from State, if applicant is not a State; 13d, amount from local government, if applicant is not a local government; 13e, amount from any other sources, explain in remarks.

14a. Self explanatory.

14b. The district(s) where most of actual work will be accomplished. If city-wide or State-wide, covering several districts, write "city-wide" or "State-wide."

15. Complete only for revisions (item 12c), or augmentations (item 12e).

STANDARD FORM 424 PAGE 3 (10–75)

Item	
16.	Approximate date project expected to begin (usually associated with estimated date of availability of funding).
17.	Estimated number of months to complete project after Federal funds are available.
18.	Estimated date preapplication/application will be submitted to Federal agency if this project requires clearinghouse review. If review not required, this date would usually be same as date in item 21.
19.	Existing Federal identification number if this is not a new request and directly relates to a previous Federal action. Otherwise write "NA".
20.	Indicate Federal agency to which this request is addressed. Street address not required, but do use ZIP.
21.	Check appropriate box as to whether Section IV of form contains remarks and/or additional remarks are attached.

APPLICANT PROCEDURES FOR SECTION II

Applicants will always complete items 23a, 23b, and 23c. If clearinghouse review is required, item 22b must be fully completed. An explanation follows for each item:

Item	
22b.	List clearinghouses to which submitted and show in appropriate blocks the status of their responses. For more than three clearinghouses, continue in remarks section. All written comments submitted by or through clearinghouses must be attached.
23a.	Name and title of authorized representative of legal applicant.
23b.	Self explanatory.
23c.	Self explanatory.
Note:	Applicant completes only Sections I and II. Section III is completed by Federal agencies.

FEDERAL AGENCY PROCEDURES FOR SECTION III

If applicant-supplied information in Sections I and II needs no updating or adjustment to fit the final Federal action, the Federal agency will complete Section III only. An explanation for each item follows:

Item	
24.	Executive department or independent agency having program administration responsibility.
25.	Self explanatory.
26.	Primary organizational unit below department level having direct program management responsibility.
27.	Office directly monitoring the program.
28.	Use to identify non-award actions where Federal grant identifier in item 30 is not applicable or will not suffice.
29.	Complete address of administering office shown in item 26.
30.	Use to identify award actions where different from Federal application identifier in item 28.
31.	Self explanatory. Use remarks section to amplify where appropriate.
32.	Amount to be contributed during the first funding/budget period by each contributor. Value of in-kind contributions will be included. If the action is a change in dollar amount of an existing grant (a revision or augmentation), indicate only the amount of change. For decreases, enclose the amount in parentheses. If both basic and supplemental amounts are included, breakout in remarks. For multiple program funding, use totals and show program breakouts in remarks. Item definitions: 32a, amount awarded by Federal Government; 32b, amount applicant will contribute; 32c, amount from State, if applicant is not a State; 32d, amount from local government if applicant is not a local government; 32e, amount from any other sources, explain in remarks.
33.	Date action was taken on this request.
34.	Date funds will become available.
35.	Name and telephone no. of agency person who can provide more information regarding this assistance.
36.	Date after which funds will no longer be available.
37.	Check appropriate box as to whether Section IV of form contains Federal remarks and/or attachment of additional remarks.
38.	For use with A-95 action notices only. Name and telephone of person who can assure that appropriate A-95 action has been taken—If same as person shown in item 35, write "same". If not applicable, write "NA".

Federal Agency Procedures—special considerations

A. *Treasury Circular 1082 compliance.* Federal agency will assure proper completion of Sections I and III. If Section I is being completed by Federal agency, all applicable items must be filled in. Addresses of State Information Reception Agencies (SCIRA's) are provided by Treasury Department to each agency. This form replaces SF 240, which will no longer be used.

B. *OMB Circular A-95 compliance.* Federal agency will assure proper completion of Sections I, II, and III. This form is required for notifying all reviewing clearinghouses of major actions on all programs reviewed under A-95. Addresses of State and areawide clearinghouses are provided by OMB to each agency. Substantive differences between applicant's request and/or clearinghouse recommendations, and the project as finally awarded will be explained in A-95 notifications to clearinghouses.

C. *Special note.* In most, but not all States, the A-95 State clearinghouse and the (TC 1082) SCIRA are the same office. In such cases, the A-95 award notice to the State clearinghouse will fulfill the TC 1082 award notice requirement to the State SCIRA. Duplicate notification should be avoided.

STANDARD FORM 424 PAGE 4 (10-75)

*79-16-83400-1 GPO

Dated: August 18, 1976.

FRANK W. NAYLOR, Jr.,
Acting Administrator, Farmers Home Administration.

[FR Doc.76-26374 Filed 9-8-76;8:45 am]

Title 13—Business Credit and Assistance

CHAPTER I—SMALL BUSINESS ADMINISTRATION

[Rev. 5, Amdt. 6]

PART 107—SMALL BUSINESS INVESTMENT COMPANIES

Deposit of Idle Funds in Savings Account

On June 29, 1976, a notice of proposed rulemaking regarding an amendment to § 107.808 of the SBA Regulations was published in the FEDERAL REGISTER (41 FR 26716) to expand current policy to permit Licensees to deposit funds not needed for current operations in savings accounts in any bank which is insured by the Federal Deposit Insurance Corporation, within the limits set by Regulation "Q," issued by the Board of Governors of the Federal Reserve System.

Interested parties were given 30 days to submit comments and no adverse comment was received. Accordingly, the substance of the amendment then proposed and hereinafter set forth shall become effective September 9, 1976.

Section 107.808 is amended to read as follows:

§ 107.808 Idle funds.

Funds of a Licensee not invested in Small Concerns or in accordance with the last sentence of section 308(b) of the Act shall be deposited without delay in a bank insured by the Federal Deposit Insurance Corporation, or may be (a) invested in Time Certificates of Deposit maturing within one year or less, issued by any bank which is insured by the Federal Deposit Insurance Corporation, or (b) deposited in a savings account of such bank: Provided, however, That a Licensee may maintain a petty cash fund up to $500.

(Catalog of Federal Domestic Assistance Program 59.0111 Small Business Investment Companies)

Dated: August 24, 1976.

MITCHELL P. KOBELINSKI,
Administrator.

[FR Doc.76-26322 Filed 9-8-76;8:45 am]

Miscellaneous Amendments

Correction

In FR Doc. 76-18573 appearing on page 26201 in the issue for Friday, June 25, 1976, in the brackets appearing under the heading for Part 119—Economic Oppor-

tunity Loans in the third column of page 26202 now reading "(Rev. 2, Amdt. 11)" should have read "(Rev. 2, Amdt. 1)".

[Rev. 13, Amdt. 12]

PART 121—SMALL BUSINESS SIZE STANDARDS

Size Standard Differential for Hawaii, the Virgin Islands, Puerto Rico, and Guam

On June 7, 1976, there was published in the FEDERAL REGISTER (41 FR 22847) a notice that the Small Business Administration proposed to adopt differentials applicable, in the case of size standards based on "dollars" to concerns that have 50 percent or more of their annual receipts attributable to business activity in Hawaii; the Virgin Islands, Puerto Rico, and Guam. A differential for Alaska has been in effect for several years.

The public was given an opportunity to comment on the proposal and no adverse comment was filed. Under the circumstances, we have decided to amend the regulation as proposed.

Accordingly, § 121.3–7(a) of Part 121, Chapter I., Title 13 of the Code of Federal Regulations is hereby revised to read as follows:

§ 121.3–7 Differentials.

(a) Alaska, Hawaii, and certain nonforeign areas outside the continental United States. In computing the annual receipts, average annual receipts, assets, net worth, or average net income of a concern (not including its affiliates) that has 50 percent or more of its annual receipts attributable to business activity within one of the States and nonforeign areas set forth below, such annual receipts, average annual receipts, assets, net worth, or average net income, shall be reduced by the percentage prescribed for such State or area.

	Percent
Alaska	25.0
Hawaii	12.5
Virgin Islands	10.0
Puerto Rico	7.5
Guam	7.5

Effective Date: This amendment shall become effective November 8, 1976, but, for the purpose of Government procurement, shall apply only to procurements for which invitations for bids or proposals are issued on or after November 8, 1976.

(All SBA programs listed in the catalog of Federal Domestic Assistance Programs under Nos. 59.001–59.025)

Dated: August 31, 1976.

MITCHELL P. KOBELINSKI,
Administrator.

[FR Doc.76–26323 Filed 9–8–76; 8:45 am]

Title 16—Commercial Practices

CHAPTER I—FEDERAL TRADE COMMISSION

[Docket 8927]

PART 13—PROHIBITED TRADE PRACTICES, AND AFFIRMATIVE CORRECTIVE ACTIONS

Maico Hearing Instruments, Inc.

Subpart—Coercing and intimidating: § 13.358 Distributors. Subpart—Combining or conspiring: § 13.388 To control allocations and solicitation of customers; § 13.395 To control marketing practices and conditions; § 13.430 To enhance, maintain or unify prices; § 13.470 To restrain or monopolize trade; § 13.497 To terminate or threaten to terminate contracts, dealing, franchises, etc. Subpart—Corrective actions and/or requirements: § 13.533 Corrective actions and/or requirements; 13.533–45 Maintain records; 13.533–75 Warranties. Subpart—Cutting off access to customers or market: § 13.535 Contracts restricting customers' handling of competing products; § 13.560 Interfering with distributive outlets; § 13.580 Organizing and controlling seller-suppliers. Subpart—Cutting off supplies or service: § 13.610 Cutting off supplies or service; § 13.635 Refusing sales to, or same terms and conditions; § 13.655 Threatening disciplinary action or otherwise. Subpart—Delaying or withholding corrections, adjustments or action owed: § 13.675 Delaying or withholding corrections, adjustments or action owed; § 13.677 Delaying or failing to deliver goods or provide services or facilities. Subpart—Maintaining resale prices: § 13.1130 Contracts and agreements; § 13.1150 Penalties; § 13.1155 Price schedules and announcements; § 13.1160 Refusal to sell.

(Sec. 6, 38 Stat. 721; 15 U.S.C. 46. Interprets or applies sec. 5, 38 Stat. 719, as amended; 15 U.S.C. 45.)

In the Matter of Maico Hearing Instruments, Inc., a corporation

Consent order requiring a Minneapolis, Minn., manufacturer of hearing aids, among other things to cease imposing on its dealers customer and territorial restrictions and exclusive dealing requirements. The order also requires the firm, under certain circumstances, to make its products available to all qualified dealers, and to maintain, for a ten-year period, a file record of any refusal to sell.

The order to cease and desist, including further order requiring report of compliance therewith, is as follows: [1]

ORDER

I

It is ordered, That Respondent and its subsidiaries, divisions, affiliates, successors, assigns, officers, directors, agents, representatives and employees, directly or indirectly, or through any corporate or other device in connection with the manufacturing, distribution, advertising, offering for sale, sale or repair of its own brand name or trademark hearing aids, or hearing aid accessories, in commerce, as "commerce" is defined in the Federal Trade Commission Act, shall forthwith cease and desist from:

1. Entering into, maintaining, preserving, or enforcing, by refusal to sell or repair, setting of sales quota or equivalent thereof, termination or threat thereof, request, or in any other manner, any arrangement or method of doing business with a dealer of hearing aids and/or accessories which has the purpose or effect of precluding or preventing a dealer from selling the product of one or more other hearing aid manufacturers.

2. Refusing to make available promptly upon request:

(a) Respondent's hearing aids, Respondent's hearing aid accessories which Respondent sells or any of Respondent's written materials relating to fitting and selling such hearing aids or accessories, to any dealer engaged in the sale of hearing aids; or

(b) Repair or replacement parts for Respondent's hearing aids or any of Respondent's written materials relating to repairing or replacing such hearing aids, to any person engaged in the repair of hearing aids, when requested for such purpose, if Respondent makes repair or replacement part available to any dealer for such purpose; *Provided, however*, That Respondent may impose a Ten Dollar ($10.00) minimum order requirement for such parts;

(c) Repair service on a nondiscriminatory basis with respect to a hearing aid manufactured by Respondent when requested by any dealer who sold such aid; *Provided, however*, That if no other provision of this Order is violated thereby:

(i) Respondent may require as a condition to the availability from it of any of its products, services or materials, that the dealer or person referred to in 2 (a), (b) and (c) above has received instruction or met standards necessary for the fitting, servicing, and/or repairing of Respondent's hearing aids which are required at that time of all then existing dealers of Respondent's products or all persons then engaged at the request of Respondent in the repair of Respondent's products, so long as such instruction, if made available to any dealer or person, is made available by Respondent on reasonable terms and conditions to all dealers or persons wanting to deal in or repair Respondent's products;

(ii) Respondent may refuse to make available directly from it any of its products or materials to any dealer or person if such requesting dealer or person is able promptly to obtain the product or materials from another dealer or distributor at Respondent's price to such dealer for a single unit (meaning the same price and discount terms available from Respondent) plus a reasonable service charge not to exceed the sum of Twenty Five Dollars ($25.00), said sum to be adjusted annually by any increase or decrease after 1974 in the Consumer Price Index as published by the United States Government;

(iii) Respondent may refuse to make available directly from it any of its products, services or materials to any dealer or person on other grounds related to that dealer's or person's professional competence or ethical conduct, so long as such refusals are uniformly made where such grounds exist;

(iv) Respondent may refuse to make available directly from it any of its products or materials to any dealer or person if such requesting dealer or person will not agree to purchase a minimum initial

[1] Copies of the Complaint, Appendices, Decision and Order, filed with the original document.

order of five (5) of Respondent's hearing aids on a cash with order basis.

3. Entering into, maintaining, preserving or enforcing by refusal to sell or repair, setting of sales quota or equivalent thereof, termination or threat thereof, request, report of sale, warranty limitation, use of names or addresses of a dealer's customers, or in any other manner, any arrangement or method of doing business which has the purpose or effect of restricting or limiting:

(a) The territory or area in which a dealer of Respondent's hearing aids advertises, offers for sale, sells or repairs such products, or

(b) The person or persons with whom a dealer of Respondent's hearing aids deals.

4. Failing to return any hearing aid submitted to Respondent for repair directly to the dealer who submitted such product for repair unless otherwise instructed in writing by such dealer.

5. Fixing, establishing, stabilizing, maintaining or suggesting the prices at which a dealer of Respondent's hearing aids may or shall advertise, offer for sale, or sell to the public, or a person repairing Respondent's hearing aid may repair such products; *Provided, however,* That nothing in this Order shall prohibit Respondent after ten years from the date of entry of this Order from exercising any lawful rights it may then have under the Miller-Tydings Act, 50 Stat. 693 (1937) and the McGuire Act, 66 Stat. 632 (1952) with respect to hearing aids, accessories or parts.

6. Requiring that a dealer participating in Respondent's cooperative advertising program must not state or imply, in such cooperative advertisements, that the dealer also deals in other brands of hearing aids; *Provided, however,* That Respondent may continue to prohibit in such cooperative advertisement the stating of other brand names of hearing aids.

7. Requiring or coercing a dealer of Respondent's hearing aids to submit to Respondent the names or addresses of any customers of such dealer, or, with respect to such customer names or addresses obtained from a dealer after the effective date of this Order, maintaining, using, publishing or disseminating them for any purpose, without securing the free and informed written consent of the dealer for each such purpose based upon full disclosure to the dealer of the specific uses and disseminations which would be made of the customer names. No such consent shall be sought for other than Respondent's advertising and promotional programs for at least One Hundred Twenty (120) days from the date of Respondent's initial shipment of hearing aids to a new dealer or, in the case of an existing dealer, at least sixty (60) days after service on the dealer of this Order and letter attached hereto as Appendix A.

8. Preventing any dealer from using Respondent's product (brand) name in connection with the advertising, offering for sale, sale or repair of any of Respondent's products, except that Respondent may protect its rights in such name recognized at law.

9. Failing to include and deliver with any of Respondent's hearing aids sold by Respondent any express product warranty for such product provided by Respondent to the user.

II

It is further ordered, That Respondent shall: (a) Forthwith distribute a copy of this Order to each of its operating units, to its present corporate officers and to its present sales and repair personnel, and shall secure from each such officer, employee or other person, a signed statement acknowledging receipt of said Order;

(b) Within Thirty (30) days after service upon it of this Order, distribute a copy of the letter attached to this Order and made a part hereof as Appendix A to each of its existing hearing aid dealers and to every person known to it to be engaged in the repair of Respondent's products;

(c) Within Sixty (60) days after service upon it of this Order, place a full-page advertisement in a trade journal or publication with circulation among hearing aid dealers, which advertisement shall clearly and conspicuously disclose the provisions of Part I of this Order;

(d) Within One Hundred and Twenty (120) days after service upon it of this Order, file with the Commission a report, in writing, setting forth in detail the manner and form in which it has complied with this Order, including a list of all dealers and other persons on whom it has served a copy of Appendix A, and a copy of the publication which includes Respondent's advertisement required by this Order;

(e) For a period of Ten (10) years from the date hereof establish and maintain a file of all records referring or relating to Respondent's refusal to sell to any hearing aid dealer, or person engaged in the business of repairing hearing aids, which file must contain a record of a communication to such dealers or persons explaining Respondent's refusal to sell, and which file will be made available for Commission inspection on reasonable notice; and annually, for a period of Five (5) years from the date hereof, submit a report to the Commission listing the names of all dealers or persons with whom Respondent has refused to deal over the preceding year, a description of the reason for the refusal, and the date of the refusal;

(f) Notify the Commission at least thirty (30) days prior to any proposed change in the corporate Respondent, such as dissolution, assignment or sale resulting in the emergence of a successor corporation, the creation or dissolution of subsidiaries, or any other change in the corporation, which may affect compliance obligations arising out of this Order.

The Decision and Order was issued by the Commission, August 4, 1976.

CHARLES A. TOBIN,
Secretary.

[FR Doc.76-26328 Filed 9-8-76;8:49 am]

Title 35—Panama Canal

CHAPTER I—CANAL ZONE REGULATIONS

PART 253—REGULATIONS OF THE SECRETARY OF THE ARMY

Subpart D—Compensation and Allowances Tropical Differential

The purpose of this amendment is to authorize payment of a tropical differential to the United States citizen employee who, pursuant to a legal separation, is living apart from his or her spouse and who otherwise would be precluded by the regulations from receiving it.

In 35 CFR Part 253, § 253.135 is amended by adding a new paragraph (d) reading as follows:

§ 253.135 Tropical differential.

* * * * *

(d) The rules set forth in paragraphs (b)(2) and (b)(3) of this section shall not disqualify for the differential the employee who is living apart from his or her spouse while subject to a separation agreement executed pursuant to 8 C.Z.C. § 275, a judgment or decree for separate maintenance, or an interlocutory judgment of divorce.

Effective date: This amendment is effective August 30, 1976.

(2 C.Z.C. 142(b), 146(2), 155, 76A Stat. 16, 17, 19; 35 CFR 251.2.)

Dated: September 1, 1976.

MARTIN R. HOFFMANN,
Secretary of the Army.

[FR Doc.76-26368 Filed 9-8-76;8:45 am]

Title 36—Parks, Forests, and Public Property

CHAPTER II—FOREST SERVICE, DEPARTMENT OF AGRICULTURE

Grazing on National Forests and National Grasslands

On May 27, 1976, a document was published in the FEDERAL REGISTER (41 FR 21644) proposing to amend the regulations in 36 CFR Parts 213, 231, and 261, concerning grazing on the National Forests and National Grasslands.

Interested parties were given 30 days to make written submissions regarding the proposal. On June 28, 1976, the period for comment was extended to July 28, 1976 (41 FR 26578). The written comments filed in response to the notice of proposed rulemaking have been carefully considered. Based on these comments, the clarification, modifications, and revisions explained below have been made in the final rule document.

Wording in § 231.2(a) has been changed to show clearly that management of private or State-owned land used in connection with National Forest land is possible only with concurrence of the owners of the private or State-owned land.

Changes proposed in § 231.7(d) have been withdrawn. The reason for this withdrawal is that special interest groups and agencies, as well as the general public, expressed concern that the Forest Service was proposing to assume full responsibility for the leadership role in cooperative management of non-Federal

forested ranges. This was not the intent.

Paragraph (d)(1) of § 231.3 has been changed to express more clearly the periods of coverage of term grazing permits. Also for clarity, paragraph (d)(1)(iv) of § 231.3 has been restated. A new paragraph (d)(1)(vii) has been added to § 231.3 to cover waiver of grazing privileges and recognition of new applicants.

Paragraph (d)(6)(ii) of § 231.3 has been restated to clarify the conditions under which horses, mules or burros may be permitted where needed to manage permitted livestock.

Paragraph (d)(9) of § 231.3 has been changed to more clearly convey the meaning of a negotiated permit. The name of the permit has been changed to eliminate the word "bid" in the title. The wording now correctly conveys what the permit is intended to do.

Changes from the amendment proposal have also been made in § 231.6. These changes were made to show authority of line officers in the Forest Service to revoke or suspend term grazing permits. This is not a change in operating procedure. Such authority has, until now, been expressed in the Forest Service Manual. The reason for this change is to make clear by regulation the authority of Forest officers concerning revocation or suspension of term grazing permits.

Accordingly, with these changes and additions, the proposed amendments are adopted as set forth below.

PART 213—ADMINISTRATION OF LANDS UNDER TITLE III OF THE BANKHEAD-JONES FARM TENANT ACT BY THE FOREST SERVICE

1. Paragraph (e) of § 213.1 is revised to read as follows:

§ 213.1 Designation, administration, and development of National Grasslands.

* * * * *

(e) National Grasslands in the following States and counties are hereby grouped and designated as indicated:

State in which grassland is located	National grassland	Counties where located
Colorado	Pawnee	Weld.
	Comanche	Baca, Los Animas, Otero.
Idaho	Curlew	Oneida, Power.
Kansas	Cimarron	Morton, Stevens.
Nebraska	Oglala	Dawes, Sioux.
New Mexico	Kiowa	Colfax, Harding, Mora, Union.
North Dakota	Cedar River	Grant, Sioux.
	Sheyenne	Ransom, Richland.
	Little Missouri.	Billings, Golden Valley, McKenzie, Slope.
Oklahoma	Rita Blanca	Cimarron.
Oklahoma-Texas	Black Kettle	Roger Mills (Okla.), Hemphill (Tex.).
Oregon	Crooked River.	Jefferson.
South Dakota	Buffalo Gap	Custer, Fall River, Jackson, Pennington.
	Grand River	Corson, Perkins, Ziebach.
	Fort Pierre	Jones, Lyman, Stanley.
Texas	Lyndon B. Johnson.	Montague, Wise.
	Rita Blanca	Dallam.
	Caddo	Fannin.
	McClellan Creek.	Gray.
Wyoming	Thunder Basin.	Campbell, Converse, Crook, Niobrara, Weston.

§ 213.5 [Removed]

2. Section 213.5, Grouping of the National Grasslands into administrative units and providing specific designations therefor is revoked.

PART 231—GRAZING

3. Paragraph (b)(1) of § 231.1 is revised to read as follows:

§ 231.1 Range resource development and administration.

* * * * *

(b) *Definitions.* (1) "National Forest System lands," as used in this part, are the National Forests, National Grasslands, Land Utilization Projects, and other Federal lands for which the Forest Service has administrative jurisdiction.

* * * * *

4. Section 231.2 is retitled and is revised to read as follows:

§ 231.2 Range planning and management.

(a) Range allotments will be designated on National Forest System lands and on other lands under Forest Service control. Associated private and other public lands should, with concurrence of the landowner, be considered in such designations to form logical range management units.

(b) Each range allotment and wild horse or burro territory will be initially analyzed and a plan of management developed and implemented. The analysis and plans will be updated whenever needed as determined by conditions on the allotment or territory.

(85 Stat. 649 (16 U.S.C. 1331–1340).)

5. Paragraph (d) of § 231.3 is amended to read as follows:

§ 231.3 Grazing permits and grazing agreements.

* * * * *

(d) Grazing permits and grazing agreements authorizing livestock use on National Forest System lands and on other lands under Forest Service control shall be as follows:

(1) Paid term permits may be issued for periods of 10 years or less to persons who own the livestock to be grazed and such base ranch property as the Chief, Forest Service, may require. Term permits will be issued to expire December 31 of the mid-year of the decade (1985, 1995, etc.). Term permits may also be issued in connection with changes of ownership of the base property or the permitted livestock of term permittees. Term permits are renewable at the end of each term period provided the provisions and requirements under which they are issued continue to be met. The term permit provides its holder first priority for its renewal at the expiration of the term permit period. The Chief, Forest Service, shall prescribe provisions and requirements under which term permits may be issued, renewed, and administered, including:

(i) Criteria for eligibility;

(ii) Ownership of base property and livestock;

(iii) Specifications for ownership of base property;

(iv) Acquisition of base property and/or permitted livestock.

(v) Conditions for the approval of nonuse of permit for specified periods;

(vi) Upper limits governing size of permit that any person, firm or corporation may hold;

(vii) Conditions whereby waiver of grazing privileges may be confirmed and new applicants recognized.

(2) Paid temporary permits may be issued annually to persons under such provisions and requirements as the Chief, Forest Service, shall prescribe.

(3) Paid term or temporary permits with a specific on-and-off provision may be issued to persons owning livestock that will graze on range only part of which is National Forest System lands and on other lands under Forest Service control.

* * * * *

(6) Free permits may be issued to:

(i) Persons who reside on ranch or agricultural lands within or contiguous to National Forest System lands for not to exceed 10 head of livestock owned or kept for domestic purposes and whose products are consumed or whose services are used directly by the family of the resident, and who distinctly need such National Forest System lands to support such domestic animals.

(ii) Persons who clearly need National Forest System lands to support the number of horses, mules or burros needed to manage permitted livestock.

(iii) Prospectors, campers, and travelers for the few head of livestock actually used during the period of occupancy.

(iv) Others as may be authorized by the Chief, Forest Service.

* * * * *

(9) Negotiated permits may be issued in the absence of applicants qualified for other permits or agreements for periods up to 5 years. Authorized use will be under a grazing management plan.

* * * * *

(64 Stat. 88 (16 U.S.C. 580 l))

6. Paragraph (a) of § 231.5 is amended by adding a paragraph (10):

§ 231.5 Fees, payments, and refunds or credits.

(a) * * *

* * * * *

(10) For negotiated permits, fees paid will be a negotiated item. It may be more or less than standard fees.

* * * * *

(Sec. 501, 65 Stat. 290, (31 U.S.C. 483a))

7. Section 231.6 is revised to read as follows:

§ 231.6 Revocation and suspension of grazing permits.

The Chief, Forest Service and Regional Foresters are authorized to revoke or suspend in whole or in part, and Forest Supervisors are authorized to revoke up to 20 percent, or suspend in whole or in part, term grazing permits or grazing agreements on all National Forest System lands and on other lands under Forest Service control if:

(a) The permittee does not comply with the provisions and requirements in the grazing permit, the regulations of the Secretary of Agriculture on which the permit is based, or instructions issued by Forest officers; and

(b) The permittee knowingly and willfully makes a false statement or representation in grazing application or amendments thereto; or

(c) The permittee violates or does not comply with, Federal laws or regulations or State laws relating to protection of air, water, soil and vegetation, fish and wildlife, and other environmental values when exercising the grazing use authorized by the permit.

8. Section 231.7 is amended to read as follows:

§ 231.7 Cooperation in management.

(a) *Cooperation with local livestock associations.* (1) *Authority.* The Chief, Forest Service, is authorized to recognize, cooperate with, and assist local livestock associations in the management of the livestock and range resources on a single range allotment, associated groups of allotments or other association-controlled lands on which the members' livestock are permitted to graze.

(2) * * *

* * * * *

(iv) Share costs for handling of livestock, construction and maintenance of range improvements or other accepted programs deemed needed for proper management of the permitted livestock and range resources.

* * * * *

(b) *Cooperation with national, State, and county livestock organizations.* The policies and programs of National, State, and county livestock organizations give direction to, and reflect in, the practices of their members. Good working relationships with these groups is conducive to the betterment of range management on both public and private lands. The Chief, Forest Service, will endeavor to establish and maintain close working relationships with National livestock organizations having an interest in the administration of National Forest System lands, and direct Forest officers to work cooperatively with State and county livestock organizations having similar interests.

(c) *Interagency cooperation.* The Chief, Forest Service, will cooperate with other Federal agencies interested in improving range management on public and private lands.

(d) *Cooperation with others.* The Chief, Forest Service, will cooperate with other agencies, institutions, organizations, and individuals who have an interest in improvement of range management on public and private lands.

9. Paragraph (a) of § 231.8 is revised to read as follows:

§ 231.8 Cooperation in control of estray or unbranded livestock, animal diseases, noxious farm weeds, and use of pesticides.

(a) Insofar as it involves National Forest System lands and other lands under Forest Service control or the livestock which graze thereupon, the Chief, Forest Service, will cooperate with:

(1) State, county, and Federal agencies in the application and enforcement of all laws and regulations relating to livestock diseases, sanitation and noxious farm weeds;

(2) The Animal Plan Health Inspection Service and other Federal and/or State Agencies and institutions in surveillance of pesticide spray programs; and

(3) State cattle and sheep sanitary or brand boards in control of estray and unbranded livestock to the extent it does not conflict with the Wild Free-Roaming Horse and Burro Act of December 15, 1971.

(85 Stat. 649 (16 U.S.C. 1331–1340))

* * * * *

10. Section 231.9 is amended to read as follows:

§ 231.9 Range improvements.

(a) The Chief, Forest Service, is authorized to install and maintain structural and nonstructural range improvements needed to manage the range resource on National Forest System lands and other lands controlled by the Forest Service.

(b) Such improvements may be installed and maintained by individuals, organizations or agencies other than the Forest Service subject to the following:

(1) All improvements must be authorized by cooperative agreement, memorandum of understanding or special use permit.

* * * * *

(c) A user of the range resource on National Forest System lands and other lands under Forest Service control may be required by the Chief, Forest Service, to maintain such improvements in a satisfactory state of repair.

* * * * *

(Sec. 12, 64 Stat. 85 (16 U.S.C. 580h))

PART 261—TRESPASS

11. Section 261.13 is amended and paragraph (g) is added as follows:

§ 261.13 Impoundment and disposal of unauthorized livestock.

Unauthorized livestock on the National Forest System lands and on other lands under Forest Service control, which are not removed therefrom within the periods prescribed by this regulation, may be impounded and disposed of by a Forest officer as provided herein.

(a) When a Forest officer determines unauthorized livestock use is occurring and has definite knowledge of the kind of unauthorized livestock, and knows the name of the owners, such livestock may be impounded any time 5 days after written notice of intent to impound unauthorized livestock is mailed by certified or registered mail or personally delivered to such owners.

(b) When a Forest officer determines that unauthorized livestock use is occurring but does not have complete knowledge of the kind of livestock, or if the name of the owners thereof are unknown, such livestock may be impounded any time 15 days after the date a notice of intent to impound unauthorized livestock is first published in a local newspaper and posted at the county courthouse and in one or more local post offices. The notice will identify the area or areas in which it will be effective.

(c) Unauthorized livestock on National Forest System lands and on other lands under Forest Service control, which are owned by persons given notice under paragraph (a) of this section, and any unauthorized livestock in areas for which a notice has been posted and published under paragraph (b) of this section, may be impounded without further notice any time within the 12-month period immediately following the effective date of the notice or notices given under paragraphs (a) and (b) of this section.

(d) Following the impoundment of unauthorized livestock, a notice of sale of impounded livestock will be published in a local newspaper, and posted at the county courthouse and in one or more local post offices. The notice will describe the livestock and specify the date, time, and place of sale. The date set shall be at least 5 days after the publication and posting of such notice.

(e) The owner may redeem the livestock any time before the date and time set for the sale by submitting proof of ownership and paying for all expenses incurred by the United States in gathering, impounding, and feeding or pasturing the livestock. However, when the impoundment costs exceed fair market value, a minimum acceptable redemption price at fair market value may be established for each head of livestock.

(f) If the livestock are not redeemed on or before the date and time fixed for their sale, they shall be sold at public sale to the highest bidder, providing his bid is at or above the minimum amount set by the Forest Service. If a bid at or above the minimum amount is not received, the livestock may be sold at private sale at or above the minimum amount, reoffered at public sale, condemned and destroyed, or otherwise disposed of. When livestock are sold pursuant to this regulation, the Forest officer making the sale shall furnish the purchaser a bill of sale or other written instrument evidencing the sale. Agreements may be made with State agencies whereby unbranded livestock or livestock of unknown ownership are released to the agency for disposition in accordance with State law.

(g) The term livestock as used in this section refers to cattle, sheep, goats, hogs, and equines not meeting the definition of wild, free-roaming horses or burrors in 36 CFR 231.11(a)(2).

(30 Stat. 35, as amended, Sec. 1, 33 Stat. 628 (16 U.S.C. 551, 472); 50 Stat. 525, as amended (7 U.S.C. 1011).)

Effective date: These provisions shall take effect on September 9, 1976.

Signed at Washington, D.C., on August 31, 1976.

ROBERT W. LONG,
Assistant Secretary
U.S. Department of Agriculture.

[FR Doc.76-26369 Filed 9-8-76;8:45 am]

Title 39—Postal Service

CHAPTER I—U.S. POSTAL SERVICE

PART 111—GENERAL INFORMATION ON POSTAL SERVICE

Reimbursement for Official Mail Service

On June 18, 1976, the Postal Service published in the FEDERAL REGISTER (41 FR 24726) a notice of proposed rulemaking on this subject, setting forth a proposed change in § 137.21 of the Postal Service Manual. The proposed change is designed to reflect more accurately the scope of the statutory provisions concerning the collection of postage and fees for official mail service provided to executive and judicial officers of the U.S. Government. Thus, the proposed regulation explicitly recognizes the broad authority of the Postal Service to obtain adequate reimbursement for official mail service, and indicates that the Manager of the Government Revenue and Examination Branch, Finance Department, of the Postal Service may require the use of postage meters, or other forms of positive accountability, where in his judgment such measures are necessary to secure adequate reimbursement.

Interested persons were invited to submit written data, views, or arguments concerning the proposed regulation. Upon request the initial comment period was extended two weeks (41 FR 30354).

Three comments were received. One commenter expressed the concerns of Federal agencies over the potential high cost to agencies if postage meters were required to be used. He said that, prior to implementing any such requirement, agency management officials would need to be assured that alternative actions had been considered and that the selected action has the best cost/benefit ratio. Another commenter requested that adequate advance notice be given to agencies of any major change in the method of official mail accountability. The third commenter expressed the fear that the use of postage meters would delay dispatch of mail because he believes that neither Congress nor the Office of Management and Budget would authorize additional personnel to handle the increased workload which he believes may result.

In our opinion, the comments generally suggest considerations and a reasonable modus operandi which we would have considered and adopted in the administration of this provision. However, in order to allay any fears we are amending the new regulation to make these suggestions explicit.

In view of the considerations discussed above, the Postal Service hereby adopts, as amended, the following amendment of the Postal Service Manual, effective immediately.

Section 137.21 of the Postal Service Manual is revised to read as follows:

§ 137.21 Collection of postage and fees.

Departments, agencies, and establishments of the United States Government must reimburse the Postal Service the equivalent amount of postage and fees due for the official mail service they receive. Instructions governing the manner of reimbursement for official mail service are issued and administered by the Manager, Government Revenue and Examination Branch, Finance Department. Federal Government offices and officers must promptly furnish, in the manner and form requested, all information the Manager considers necessary to assure the accuracy of measurements of official mail use and the adequacy of budgeting to facilitate timely payment. The Manager may require offices and officers to establish improved methods of estimating or measuring official mail volume, or to initiate the use of postage meters or other forms of positive accountability for the use of official mail services, where he determines such action is necessary to secure adequate reimbursement to the Postal Service. Prior to making any such determination the Manager will consult with the office or officer involved as to possible alternative actions that might be taken which would be effective but which might have a better cost/benefit ratio. If the Manager, nevertheless, decides to require the use of postage meters or other forms of positive accountability for the use of official mail services, adequate advance notice will be given to affected agencies.

A Post Office Services (Domestic) transmittal letter making these changes in the pages of the Postal Service Manual will be published and will be transmitted to subscribers automatically. These changes will be published in the FEDERAL REGISTER as provided in 39 CFR 111.3.

(39 U.S.C. 401, 3206, 3209).

W. ALLEN SANDERS,
Assistant General Counsel.

[FR Doc.76-26307 Filed 9-8-76;8:45 am]

Title 40—Protection of Environment

CHAPTER I—ENVIRONMENTAL PROTECTION AGENCY

SUBCHAPTER I—AIR PROGRAMS

[ERL 613-3]

PART 52—APPROVAL AND PROMULGATION OF IMPLEMENTATION PLANS

Notice of Correction

On February 13, 1976, EPA published in the FEDERAL REGISTER (41 FR 6765) approval of regulations for review of Indirect Sources in the State of Connecticut. In that approval notice 40 CFR § 52.375, Review of New Sources and Modifications, was deleted. However, the section number, 52.375, was wrong and is hereby being corrected. The number 52.381 should have been deleted rather than the number 52.375. Therefore, Subpart H of Chapter I, Title 40, Part 52 of the Code of Federal Regulations is corrected as follows:

§ 52.381 [Deleted]

Section 52.381. Review of New Sources and Modifications is deleted.

Dated: September 2, 1976.

ROGER STRELOW,
Assistant Administrator for Air and Waste Management.

[FR Doc.76-26283 Filed 9-8-76;8:45 am]

Title 41—Public Contracts and Property Management

CHAPTER 1—FEDERAL PROCUREMENT REGULATIONS

[FPR Amdt. 169]

PART 1-1—GENERAL

Subpart 1-1.3—General Policies

OFFERS BY FEMALE ENTERPRISES

This amendment of the Federal Procurement Regulations (FPR) changes § 1-1.302, Procurement sources, with respect to the solicitation of offers. The Special Assistant to the President for Women's Affairs has expressed the view that procurement regulations need to be revised to ensure that female enterprises are not discriminated against during the solicitation process. The amendment requires that offers shall not knowingly be solicited on the basis of race, creed, color, sex, age, or national origin.

Section 1-1.302-1 is amended to change paragraph (b), as follows:

§ 1-1.302-1 General.

* * * * *

(b) Irrespective of whether the procurement of supplies or services from sources outside the Government is to be effected by formal advertising or by negotiation, competitive offers ("bids" in the case of procurement by formal advertising, "proposals" in the case of procurement by negotiation) shall be solicited from all such qualified sources as are deemed necessary by the contracting officer to ensure such full and free competition as is consistent with the procurement of types of supplies and services necessary to meet the requirements of the agency concerned. Offers shall not knowingly be solicited on the basis of race, creed, color, sex, age, or national origin of prospective sources.

Effective date: This amendment is effective October 26, 1976.

Dated: September 2, 1976.

NOTE: It is hereby certified that the impact does not meet the inflation impact criteria for major rules or regulations.

JACK ECKERD,
Administrator of General Services.

[FR Doc.76-26534 Filed 9-8-76;8:45 am]

CHAPTER 101—FEDERAL PROPERTY MANAGEMENT REGULATIONS

SUBCHAPTER H—UTILIZATION AND DISPOSAL

[FPMR Amendment H–98]

PART 101–46—UTILIZATION AND DISPOSAL OF PERSONAL PROPERTY PURSUANT TO EXCHANGE/SALE AUTHORITY

Subpart 101–46.4—Disposal

AVAILABILITY OF PROCEEDS OF SALE

This regulation provides updated references to title 7 of the General Accounting Office Policy and Procedures Manual for Guidance of Federal Agencies.

Section 101–46.404 is amended as follows:

§ 101–46.404 **Availability of proceeds of sale.**

Except as otherwise authorized by law, proceeds from sales of personal property disposed of pursuant to this Subpart 101–46.4 shall be accounted for in accordance with General Accounting Office Policy and Procedures Manual for Guidance of Federal Agencies, Title 7, Fiscal Procedures, section 15.4. The requirements for a written administrative determination to establish that a bona fide replacement is involved are set forth in § 101–46.202(a)(4). Procedures for the application of the proceeds from sale for the acquisition of similar items follow:

(a) *Sale of property before the purchase of replacement property.* (1) When the property to be replaced is sold before the acquisition of the replacement property, the proceeds of such sales will be credited to the agency's budget clearing account," ____F3875."

(2) * * *

(3) When the acquisition of the replacement property is subsequently made and the obligation incurred, Standard Form 1081, Voucher and Schedule of Withdrawals and Credits, or other approved form should be processed to charge the budget clearing account, "___ F3875", and credit the appropriation charged for the replacement. For audit purposes, the voucher must include or be supported by sufficient evidence to show that the reimbursement to the appropriation is applicable to the obligation incurred for the acquisition of similar replacement personal property.

* * * * *

(Sec. 205(c), 63 Stat. 390; 40 U.S.C. 486(c))

Effective date. This regulation is effective September 9, 1976.

It is hereby certified that the impact does not meet the inflation impact criteria for major rules or regulations.

Dated: August 30, 1976.

JACK ECKERD,
Administrator of General Services.

[FR Doc.76–26291 Filed 9–8–76;8:45 am]

Title 46—Shipping

CHAPTER I—COAST GUARD, DEPARTMENT OF TRANSPORTATION

[Docket No. HM–134; Amdt. No. 146–1]

PART 146—TRANSPORTATION OR STORAGE OF MILITARY EXPLOSIVES ON BOARD VESSELS

Authority Citations

For reasons set forth in a document amending the authority citations in Parts 171–179 of title 49, Code of Federal Regulations, appearing elsewhere in this issue of the FEDERAL REGISTER, 46 CFR Part 146 is amended by adding an authority citation immediately following the table of contents to read as follows:

* * * * *

AUTHORITY: 46 U.S.C. 170(7) (a–c); 49 U.S.C. 1803, 1804, 1808; 49 CFR 1.53 (e), (f), unless otherwise noted.

(46 U.S.C. 170(7); 49 U.S.C. 1803, 1804, 1808; 49 CFR 1.53 (e), (f).)

Effective date: This amendment is effective on January 3, 1977.

Issued in Washington, D.C., on August 31, 1976.

JAMES T. CURTIS, Jr.,
Director, Materials Transportation Bureau.

[FR Doc.76–26377 Filed 9–8–76;8:45 am]

Title 47—Telecommunication

CHAPTER I—FEDERAL COMMUNICATIONS COMMISSION

[FCC 76–820]

PART 0—COMMISSION ORGANIZATION

Review Board

Adopted: August 31, 1976.

Released: September 3, 1976.

By the Commission: 1. Section 0.361 (f) of the rules provides that a minimum of three members will participate in each "case" referred to the Review Board. While it is relatively clear that the term "case" refers to the review of initial decisions only, and not to interlocutory matters, it is desirable that the provision be clarified. Action on urgent interlocutory matters (e.g., motions for extension of time) should not be deferred if less than three Board members are available to act. We are therefore amending the first sentence of § 0.361(f) to read as follows:

(f) Except for interlocutory matters, a minimum of three members will participate in each matter referred to the Board. * * *

2. Accordingly, it is ordered, effective September 15, 1976, That § 0.361 is amended as set out below. Authority for the amendment is set out in sections 4 (i) and (j), 5(d) and 303(r) of the Communications Act of 1934, as amended, 47 U.S.C. 154 (i) and (j), 155(d) and 303 (r). Because the amendment involves a matter of procedure and merely clarifies an existing provision, the prior notice and effective date provisions of 5 U.S.C. 553 are inapplicable.

(Secs. 4, 5, 303, 48 Stat., as amended, 1066, 1068, 1082; 47 U.S.C. 154, 155, 303.

FEDERAL COMMUNICATIONS COMMISSION,
VINCENT J. MULLINS,
Secretary.

In Part 0 of Chapter I of Title 47 of the Code of Federal Regulations, § 0.361 (f) is revised to read as follows:

§ 0.361 **General authority.**

* * * * *

(f) Except for interlocutory matters, a minimum of three members will participate in each matter referred to the Board. A majority of the members who participate in a case shall constitute a quorum. Any member assigned to a case who is not present at oral argument may, after reading the transcript of oral argument, participate in the Board's decision. However, so far as practicable, all of the members of the Board assigned to a case shall hear oral argument.

[FR Doc.76–26351 Filed 9–8–76;8:45 am]

Title 49—Transportation

SUBTITLE B—OTHER REGULATIONS RELATING TO TRANSPORTATION

CHAPTER I—MATERIALS TRANSPORTATION BUREAU, DEPARTMENT OF TRANSPORTATION

[Docket HM–138; Amdt. No. 107–3]

PART 107—PROCEDURES

Preemption and Enforcement Procedures

The purpose of these amendments to 49 CFR Part 107 is to (1) establish procedural regulations that implement the preemption provisions of section 112 of the Hazardous Materials Transportation Act (Title I of Pub. L. 93–633), (2) prescribe procedures to be followed by the Materials Transportation Bureau (MTB) in carrying out its enforcement responsibilities under sections 109, 110, and 111 of the same Act, and (3) add several general procedural provisions covering the MTB's hazardous materials public docket room, service of documents and subpoenas.

AMENDMENTS TO GENERAL PROVISIONS

The list of definitions in § 107.3 is expanded to include a definition of "person" which covers all of the commonly recognized classes of legal entities regularly doing business, as well as individuals. A definition of "respondent" is added for use in connection with the new Subpart D enforcement procedures. A definition of "State" is being incorporated verbatim from section 103(5) of the Hazardous Materials Transportation Act.

A new § 107.9 is added setting forth a general description of the materials available for public inspection and copying in the MTB's hazardous materials public docket room.

A new § 107.11 prescribes the means for effecting service of documents for purposes of the various hazardous material procedural regulations.

A new § 107.13 specifies who has authority to issue subpoenas under section 109(a) of the Hazardous Materials Transportation Act and prescribes the procedures for their issuance and service, the payment of witness fees, the handling of motions to quash or modify, and their enforcement.

PREEMPTION

In enacting section 112 of the Hazardous Materials Transportation Act, the Congress endorsed the principle of Federal preemption in order to preclude a multiplicity of State and local regulations and the potential for varying, as well as conflicting, regulations in the area of hazardous materials transportation (S. Rep. No. 93–1193, 93rd Cong., 2d Sess. 37 (1974)). The pertinent provisions of section 112 read as follows:

Sec. 112. (a) *General.*—Except as provided in subsection (b) of this section, any requirement of a State or political subdivision thereof, which is inconsistent with any requirement set forth in this title, or in a regulation issued under this title, is preempted.

(b) *State Laws.*—Any requirement of a State or political subdivision thereof, which is not consistent with any requirement set forth in this title, or in a regulation issued under this title, is not preempted if, upon the application of an appropriate State agency, the Secretary determines, in accordance with procedures to be prescribed by regulation, that such requirement (1) affords an equal or greater level of protection to the public than is afforded by the requirements of this title or of regulations issued under this title and (2) does not unreasonably burden commerce. Such requirement shall not be preempted to the extent specified in such determination by the Secretary for so long as such State or political subdivision thereof continues to administer and enforce effectively such requirement.

Section 112(a) operates to preempt and nullify requirements of States and their political subdivisions pertaining to the transportation of hazardous materials which are inconsistent with Federal requirements. The determination as to whether a State or local requirement is consistent or inconsistent with a Federal statute or Federal regulations is traditionally judicial in nature. It is to be expected that conflicts between State and local hazardous materials requirements and the Hazardous Materials Transportation Act and related regulations will be the subject of future litigation. The Bureau, however, does not see the courts as the exclusive arbitrators of the inconsistency questions that may be posed by § 112(a). Therefore, to facilitate the operation of section 112(a), procedures are established in new Subpart C providing States and their political subdivisions and persons affected by requirements of States or political subdivisions the opportunity to seek administrative rulings as to the consistency or inconsistency of any particular State or political subdivision requirement. Also established are the procedures required by section 112(b) by which States or political subdivisions may obtain formal determinations that their inconsistent requirements are not preempted.

The new Subpart C prescribes means for obtaining inconsistency rulings and preemption determinations with respect to existing hazardous materials requirements of States and political subdivisions of States. These procedures are not a vehicle for receiving pre-enactment approval by the MTB. The Bureau does not hold itself out as legislative drafting or editorial service nor will it provide legal research service for State or local governments or legislators. It will, however, upon application, review State and political subdivision requirements which have been officially adopted by a State or political subdivision.

In defining the term "political subdivision" used in section 112 of the Act, the Bureau has taken the view that it includes not only the agencies of a State government, as well as municipalities and other local governments, but also entities created by one or more States or municipalities.

Section 107.203 invites applications for inconsistency rulings from States, political subdivisions, and persons affected by hazardous materials requirements of States and political subdivisions. It also specifies what each applicant must submit as part of his application. Section 107.205 requires private applicants to serve a copy of their application on the State or political subdivision concerned and gives the State or political subdivision 45 days in which to comment. Irrespective of who files an application, the Office of Hazardous Materials Operations (OHMO) may serve notice on additional parties or publish notice of the application in the FEDERAL REGISTER and invite interested persons to file written comments. Under § 107.207 the Director, OHMO, exercises broad investigative authority to fully develop the information necessary for his evaluation of the application. Section 107.209 reserves to the Director, OHMO, the authority to review and issue an inconsistency ruling on his own motion, invoking as necessary the same procedural mechanisms as are available in the case initiated by an application. Paragraph (c) of this section sets forth criteria employed by the Director, OHMO, in making his ruling. These criteria comport with the test for conflicts between Federal and State statutes enunciated by the Supreme Court in *Hines* v. *Davidowitz*, 312 U.S. 52 (1941). Each ruling is issued in writing and is served on the applicant and others who may be involved in the proceeding. When major issues are involved or the ruling has broad application, it may be published in the FEDERAL REGISTER in addition to being served on interested individuals.

Section 107.211 provides a 30-day appeal period for any person aggrieved by a particular ruling.

Section 107.215 invites States and political subdivisions (not private parties) to submit applications for non-preemption determinations. As specified in paragraph (b) of this section, each application must set forth the facts and the applicant's rationale and arguments in support of the non-preemption determination sought.

Section 107.217 requires a State or political subdivision applying for a preemption determination to serve notice of that application on those persons which the State or political subdivision can reasonably identify as being affected by the requested determination. The OHMO may add to the service list or publish notice in the FEDERAL REGISTER, or both. All persons upon whom notice is served or who are identified in the FEDERAL REGISTER notice will have the opportunity to submit written comments. Under § 107.219, as in the case of inconsistency rulings, the Director, OHMO, has broad procedural authority to fully develop the necessary information for making his determination. This includes the authority to require supplemental submissions from the applicant. The Director may dismiss an application without prejudice if there is insufficient information to make his determination; if the applicant fails to provide requested additional information; or if the applicant fails to provide notice to affected persons. The Director will only consider a request for a preemption determination if the inconsistency of the State or political subdivision requirement in issue has been affirmatively fixed by the order of a court of competent jurisdiction by a § 107.209 administrative ruling that has become final, or through the express acknowledgement of inconsistency by the applicant. When the OHMO has received all of the information necessary for reaching a determination, all participants are so notified and, if a formal determination is not issued within 90 days, § 107.223 affords the applicant the same opportunity for appeal as in the case of a denial.

Section 107.221, which provides for the issuance of a written determination, specifies the principal factors considered by the Director, OHMO, in reaching that determination. Whether a particular inconsistent State or political subdivision requirement unreasonably burdens commerce is a question of fact and requires a balancing of the State's or political subdivision's interest in public health and safety against the national interest in maintaining a free flow of commerce. The factors listed in § 107.221(b), no single one of which is dispositive in determining whether a State or political subdivision requirement creates an unreasonable burden, provide in combination the test by which that determination is to be made. Such have been the factors employed by the Supreme Court in deciding whether various State transportation safety requirements impose an unreasonable burden on interstate commerce. See e.g. *South Carolina State Highway Department* v. *Barnwell*, 303 U.S. 177 (1938); *Southern Pacific* v. *Arizona*, 325 U.S. 761 (1945); *Bibb* v.

Navajo Freight Lines, 359 U.S 520 (1959). Section 107221 also provides for service of each preemption determination upon the applicant and other interested persons.

As in the case of inconsistency rulings, a 30-day appeal period for preemption determinations is provided by § 107.225. An appeal may be filed by any person aggrieved by a particular preemption determination.

ENFORCEMENT

New Subpart D describes the investigative procedures and enforcement authorities of the MTB with respect to its assigned area of responsibility for enforcement of the hazardous materials regulations. It also sets forth the MTB's procedures governing the imposition of sanctions with respect to violations of those regulations.

Section 107.301 describes the division of enforcement responsibilities among the operating elements of the Department of Transportation, including the MTB. The MTB exercises its hazardous materials enforcement responsibility through the OHMO. As stated in § 107.303, Subpart D covers the OHMO segment of this enforcement responsibility. Section 107.305 describes the investigative procedures followed by OHMO inspectors.

Under separate headings the remainder of Subpart D describes the various enforcement sanctions available to the OHMO and with respect to those which are primarily administrative to nature (i.e., compliance orders and civil penalties) sets forth procedures governing the processing of individual actions. The choice of which enforcement action or combination of actions to be initiated in a given case is, of course, a matter of administrative discretion with the OHMO acting under the policy direction of the Director, MTB. The four types of enforcement sanctions available to the OHMO are compliance orders, injunctive actions, civil penalties, and criminal penalties.

Sections 107.307 through 107.321 set forth the procedures applicable to the issuance of compliance orders under section 109(a) of the Hazardous Materials Transportation Act. Sections 107.431 through 107.359 set forth the procedures applicable to civil penalties assessed under section 110(a) of the Hazardous Materials Transportation Act. In many respects of the compliance order and civil penalty procedures are similar. Both are initiated by the issuance of a notice of probable violation with the respondent having 30 days in which to reply. Both provide the respondent with an opportunity to present a rebuttal to the allegations, in writing or orally, or a combination of both. They also provide means for settlement through informal compromise. In addition, both provide the respondent with options as to the degree of formality with which the matter is to be processed.

After receiving a notice of probable violation indicating that the OHMO is considering issuance of a compliance order, the respondent may (1) elect not to contest the allegations, (2) proposed the negotiation of a consent order, or (3) contest the allegations. If a consent order cannot be worked out or the respondent contests the allegations, a hearing is held before an official who has the authority to dismiss the case or issue an order directing compliance. His order may be appealed within 20 days after service.

In a situation where an ongoing or impending violation poses a risk requiring corrective steps be taken for the protection of public health and safety without delay, an order directing immediate compliance can be issued under § 107.319. Although prior notice and opportunity for a hearing procedure do not apply in such a situation, the order is subject to administrative appeal.

Section 107.331 and 107.333 reflect generally the authority contained in section 111 (a) and (b), respectively, of the Hazardous Materials Transportation Act. These provisions provide for injunctive relief and punitive damages for violations of the hazardous materials regulations and for the enforcement of compliance orders. When time permits the Department of Justice will bring an action on behalf of the MTB in the appropriate U.S. District Court. However, when the situation involves an imminent hazard the Director, MTB, may bring the action on his own motion in the appropriate U.S. District Court.

When a respondent receives a notice of probable violation indicating that the Director, OHMO, is considering assessing a civil penalty, the respondent may, within 30 days of service, (1) pay the amount of the preliminary assessment, (2) make an informal response denying the allegations in whole or in part and offering explanatory information, or (3) request a hearing. The filing of an informal response provides the opportunity for informal conference and possible compromise of the case. If a hearing is requested it will be conducted before an OHMO official who may dismiss the case or issue an order assessing a civil penalty. His order may be appealed within 20 days after service. In any case in which a civil penalty is assessed, the factors listed in § 107.359 are considered.

At any time after the issuance of a notice of probable violation in a civil penalty case and before it is referred to the Department of Justice for collection, the civil penalty can be compromised and settled by payment of the amount agreed upon in compromise.

Section 107.371 reflects the criminal penalty provided for in section 110(b) of the Hazardous Materials Transportation Act. Section 107.373 describes generally the procedures followed by the OHMO and the MTB with respect to possible criminal violations.

Since these amendments relate to practices and procedures of the MTB and its Office of Hazardous Materials Operations, notice and public procedure thereon is not necessary. Because these amendments are intimately related to action being taken in Docket HM–134 appearing elsewhere in this edition of the FEDERAL REGISTER, these amendments are being made effective concurrently with those in HM–134. However, because the MTB contemplates a review of the procedures established by these amendments after they have been in operations for at least six months and since it is desirous of public participation in that review, interested persons are invited to submit such comments as they may desire with respect to the new preemption and enforcement provisions of new Subparts C and D of 49 CFR Part 107 to the Docket Section, Materials Transportation Bureau, U.S. Department of Transportation, Trans Point Building, Washington, D.C. 20590. All comments received before the close of business on June 1, 1977, will be considered during the review, and will be available in the docket for examination, both before and after that date.

To be given particular attention during the review will be the civil penalty hearing procedures set forth in § 107.355 which the Bureau recognizes may be more formal and burdensome than necessary to fulfill the statutorily required "opportunity for hearing". Accordingly, the Bureau is particularly desirous of receiving comments with respect to this specific subject.

In consideration of the foregoing, 49 CFR Part 107 is amended as follows:

1. The table of sections is amended by adding the following new section numbers and headings:

Subpart A—General Provisions

Sec.

* * * * *

107.9 Public docket room.
107.11 Service.
107.13 Subpoenas; witness fees.

* * * * *

Subpart C—Preemption

107.201 Purpose and scope.

INCONSISTENCY RULINGS

107.203 Application.
107.205 Notice.
107.207 Processing.
107.209 Ruling.
107.211 Appeal.

NON-PREEMPTION DETERMINATIONS

107.215 Application.
107.217 Notice.
107.219 Processing.
107.221 Determination and order.
107.223 Timeliness.
107.225 Appeal.

Subpart D—Enforcement

107.301 Responsibility for enforcement.
107.303 Purpose and scope.
107.305 Investigations.

COMPLIANCE ORDERS

107.307 Compliance orders generally.
107.309 Notice of probable violation.
107.311 Reply.
107.313 Consent order.
107.315 Hearing.
107.317 Presiding officer's decision.
107.319 Compliance order for immediate compliance.
107.321 Appeal.

INJUNCTIVE ACTION

107.331 Injunctions generally.
107.333 Imminent hazards.

CIVIL PENALTIES

Sec.
107.341 Civil penalties generally.
107.343 Maximum penalties.
107.345 Notice of probable violation.
107.347 Reply.
107.349 Payment of penalty.
107.351 Informal response and assessment.
107.353 Request for hearing.
107.355 Hearing.
107.357 Presiding officer's decision.
107.359 Assessment considerations.
107.361 Appeal.

CRIMINAL PENALTIES

107.371 Criminal penalties generally.
107.373 Referral for prosecution.

2. The authority citation following the table of sections is revised to read as follows:

AUTHORITY: 18 U.S.C. 831–835; 46 U.S.C. 170(11); 49 U.S.C. 1421(c); 49 U.S.C. 1802, 1806, 1808–1811; 49 CFR 1.53(e)–(h).

3. 49 CFR 107.3 is amended by adding new definitions of "Act", "Person", "Respondent", and "State" and as amended reads as follows:

§ 107.3 Definitions.

As used in this part:

"Act" means the Hazardous Materials Transportation Act.

"OHMO" means the Office of Hazardous Materials Operations.

"MTB" means the Materials Transportation Bureau.

"Person" includes a corporation, company, association, firm, partnership, society, and joint stock company, joint venture, sole proprietorship, as well as any officer, director, owner or duly authorized representative of any such unit or an individual.

"Respondent" means a person upon whom the OHMO has served a notice of probable violation.

"State" means a State of the United States, the District of Columbia, the Commonwealth of Puerto Rico, the Virgin Islands, American Samoa, or Guam.

4. Subpart A is amended by adding new §§ 107.9, 107.11, and 107.13 immediately following § 107.7 to read as follows:

§ 107.9 Public docket room.

There is established in the MTB offices at 2100 2nd Street, SW., Washington, D.C., a public docket room in which there is available for public inspection and copying:

(a) Copies of notices of proposed rulemaking issued by the OHMO or its predecessor agency, including advance notices, together with the comments received thereon during rulemaking proceedings, copies of any related FEDERAL REGISTER notices, final rules, petitions for reconsideration, and decisions issued in response to petitions for reconsideration;

(b) Applications for exemptions from the Department of Transportation's regulations governing the transportation of hazardous materials, including supporting data, memoranda of any informal meetings with applicants, related FEDERAL REGISTER notices, comments received thereon during the public comment period and copies of decisions issued granting or denying applications for exemptions;

(c) Applications for inconsistency rulings and nonpreemption determinations under Subpart C of this part, together with the comments received thereon, related documents filed with the MTB, copies of related FEDERAL REGISTER notices, and rulings, determinations and orders issued in response to those applications;

(d) Records of compliance order proceedings and copies of OHMO compliance orders;

(e) Appeals filed under this part and MTB decisions issued in response to those appeals; and

(f) Such other information pertaining to the MTB's hazardous materials program required by statute to be made available for public inspection and copying and any information which the MTB or OHMO determines should be made available to the public.

§ 107.11 Service.

(a) Each order, notice, or other document required to be served under this part shall be served personally or by registered or certified mail, except as otherwise provided.

(b) Service upon a person's duly authorized representative constitutes service upon that person.

(c) Service by registered or certified mail is complete upon mailing. An official United States Postal Service receipt from the registered or certified mailing constitutes prima facie evidence of service.

§ 107.13 Subpoenas; witness fees.

(a) The Director, MTB, the Assistant General Counsel for Materials Transportation Law, or the MTB official designated to preside over a hearing convened in accordance with this part, may sign and issue subpoenas either on his own initiative or, upon an adequate showing that the information sought will materially advance the proceeding, upon the request of any person participating in that proceeding.

(b) A subpoena may require the attendance of a witness, or the production of documentary or other tangible evidence in the possession or under the control of the person served, or both.

(c) A subpoena may be served personally by any person who is not an interested person and is not less than 18 years of age, or by certified or registered mail.

(d) Service of a subpoena upon the person named therein shall be made by delivering a copy of the subpoena to such person and by tendering the fees for one day's attendance and mileage as specified by paragraph (f) of this section. When a subpoena is issued at the instance of any officer or agency of the United States, fees and mileage need not be tendered at the time of service. Delivery of a copy of a subpoena and tender of the fees to a natural person may be made by handing them to the person, leaving them at his office with the person in charge thereof, leaving them at his dwelling place or usual place of abode with some person of suitable age and discretion then residing therein, by mailing them by registered or certified mail to him at his last known address, or by any method whereby actual notice is given to him and the fees are made available prior to the return date. When the person to be served is not a natural person, delivery of a copy of the subpoena and tender of the fees may be effected by handing them to a registered agent for service, or to any officer, director, or agent in charge of any office of the person, or by mailing them by registered or certified mail to that representative at his last known address or by any method whereby actual notice is given to the representative and the fees are made available prior to the return date.

(e) The original subpoena bearing a certificate of service shall be filed with the MTB official having responsibility for the proceeding in connection with which the subpoena was issued.

(f) A witness subpoenaed by the MTB shall be paid the same fees and mileage as would be paid to a witness in a proceeding in the district courts of the United States. The witness fees and mileage shall be paid by the person at whose instance the subpoena was issued.

(g) Notwithstanding the provisions of paragraph (f) of this section, and upon request, the witness fees and mileage may be paid by the MTB if the MTB official who issued the subpoena determines on the basis of good cause shown, that:

(1) The presence of the subpoenaed witness will materially advance the proceeding; and

(2) The person at whose instance the subpoena was issued would suffer a serious hardship if required to pay the witness fees and mileage.

(h) Any person to whom a subpoena is directed may, prior to the time specified therein for compliance, but in no event more than 10 days after the date of service of such subpoena, apply to the designated MTB official who issued the subpoena, or if he is unavailable, to the Director, MTB, to quash or modify the subpoena. The application shall contain a brief statement of the reasons relied upon in support of the action sought therein. The Director, MTB, or the designated MTB official, as the case may be, may:

(1) Deny the application;

(2) Quash or modify the subpoena; or

(3) Condition denial of the application to quash or modify the subpoena upon the satisfaction of certain just and reasonable requirements. The denial may be summary.

(i) If there is a refusal to obey a subpoena served upon any person under the provisions of this section, the MTB may request the Attorney General to seek the aid of the United States District Court for any District in which the person is found to compel that person, after notice, to appear and give testimony, or to appear and produce the subpoenaed documents before the MTB, or both.

5. New Subparts C and D are added immediately following Appendix B to Subpart B to read as follows:

Subpart C—Preemption

§ 107.201 Purpose and scope.

(a) This subpart prescribes procedures by which (1) a State or a political subdivision of a State having a requirement pertaining to the transportation of hazardous materials or any person affected by the requirement may obtain an administrative ruling as to whether the requirement is inconsistent with the Act or regulations issued under the Act, and (2) a State or a political subdivision of a State may obtain a determination as to whether a requirement of that State or political subdivision, which is inconsistent with the Act or regulations issued under the Act and therefore preempted by section 112(a) of the Act is not so preempted.

(b) For purposes of this subpart "political subdivision" includes a municipality; a public agency or other instrumentality of one or more States, municipalities, or other political subdivisions of a State; or a public corporation, board, or commission established under the laws of one or more States.

(c) For purposes of this subpart regulations issued under the Act means the regulations contained in this subchapter, Subchapter C of this chapter and 46 CFR Part 146.

(d) Unless otherwise ordered by the Director, OHMO, an application for an inconsistency ruling which includes an application for a determination that the requirement is not preempted will be treated and processed solely as an application for an inconsistency ruling.

Inconsistency Rulings

§ 107.203 Application.

(a) Any State or political subdivision or any person affected by a requirement of a State or political subdivision may apply to the OHMO for an administrative ruling as to whether a particular existing requirement of the State or political subdivision concerned is inconsistent with a requirement of the Act or the regulations issued under the Act.

(b) Each application filed under this section for a ruling must:

(1) Be submitted to the Office of Hazardous Materials Operations, U.S. Department of Transportation, Washington, D.C. 20590. Attention: Hazardous Materials Preemption Docket;

(2) Set forth the text of the State or political subdivision requirement for which the determination is being sought;

(3) Specify each requirement of the Act or the regulations issued under the Act with which the applicant seeks the State or political subdivision requirement to be compared for consistency; and

(4) State why the applicant believes the State or political subdivision requirement to be consistent or inconsistent with the requirements of the Act or the regulations issued under the Act.

(c) The filing of an application for a ruling under this section does not constitute grounds for noncompliance with any requirement of the Act or a regulation issued under the Act.

§ 107.205 Notice.

(a) If the applicant is other than a State or political subdivision, the applicant shall mail a copy of the application to the State or political subdivision concerned accompanied by a statement that the State or political subdivision may submit comments regarding the application to the OHMO within 45 days. The application filed with the OHMO must include a certification that the applicant has complied with this paragraph and must include the names and addresses of each State or political subdivision official to whom a copy of the application was sent.

(b) The OHMO may be serving notice on any other persons readily identifiable by the OHMO as persons who will be affected by the ruling sought or by publication in the Federal Register afford those persons an opportunity to file written comments on the application.

(c) Each person submitting written comments to the OHMO with respect to an application filed under this section shall send a copy of the comments to the applicant and certify to the OHMO that he has complied with this requirement. The OHMO may notify other persons participating in the proceeding of the comments and provide an opportunity for those other persons to respond.

§ 107.207 Processing.

(a) The Director, OHMO, may initiate an investigation of any statement in an application and utilize in his evaluation any relevant facts obtained by that investigation. The Director, OHMO, may solicit and accept submissions from third persons relevant to an application and will provide the applicant an opportunity to respond to all third person submissions. In evaluating an application, the Director, OHMO, may consider any other source of information. The Director, OHMO, on his own initiative may convene a hearing or conference, if he considers that a hearing or conference will advance his evaluation of the application.

(b) The Director, OHMO, may dismiss the application without prejudice if:

(1) He determines that there is insufficient information upon which to base a ruling; or

(2) He requests additional information from the applicant and it is not submitted.

§ 107.209 Ruling.

(a) Upon consideration of the application and other relevant information received or obtained during the proceeding, the Director, OHMO, issue his ruling.

(b) Notwithstanding that application for a ruling has not been filed under § 107.203, the Director, OHMO, on his own initiative, may issue a ruling as to whether a particular State or political subdivision requirement is inconsistent with the Act or the regulations issued under the Act.

(c) In determining whether a State or political subdivision requirement is inconsistent with the Act or the regulations issued under the Act, the Director, OHMO, considers:

(1) Whether compliance with both the State or political subdivision requirement and the Act or the regulations issued under the Act is possible; and

(2) The extent to which the State or political subdivision requirement is an obstacle to the accomplishment and execution of the Act and the regulations issued under the Act.

(d) The ruling includes a written statement setting forth the relevant facts and the legal basis for the ruling and provides that any person aggrieved thereby may file an appeal with the Director, MTB.

(e) The OHMO serves a copy of the ruling upon the applicant, any other person who participated in the proceeding and upon any other person readily identifiable by the OHMO as one who is affected by the ruling. A copy of each ruling is placed on file in the public docket. The OHMO may publish the ruling or notice of the ruling in the Federal Register.

(f) A ruling issued under this section constitutes an administrative determination as to whether a particular requirement of a State or local subdivision is inconsistent with the Act or the regulations issued under the Act. The fact that a ruling has not been issued under this section with respect to a particular requirement of a State or political subdivision carries no implication as to the consistency or inconsistency of that requirement with the Act or any regulations issued under the Act.

§ 107.211 Appeal.

Any person aggrieved by a ruling issued under § 107.209 may file an appeal with the Director, MTB. The appeal must be filed within 30 days of service of the ruling. There has not been an exhaustion of administrative remedies until an appeal has been filed and the appellate process is completed by the issuance of an order by the Director, MTB, granting or denying the appeal.

Non-Preemption Determinations

§ 107.215 Application.

(a) Any State or political subdivision may apply to the OHMO for a determination that a particular existing requirement of that State or political subdivision which is inconsistent with the Act or the regulations issued under the Act is not preempted.

(b) Each application filed under this section for a nonpreemption determination must:

(1) Be submitted to the Office of Hazardous Materials Operations, U.S. Department of Transportation, Washington, D.C. 20590. Attention: Hazardous Materials Preemption Docket;

(2) Set forth the text of the State or political subdivision requirement for which the determination is being sought;

(3) Include a copy of any court order and any ruling issued under § 107.209 having a bearing on the application;

(4) Contain an express acknowledgment by the applicant that the State or political subdivision requirement is in-

consistent with one or more requirements of the Act or the regulations issued under the Act, unless it has been so determined by a court of competent jurisdiction or in a ruling issued under § 107.209;

(5) Specify each requirement of the Act or the regulations issued under the Act with which the State or political subdivision requirement is acknowledged or has been determined to be inconsistent;

(6) State why the applicant believes the State or political subdivision requirement affords an equal or greater level of protection to the public than is afforded by the requirements of the Act or the regulations issued under the Act;

(7) State why the applicant believes the State or political subdivision requirement does not unreasonably burden commerce; and

(8) Specify what steps the State or political subdivision is taking to administer and enforce effectively its inconsistent requirement.

§ 107.217 Notice.

(a) The applicant State or political subdivision shall mail a copy of the application and any subsequent amendments or other documents relating to the application to each person who is reasonably ascertainable by the applicant as a person who will be affected by the determination sought. The copy of the applition must be accompanied by a statement that the person may submit comments regarding the application to the OHMO within 45 days. The application filed with the OHMO must include a certification that the application has complied with this paragraph and must include the names and addresses of each person to whom the application was sent.

(b) Notwithstanding the provisions of paragraph (a) of this section, if the State or political subdivision determines that compliance with paragraph (a) of this section would be impracticable, the applicant shall:

(1) Comply with the requirements of paragraph (a) of this section with regard to those persons whom it is reasonable and practicable to notify; and

(2) Include with the application filed with the OHMO a description of the persons or class or classes of persons to whom notice was not sent.

(c) The OHMO may require the State or political subdivision to provide notice in addition to that required by paragraphs (a) and (b) of this section, or may determine that the notice required by paragraph (a) of this section is not impracticable, or that notice should be published in the FEDERAL REGISTER.

(d) The OHMO may serve notice on any other persons readily identifiable by the OHMO as persons who will be affected by the determination sought and may afford those persons an opportunity to file written comments on the application.

(e) Any person submitting written comments to the OHMO with respect to an application filed under this section shall send a copy of the comments to the applicant. The person shall certify to the OHMO that he has complied with the requirements of this paragraph. The OHMO may notify other persons participating in the proceeding of the comments and provide an opportunity for those other persons to respond.

§ 107.219 Processing.

(a) The Director, OHMO, may initiate an investigation of any statement in an application and utilize in his evaluation any relevant facts obtained by that investigation. The Director, OHMO, may solicit and accept submissions from third persons relevant to an application and will provide the applicant an opportunity to respond to all third person submissions. In evaluating an application, the Director, OHMO, on his own initiative may convene a hearing or conference, if he considers that a hearing or conference will advance his evaluation of the application.

(b) The Director, OHMO, may dismiss the application without prejudice if:

(1) He determines that there is insufficient information upon which to base a determination;

(2) Upon his request, additional information is not submitted by the applicant; or

(3) The applicant fails to provide the notice required by § 107.217.

(c) Except as provided in § 107.201(c), the Director, OHMO, will only consider an application for a non-preemption determination if—

(1) The applicant State or political subdivision expressly acknowledges in its application that the State or political subdivision requirement for which the determination is sought is inconsistent with the requirements of the Act or the regulations issued under the Act; or

(2) The State or political subdivision requirement has been determined by a court of competent jurisdiction or in a ruling issued under § 107.209 to be inconsistent with the requirements of the Act or the regulations issued under the Act.

(d) When the OHMO has received all substantive information it considers necessary to process an application for a non-preemption determination, it serves notice of that fact upon the applicant and all other persons who received notice of the proceeding pursuant to § 107.217.

(e) To the extent possible, each application for a non-preemption determination will be acted upon in a manner consistent with the disposition of previous applications for non-preemption determinations.

§ 107.221 Determination and order.

(a) Upon consideration of the application and other relevant information received or obtained during the proceeding, the Director, OHMO, issues an order setting forth his determination.

(b) The Director, OHMO, may issue a non-preemption order only if he finds that the State or political subdivision requirement affords to the public a level of safety at least equal to that afforded by the requirements of the Act and the regulations issued under the Act and does not unreasonably burden commerce. In determining whether the State or political subdivision requirement unreasonably burdens commerce, the Director, OHMO, considers the following factors:

(1) The extent to which increased costs and impairment of efficiency result from the State or political subdivision requirement.

(2) Whether the State or political subdivision requirement has a rational basis.

(3) Whether the State or political subdivision requirement achieves its stated purpose.

(4) Whether there is need for uniformity with regard to the subject concerned and if so, whether the State or political subdivision requirement competes or conflicts with those of other States and political subdivisions.

(c) The order includes a written statement setting forth the relevant facts and the legal basis for the determination. The order provides that any person aggrieved thereby may file an appeal with the Director, MTB.

(d) The OHMO serves a copy of the order upon the applicant, any other person who participated in the proceeding and upon any other person readily identifiable by the OHMO as one who is affected by the order. A copy of each order is placed on file in the public docket. The Director, OHMO, may publish the order or notice of the order in the FEDERAL REGISTER.

(e) An order issued under this section constitutes an administrative determination as to whether a particular requirement of a State or local subdivision of a State, which is inconsistent with the requirements of the Act or the regulations issued under the Act is not preempted.

§ 107.223 Timeliness.

If the OHMO fails to take action on the application within 90 days of serving the notice required by § 107.219(d), the applicant may treat the application as having been denied in all respects and may appeal therefrom as provided in § 107.225.

§ 107.225 Appeal.

Any person aggrieved by an order issued under § 107.221 may file an appeal with the Director, MTB. The appeal must be filed within 30 days of service of the order. There has not been an exhaustion of administrative remedies until an appeal has been filed and the appellate process is completed by the issuance of an order by the Director, MTB, granting or denying the appeal.

Subpart D—Enforcement

§ 107.301 Responsibility for enforcement.

In accordance with delegations of authority from the Secretary of Transportation set forth in Part 1 of this title, responsibility for enforcement of this subchapter and Subchapter C of this chapter is exercised by:

(a) The Federal Aviation Administration with respect to the transportation or shipment of hazardous materials by aircraft;

(b) The United States Coast Guard with respect to the transportation or shipment of hazardous materials by vessels;

(c) The Federal Highway Administration with respect to the transportation or shipment of hazardous materials by highway vehicles;

(d) The Federal Railroad Administration with respect to the transportation or shipment of hazardous materials by railroad; and

(e) The MTB in all other respects. The MTB exercises this enforcement responsibility through the OHMO.

§ 107.303 Purpose and scope.

This subpart describes the various enforcement authorities exercised by the OHMO and the associated sanctions and prescribes the procedures governing the exercise of those authorities and the imposing of those sanctions.

§ 107.305 Investigations.

(a) *General.* The OHMO may initiate investigations relating to compliance by any person with any provision of this subchapter [or Subchapter C of this chapter], and order issued thereunder, or any court decree relating thereto. The OHMO encourages voluntary cooperation with its investigations. When circumstances warrant, however, subpoenas may be issued to compel the attendance of witnesses or the production of documents in accordance with and subject to § 107.13 and hearings may be conducted, and depositions taken pursuant to section 109(a) of the Act. The OHMO may conduct investigative conferences and hearings in the course of any investigation.

(b) *Investigators.* Investigations are conducted by officials of the OHMO who are duly designated for that purpose. Each official so designated may administer oaths and receive affirmations in any matter under investigation by the OHMO.

(c) *Notification.* Any person who is under investigation by the OHMO and who is requested to furnish information or documentary evidence is notified as to the general purpose for which the information or evidence is sought.

(d) *Termination.* When the facts disclosed by an investigation indicate that further action is unnecessary or unwarranted at that time, the investigative file is closed without prejudice to further investigation by the OHMO at any time that circumstances so warrant.

(e) *Confidentiality.* Information received in an investigation under this section, including the identity of the person investigated and any other person who provides information during the investigation, shall, unless otherwise determined by the OHMO, remain confidential under the investigatory file exception to the public disclosure requirements of 5 U.S.C. 552.

COMPLIANCE ORDERS

§ 107.307 Compliance orders generally.

When the OHMO has reason to believe that a person is engaging in conduct which involves a violation of any provision of this subchapter or Subchapter C of this chapter for which the OHMO exercises enforcement responsibility, or of any exemption issued under Subpart B of this Part, and if time, the nature of the violation, and the public interest permit, the OHMO may conduct proceedings pursuant to section 109(a) of the Act to determine the nature and extent of the violation and may thereafter issue an order directing compliance.

§ 107.309 Notice of probable violation.

(a) The OHMO begins a compliance order proceeding by serving a notice of probable violation on a person charging him with violating one or more provisions of this subchapter.

(b) A notice of probable violation issued under this section includes;

(1) A statement of the provision[s] of this subchapter or Subchapter C of this chapter which the respondent is believed to be violating;

(2) A statement of the factual allegations upon which remedial action is being sought; and

(3) A statement of the remedial action being sought in the form of a proposed compliance order.

(c) The OHMO may amend a notice of probable violation issued under this section at any time before the entry of a final compliance order. If an amendment includes any new material allegation of fact or seeks new or additional remedial action, the respondent is given an opportunity to respond.

§ 107.311 Reply.

(a) Within 30 days of the service of a notice of probable violation issued under § 107.309, the respondent may file a reply with the OHMO official who issued the notice of probable violation. That official may extend the 30-day period for good cause shown.

(b) The reply must be in writing, signed by the person filing it, and state with respect to each factual allegation whether it is admitted or denied. Even though formally denied, a factual allegation set forth in a notice of probable violation is considered to be admitted for purposes of the proceeding unless:

(1) Opposed by the written statement of an individual having personal knowledge of the subject matter;

(2) Challenged as defective on its face together with a supporting explanation as to why it is believed to be defective; or

(3) Otherwise actively put at issue through the submission of relevant evidence.

(c) The reply must set forth any affirmative defenses and include a statement of the form and nature of proof by which those defenses are to be established.

(d) If it is necessary to respond to an amendment to the notice of probable violation, the respondent may amend his reply at any time before the issuance of an order under § 107.317.

(e) If the respondent elects not to contest one or more factual allegations, he should so state in the reply. An election not to contest a factual allegation is an admission of that allegation solely for the purpose of issuing a compliance order and constitutes a waiver of hearing as to that allegation but does not, by itself, constitute a waiver of the right to be heard on other issues. In connection with a statement of election not to contest a factual allegation, the respondent may propose an appropriate order for issuance by the Director, OHMO, or propose the negotiation of a consent order.

(f) Failure of the respondent to file a reply within the period provided constitutes a waiver of his right to appear and contest the allegation and authorizes the Director, OHMO, without further notice to the respondent, to find the facts to be as alleged in the notice of proposed violation and to issue an appropriate order directing compliance.

§ 107.313 Consent order.

(a) At any time before the issuance of an order under § 107.317, the OHMO and the respondent may execute an agreement for disposing of the case by the entry of a consent order. If the Director, OHMO, accepts the agreement, he issues an order in accordance with its terms. If the Director, OHMO, rejects the agreement, he directs that the proceeding continue.

(b) An agreement submitted to the Director, OHMO, under this section must include:

(1) A proposed compliance order suitable for the Director's signature;

(2) An admission of all jurisdictional facts;

(3) An express waiver of further procedural steps and of all right to seek judicial review or otherwise challenge or contest the validity of the order; and

(4) An acknowledgement that the notice of probable violation may be used to construe the terms of the order.

§ 107.315 Hearing.

(a) When a respondent files a reply contesting allegations in a notice of proposed violation issued under § 107.309 or when the OHMO and the respondent fail to agree upon an acceptable consent order, the Director, OHMO, or an official designated by him, convenes and presides over a hearing on the proposed compliance order.

(b) The presiding official may:

(1) Administer oaths and affirmations;

(2) Issue subpoenas as provided by § 107.13;

(3) Adopt procedures for the submission of evidence;

(4) Take or cause depositions to be taken;

(5) Rule on offers of proof and receive relevant evidence;

(6) Examine witnesses at the hearing;

(7) Convene, recess, reconvene, adjourn and otherwise regulate the course of the hearing;

(8) Hold conferences for settlement, simplification of the issues or any other proper purpose; and

(9) Take any other action authorized by or consistent with the provisions of this subpart pertaining to compliance orders and permitted by law which may expedite the hearing or aid in the disposition of an issue raised therein.

(c) The OHMO official who issued the notice of proposed violation, or his representative, has the burden of proving the facts alleged in the notice of proposed violation and may offer such relevant information as may be necessary to fully inform the presiding officer as to the matter concerned.

(d) The respondent may appear and be heard on his own behalf or through counsel of his choice. The respondent or his counsel may offer relevant information including testimony which he believes should be considered in defense of the allegations or which may bear on the remedial action being sought and conduct such cross-examination as may be required for a full disclosure of the facts.

§ 107.317 Presiding officer's decision.

(a) After consideration of evidence, the presiding officer may dismiss the notice of proposed violation or issue an order directing compliance. The order will include a statement of findings and conclusions as well as the reasons therefor on all material issues of fact, law, and discretion.

(b) A compliance order issued under this section is effective upon service on the respondent unless otherwise provided therein.

§ 107.319 Compliance order for immediate compliance.

(a) Notwithstanding §§ 107.309 through 107.317, the Director, OHMO, may issue a compliance order for immediate compliance, which is effective upon issuance, and until rescinded or suspended, if he finds

(1) There is strong probability that a violation is occurring or is about to occur;

(2) The violation poses an unreasonable risk to health or to safety of life or property; and

(3) The public interest requires the avoidance or amelioration of that unreasonable risk through immediate compliance and waiver of the procedures afforded under §§ 107.309 through 107.317.

(b) A compliance order for immediate compliance is served promptly upon the person against whom the order is issued by telex or telegram, with a copy served in the manner provided in § 107.11. The copy contains a written statement of the relevant facts and the legal basis for the order, including the findings required by paragraph (a) of this section.

(c) The Director, OHMO, may rescind or suspend a compliance order for immediate compliance if it appears that the criteria set forth in paragraph (a) of this section are no longer satisfied. When appropriate, however, such a suspension or rescission may be accompanied by a notice of probable violation issued under § 107.309.

(d) If at any time in the course of a proceeding commenced by a notice of probable violation the criteria set forth in paragraph (a) of this section are satisfied, the Director, OHMO, may issue a compliance order for immediate compliance, even if the 30-day period for reply specified in § 107.311(a) has not expired.

(e) At any time after a compliance order for immediate compliance has become effective, the Director, MTB, or his delegate may request the Attorney General to bring an action for appropriate relief in accordance with § 107.331.

§ 107.321 Appeal.

(a) A respondent aggrieved by a compliance order or a compliance order for immediate compliance may file an appeal with the Director, MTB. The appeal must be filed within 20 days after service of the compliance order.

(b) The filing of an appeal does not stay the effectiveness of the order unless the Director, MTB, expressly so provides.

INJUNCTIVE ACTION

§ 107.331 Injunctions generally.

Whenever it appears to the OHMO that a person has engaged, is engaged, or is about to engage in any act or practice constituting a violation of any provision of this subchapter or Subchapter C of this chapter for which the OHMO exercises enforcement responsibility or of any order issued thereunder, the Director, MTB, or his delegate, may request the Attorney General to bring an action in the appropriate United States District Court for such relief as is necessary or appropriate, including mandatory or prohibitive injunctive relief, interim equitable relief, and punitive damages as provided by section 111(a) of the Act.

§ 107.333 Imminent hazards.

Whenever it appears to the OHMO that there is a substantial likelihood that death, serious illness, or severe personal injury will result from the transportation of a particular hazardous material before a compliance order proceeding or other administrative hearing or formal proceeding to abate the risk of that harm can be completed, the Director, MTB, or his delegate, may bring an action in the appropriate United States District Court for an order suspending or restricting the transportation of that hazardous material or for such other equitable relief as is necessary or appropriate to ameliorate the hazard as provided by section 111(b) of the Act.

CIVIL PENALTIES

§ 107.341 Civil penalties generally.

When the OHMO has reason to believe that a person has knowingly committed an act which is a violation of any provision of this subchapter or Subchapter C of this chapter for which the OHMO exercises enforcement responsibility or of any exemption issued under Subpart B of this part, it may conduct proceedings to assess and, if appropriate, compromise a civil penalty.

§ 107.343 Maximum penalties.

(a) A person who knowingly violates a requirement of this subchapter applicable to the transporting of hazardous materials or to the causing of them to be transported or shipped is liable for a civil penalty of not more than $10,000 for each violation. When the violation is a continuing one, each day of the violation constitutes a separate offense.

(b) A person who knowingly violates a requirement of this subchapter applicable to the manufacture, fabrication, marking, maintenance, reconditioning, repair, or testing of a package or container which is represented, marked, certified or sold by that person for use in the transportation of hazardous materials in commerce is liable for a civil penalty of not more than $10,000.

§ 107.345 Notice of probable violation.

(a) The OHMO begins a civil penalty proceeding by serving a notice of probable violation on a person charging him with having violated one or more provisions of this subchapter or Subchapter C of this chapter.

(b) A notice of probable violation issued under this section includes:

(1) A statement of the provision(s) of this subchapter or Subchapter C of this chapter which the respondent is believed to have violated;

(2) A statement of the factual allegations upon which the proposed civil penalty is being sought;

(3) Notice of the maximum amount of civil penalty for which the respondent may be liable;

(4) Notice of the amount of the preliminary assessed civil penalty;

(5) A description of the manner in which the respondent should make payment of any money to the United States;

(6) A statement of the respondent's right to present written or oral explanations, information or any materials in answer to the allegations or in mitigation of the penalty; and

(7) A statement of the respondent's right to request a hearing and the procedures for requesting a hearing.

§ 107.347 Reply.

(a) Within 30 days of the service of a notice of probable violation issued under § 107.345, the respondent may:

(1) Pay the preliminary assessment as provided in § 107.349(a) and thereby close the case;

(2) Make an informal response as provided in § 107.351; or

(3) Request a hearing as provided in § 107.353.

(b) The OHMO official who issued the notice of probable violation may extend the 30-day period for good cause shown.

(c) Failure of the respondent to reply by taking one of the three actions described in paragraph (a) of this section within the period provided constitutes a waiver of his right to appear and contest the allegations and authorizes the Director, OHMO, without further notice to the respondent, to find the facts to be as alleged in the notice of probable violation and order the assessment of an appropriate civil penalty.

§ 107.349 Payment of penalty.

(a) Payment of a civil penalty should be made by certified check or money order payable to the Treasurer of the United States and sent to the Assistant General Counsel for Materials Transportation Law, Department of Transportation, Washington, D.C. 20590.

(b) At any time before an order assessing a civil penalty is referred to the Attorney General for collection, the respondent may offer to comprise for a specific amount by submitting a certified check or money order for that amount to the Assistant General Counsel who may accept or reject it. If it is accepted, the respondent is notified in writing that the acceptance is in full settlement of the civil penalty for the violation.

§ 107.351 Informal response and assessment.

(a) If a respondent elects to make an informal response to a notice of probable violation, he shall submit to the OHMO official who issued the notice such written explanations, information or other materials as he may desire in answer to the charges or in mitigation of the proposed penalty.

(b) The respondent may include in his informal written response a request for a conference. Upon receipt of such a request, the OHMO arranges for a conference as soon as practicable at a time and place of mutual convenience.

(c) Written explanations, information or material submitted by the respondent and relevant information presented during any conference held under this section are considered by the OHMO in reviewing the notice of proposed violation and determining the fact of violation and the amount of any penalty to be assessed.

(d) After consideration of an informal response including any relevant information presented at a conference, the Director, OHMO, may dismiss the notice of probable violation in whole or in part. If he does not dismiss it in whole he may issue an order assessing a civil penalty.

§ 107.353 Request for hearing.

(a) If a respondent elects to request a hearing, he shall submit a written request to the Director, OHMO. The request must:

(1) State the name and address of the respondent and of the person signing the request if different from the respondent;

(2) State with respect to each allegation whether it is admitted or denied; and

(3) State with particularity the issues to be raised by the respondent at the hearing.

(b) After a request for hearing which complies with the requirements of paragraph (a) of this section, the Director, OHMO, schedules a hearing for the earliest practicable date.

(c) The Director, OHMO, may grant extensions of the time of the commencement of the hearing for good cause shown.

§ 107.355 Hearing.

(a) When a hearing is requested and scheduled under § 107.353, the Director, OHMO, or an official designated by him, convenes and presides over the hearing. To the extent practicable, the hearing will be held in the general vicinity of the place where the alleged violation occurred or at a place convenient to the respondent. Testimony by witnesses shall be given under oath and the hearing shall be recorded verbatim.

(b) The presiding official may:

(1) Administer oaths and affirmations;

(2) Issue subpoenas as provided by § 107.13;

(3) Adopt procedures for the submission of evidence in written form;

(4) Take or cause depositions to be taken;

(5) Rule on offers of proof and receive relevant evidence;

(6) Examine witnesses at the hearing;

(7) Convene, recess, reconvene, adjourn and otherwise regulate the course of the hearing;

(8) Hold conferences for settlement, simplification of the issues or any other proper purpose; and

(9) Take any other action authorized by or consistent with the provisions of this subpart pertaining to civil penalties and permitted by law which may expedite the hearing or aid in the disposition of an issue raised therein.

(c) The OHMO official who issued the notice of proposed violation, or his representative, has the burden of providing the facts alleged in the notice of proposed violation and may offer such relevant information as may be necessary to fully inform the presiding officer as to the matter concerned.

(d) The respondent may appear and be heard on his own behalf or through counsel of his choice. The respondent or his counsel may offer relevant information including testimony which he believes should be considered in defense of the allegations or which may bear on the penalty to be assessed and conduct such cross-examination as may be required for a full disclosure of the facts.

§ 107.357 Presiding officer's decision.

(a) After consideration of the evidence of record, the presiding officer may dismiss the notice of probable violation in whole or in part. If he does not dismiss it in whole, he will issue and serve on the respondent an order assessing a civil penalty. The order will include a statement of findings and conclusions as well as the reasons therefor on all material issues of fact, law, and discretion.

(b) If, within 20 days after service of an order assessing a civil penalty, the respondent does not pay the civil penalty or file an appeal as provided in § 107.361 (a), the case may be referred to the Attorney General with a request that an action to collect the penalty be brought in the appropriate United States District Court.

§ 107.359 Assessment considerations.

In assessing a civil penalty under §§ 107.351 and 107.355, the assessment is made only after considering:

(1) The nature and circumstances of the violation;

(2) The extent and gravity of the violation;

(3) The degree of the respondent's culpability;

(4) The respondent's history of prior offenses;

(5) The respondent's ability to pay;

(6) The effect on the respondent's ability to continue in business; and

(7) Such other matters as justice may require.

§ 107.361 Appeal.

(a) A respondent aggrieved by a presiding officer's decision and order issued under § 107.357 assessing a civil penalty may file an appeal with the Director, MTB. The appeal must be filed within 20 days of service of the presiding officer's order.

(b) If the Director, MTB, affirms the assessment and the respondent does not pay the civil penalty within 20 days after service of the Director's decision on appeal, the case may be referred to the Attorney General with a request that an action to collect the penalty be brought in the appropriate United States District Court.

CRIMINAL PENALTIES

§ 107.371 Criminal penalties generally.

Section 110(b) of the Act (49 U.S.C. 1809(b)) provides a criminal penalty of a fine of not more than $25,000 and imprisonment for not more than five years, or both, for any person who willfully violates a provision of the Act or a regulation issued under the Act.

§ 107.373 Referral for prosecution.

If an inspector or other employee of the OHMO becomes aware of a possible willful violation of the Act, this subchapter or Subchapter C of this chapter for which the OHMO exercises enforcement responsibility, he reports it to the Office of the Assistant General Counsel for Materials Transportation Law. If appropriate, the Assistant General Counsel refers the report to the Department of Justice for criminal prosecution of the offender.

Effective date: This amendment is effective on January 3, 1977.

(49 U.S.C. 1808–1811 and 49 CFR 1.53(e).)

Issued in Washington, D.C., on August 31, 1976.

JAMES T. CURTIS, Jr.,
Director,
Materials Transportation Bureau.

[FR Doc.76-26375 Filed 9-8-76;8:45 am]

[Docket No. HM-134; Amdt. Nos. 171-34, 172-32, 173-100, 174-27, 175-2, 176-2, 177-37, 178-40, 179-17]

HAZARDOUS MATERIALS REGULATIONS

Reissuance

On March 3, 1976, the Materials Transportation Bureau (MTB) pub-

lished a notice of proposed rulemaking in the FEDERAL REGISTER identified as Docket No. HM–134; Notice No. 76–2. In that notice the MTB proposed to amend certain of the hazardous materials regulations for which it has responsibility to expressly reflect a reissuance of those regulations under the authority of the Hazardous Materials Transportation Act (Title I of Pub. L. 93–633) (HMTA). To accomplish that purpose the MTB proposed to revise the authority citations and, where necessary, the applicability of the hazardous materials regulations in 14 CFR Part 103, 46 CFR Parts 64 and 146, and 49 CFR Parts 170–179.

The basis for the March 3 proposal is found in § 114(b)(2) of the HMTA:

> The Secretary shall take all steps necessary to bring orders, determinations, rules, and regulations into conformity with the purposes and provisions of this title as soon as practicable * * *

This reissuance, one step in meeting the mandate of section 114(b)(2), provides the necessary legal connection being made between the hazardous materials regulations and the HMTA so that the provisions of the HMTA and the authorities vested in the Secretary of Transportation by the HMTA can be implemented in relation to those regulations.

By virtue of the reissuance, a number of HMTA provisions will come into operation in such a way as to modify the overall application of the hazardous materials regulations. Specifically, reissuance of the regulations under the HMTA:

Extends the MTB's regulatory authority to the manufacturers of packages and containers that are represented, marked, certified, or sold for use in the transportation of hazardous materials;

Preempts inconsistent State and local regulations and law unless the State or local political subdivision concerned applies to the MTB for and is granted a determination that the inconsistent law or regulation is not preempted;

Extends to the concerned operating elements of the Department of Transportation authority to impose civil penalties for violations committed in the rail and highway modes;

Significantly increases the criminal fines for all violations of the hazardous materials regulations;

Provides, as additional enforcement tools, authority for the administrative issuance of compliance orders and judicial issuance of injunctions and awarding of punitive damages; and

Makes the hazardous materials regulations as fully applicable in Puerto Rico, the Virgin Islands, Samoa and Guam as they already are in the 50 States and the District of Columbia.

In addition to these specific changes which will become operational on the effective date of this reissuance, there is another significant feature of the HMTA yet to be exercised. In proscribing the range of transportation which may be regulated through the issuance of hazardous materials regulations, § 103(1) of the HMTA includes transportation which affects interstate transportation. Clearly, the scope of this new regulatory authority as described by § 103(1) of the HMTA, is broader than that which has been exercised under 18 U.S.C. 834 as limited by the definition of "interstate and foreign commerce" in 18 U.S.C. 831. The Bureau now contemplates exercising his expanded HMTA authority through individual rulemaking proceedings which it would initiate as the need for extending the hazardous materials regulations to particular intrastate situations affecting interstate commerce come into focus. Meanwhile the classes of shippers and transporters who are subject to the reissued hazardous materials regulations remain the same as immediately prior to the reissuance.

Although the MTB considered the proposed reissuance to be mandatory and therefore leaving the Bureau without discretion in the matter, interested persons were invited to participate in the HM–134 rulemaking by submitting comments with respect to matters which they regarded as being affected by the proposed reissuance. All comments received on Docket HM–134 have been given full consideration by the Bureau before a decision was made on the on the amendments contained herein. Of the many comments received, a number have been determined to be outside the scope of the HM–134 proposal. Such comments have been or will be given separate consideration and may be the subject of future rulemaking action. The remaining comments, including those offering full support for the proposed reissuance, concerned themselves with the following:

Lack of adequate notice in HM–134 as to specific substantive changes to existing regulations.

Retaining certain existing citations of authority to the regulations.

Deferring the proposed reissuance until the amendments under Dockets HM–112 and HM–103 are finalized.

Deferring the proposed reissuance pending recodification and simplification of the regulations.

DOT jurisdiction over non-commercial as well as commercial transportation.

Preemption of State and local laws and regulations.

An allegation that the reissuance of 49 CFR 173.115(a) under the terms of the proposal would be in violation of Sections 104 and 105(a) of the HMTA.

The need to clarify what have been called ambiguities in the Shipping Container Specifications of Part 178 of 49 CFR before reissuing those specifications.

The issues raised by these comments will be addressed separately in the discussion that follows.

ADEQUACY OF NOTICE

Several comments expressed the attitude that the proposed reissuance was merely a technical or housekeeping amendment and that HM–134 could not legally be used as the vehicle to make any substantive changes in the nature, extent and effect of the hazardous materials regulations.

The Materials Transportation Bureau does not consider the amendments to be made under the proposed reissuance to be merely technical or housekeeping in nature. The Congressional mandate of Section 114(b)(2), to which the proposal was in response, envisions much more than that. As previously stated, the reissuance will result in the necessary legal connection being made between the hazardous materials regulations and the HMTA so that the provisions of the HMTA and the authorities vested in the Secretary of Transportation by the HMTA can be implemented in relation to those regulations. The proposal gave notice of this result when it was stated that, "This proposal to revise the citations of authority and, where necessary, the applicability of certain hazardous materials regulations * * *, to expressly reflect a reissuance of those regulations under the authority of the HMTA is one step in meeting" the "Congressional mandate" of Section 114(b)(2) of the HMTA. This amendment will do no more than what was proposed in the March 3rd notice.

RETENTION OF EXISTING AUTHORITY CITATIONS

Because the Transportation of Explosives Act (18 U.S.C. 831–835) has not been repealed, one comment urged that the existing authority citations to that Act in 49 CFR Parts 171–179 be retained. The Bureau believes that to do so would not be consistent with the statutory mandate of section 114(b)(2) of the HMTA which requires the hazardous materials regulations to be brought into "conformity with the purposes and provisions of [the HMTA] as soon as practicable."

RELATIONSHIP TO HM–112 & HM–103

Subsequent to the March 3rd notice, the amendments under Dockets HM–112 and HM–103 were published (41 FR 15972, April 15, 1976). Those amendments became effective July 1, 1976, and resulted in a consolidation of hazardous materials regulations for all modes in 49 CFR. The consolidation revised and relocated to 49 CFR certain hazardous materials regulations previously in 14 and 46 CFR. The action resulted in the revocation of 14 CFR Part 103 and a substantial reduction of 46 CFR Part 146 (41 FR 15972, 41 FR 28116). Therefore, amendments to authority citations in 14 CFR Part 103 proposed by this rulemaking are unnecessary and amendments to authority citations in 46 CFR Part 146 need not be as extensive as originally anticipated.

The comments requesting the Bureau to defer action on the proposed reissuance until final action was taken on outstanding hazardous material Dockets HM–103 and HM–112 have been overtaken by events. Since that time those dockets have been finalized and became effective July 1, 1976 (41 FR 15972). The fact that mandatory compliance with various amendments under Dockets HM–103 and HM–112 is not required until after July 1, 1976, is not considered by

the Bureau to be a valid reason for further delay in finalizing HM–134. The regulations as amended by HM–103 and HM–112 set forth the currently applicable standards. A violation of any of those standards subjects the violator to the applicable penalty provided by statute unless (1) the action constituting the violation is an action authorized in the effective date provision under Dockets HM–103 and HM–112, as amended at 41 FR 26014, to be performed in the manner provided by the regulations in existence on June 30, 1976, and (2) that action does in fact comply with the regulations as they existed on June 30, 1976.

RECODIFICATION

One comment urged the Bureau to consider completely recodifying the existing hazardous material regulations prior to their reissuance under the HMTA. In light of the Congressional mandate embodied in § 114(b) (2) of the HMTA and a recodification that may take a year or more to complete, the Bureau must reject this suggested approach.

By finalizing the proceedings in Dockets HM–103 and HM–112 the Materials Transportation Bureau completed the first major phase of its continuing effort to improve, update, and simplify the regulations governing the shipment and transportation of hazardous materials. The next phase will be a recodification of those hazardous materials regulations over which the Bureau has authority. Whereas the principal purpose of HM–103 and HM–112 was the consolidation and substantive improvement of specific segments of the regulations, the purpose of the recodification phase will be to rearrange and revise the language of the regulations in a more comprehensible and accessible form to reduce inconsistency, redundancy and obsolescence. The changes made in 49 CFR Parts 171, 172, 174, 175 and 176 by Dockets HM–103 and HM–112 have already instituted many of the changes that would be ordinarily achieved by a pure codification. Therefore, future codification efforts will be directed towards 49 CFR Parts 173, 177, 178 and 179.

Even if it were prepared to initiate formal codification rulemaking focusing on Parts 173 and 177–179, the Bureau believes that first a reasonable period should be allowed for the major changes effected by HM–103 and HM–112 to season and for persons affected by those changes to become accommodated to them.

NONCOMMERCIAL TRANSPORTATION

One comment read as follows:

> The statute [HMTA] does not limit the DOT's jurisdiction to commercial transportation. Historical experience in administering the hazardous materials regulations, however, supports the conclusion that concerns for public safety do not require regulations governing personal transportation in personal vehicles. [It is recommended] that this conclusion be reflected in regulations adopted under HM–134, thereby continuing the traditional limitation of coverage to commercial transportation.

While, as pointed out earlier, the action being taken by the Bureau in this proceeding does not expand the coverage of the hazardous materials regulations to any class of shippers or transporters who are not already subject to those regulations, it should be recognized that the express policy of Congress in enacting the HMTA was "to improve the regulatory and enforcement authority of the Secretary of Transportation to protect the Nation adequately against the risks to life and property which are inherent in the transportation of hazardous materials in commerce." For the Bureau to do as this commentor suggests and circumvent that declared policy by attempting to divest itself of the responsibility and jurisdiction authority placed in it is neither appropriate nor wise. The Bureau must remain unhampered in its ability to act, within its now expanded jurisdictional authority, in the best interest of health and safety. In exercising its new broader jurisdiction in future rulemakings, the Bureau, of course, is not precluded from giving consideration to what this commentor calls "traditional limitations of coverage" or to the practical and economic impact that is likely to accompany actual exercises of this broadened jurisdiction.

PREEMPTION

Another series of comments addressed the issue of Federal preemption as provided for by § 112 of the HMTA. Some of these comments presented a pro or con position on the concept of preemption. Because preemption of inconsistent State and local laws and regulations is Congressionally mandated, a discussion of the advantages or disadvantages of preemption in this rulemaking is moot. Appearing elsewhere in this edition of the FEDERAL REGISTER are procedural regulations for the full implementation of section 112.

Other comments made the unfounded accusation that the Materials Transportation Bureau had proposed the reissuance solely to seek an advantage in current litigation where preemption is a central issue. Though coincidence might lend support to that belief, it is regrettable that lack of confidence in the Bureau's concern for public safety led to that distorted conclusion. In February of this year the Bureau was asked by the Senate Subcommittee on Transportation why it did not, upon enactment of the HMTA on January 3, 1975, immediately move to reissue the existing hazardous materials regulations under the authority of the HMTA. The Bureau responded:

> The consolidation rulemaking identified as Docket No. HM–112 was published in January 1974. DOT efforts with regard to the HM–112 rulemaking began in 1971. By July 1975, when the reorganization within DOT to implement the provisions of the HMTA was completed, a vast amount of time by both the Department and the affected public had already been invested in the HM–112 rulemaking. Because of that time and because further delay of the rulemaking would have major consequences on persons associated with all modes of transportation, the MTB considered finalizing of HM–112 to be its foremost priority.
>
> Upon completion of HM–112, it was the MTB's intention to immediately move to reissue the consolidated regulations under the authority of the HMTA and develop procedural regulations to implement certain provisions of the Act.

In accord with that stated intention, when the Bureau committed itself to submitting the final HM–112 rulemaking to the FEDERAL REGISTER on April 1, 1976, the Bureau published HM–134 on March 3, 1976, and at the same time continued its development of procedural regulations to implement the preemption and enforcement provisions of the HMTA.

The remaining comments with regard to preemption ran the spectrum from full support of the reissuance and its effect on the preemption provision of the HMTA; to suggesting that until efficient procedures for making preemption determinations have been established, State and local regulations in existence on the effective date of the HMTA be presumed to be not preempted unless the Bureau makes a determination to the contrary; to urging the MTB to reject any proposal to amend its regulations which would result in the preemption of any inconsistent State and local regulations and law. These last two comments reveal a basic misunderstanding of the relationship between reissuance and the preemption provisions of the HMTA. The Bureau believes a discussion to clarify this misunderstanding is in order.

The relationship between the authority of the Federal Government and that of State and local governments, with respect to the safe transportation of hazardous materials, was specifically addressed by Congress in section 112 of the HMTA.

In Senate Report No. 93–1192 accompanying S. 4057, which was eventually enacted as the HMTA, the Committee on Commerce in discussing section 112 stated:

> The Committee endorses the principle of Federal preemption in order to preclude a multiplicity of State and local regulations and the potential for varying as well as conflicting regulations in the area of hazardous materials transportation.

The express provision of preemption in section 112 of the HMTA provides that, "Except as provided in subsection (b) of this section, any requirement, of a State * * * which is inconsistent with any requirement set forth" in the Act "or in a regulation issued under" the HMTA "is preempted." Section 112(a))

Section 112(b) provides that a State requirement not consistent with any requirements set forth in the HMTA or in a regulation issued under the HMTA is not preempted if upon the application of an appropriate State agency, the Secretary determines, in accordance with procedures prescribed by regulation, that such requirement (1) affords an equal or greater level of protection to the public than is afforded by the requirements of the HMTA or of regulations issued under the HMTA, and (2) does not unreasonably burden commerce. The contem-

plated procedural regulations appear elsewhere in this edition of the FEDERAL REGISTER.

In order to fully implement the provisions of section 112(a), reissuance of existing hazardous materials regulations under the authority of the HMTA is necessary. Without this reissuance, section 112 would be inoperative with respect to those regulations. The procedures for State and local governments and individuals to seek administrative determinations under sections 112(a) and 112 (b) with regard to State and local laws and regulations appearing elsewhere in this edition of the FEDERAL REGISTER are effective on the same date this reissuance becomes effective.

Additionally, Congress did not intend to limit section 112 to a prospective application. The section applies to any requirement * * * which is inconsistent. In addition, the language of section 112(a) is self operative, i.e., "inconsistent" State requirements are, by law, preempted. The procedures published elsewhere in this edition of the FEDERAL REGISTER merely provide the opportunity to receive an administrative ruling as to consistency or inconsistency (as well as the procedures to seek non-preemption determinations under section 112(b)). The fact that such an administrative ruling had not been issued under section 112 with respect to a particular requirement of a State or political subdivision will carry no implication as to the consistency or inconsistency of that requirement with the Act or any regulations issued under the Act.

PROCEDURAL REQUIREMENTS OF HMTA

Several comments alleged that the proposed reissuance of 49 CFR 173.115 (a) under the terms of the proposal would be in violation of sections 104 and 105(a) of the HMTA.

Section 173.115(a) defines a flammable liquid for purposes of transportation as any liquid having a flashpoint below 100° F, (37.8° C) with certain exceptions. Because the material polyester resin has a flashpoint below 100° F, it is classed as a flammable liquid. The basis for the definition of flammable liquid was the subject of various rulemaking actions and will not be rediscussed here. Participants to those rulemakings have since sought to have polyester resin exempted from the flammable liquid class even though it met the definition. Every available procedure has been used to gain this relief including a still to be completed appeal from the denial of the exemption request under the procedures of 49 CFR 107.121. These same participants now seek to argue their case by alleging procedural inadequacies in this rulemaking.

The first claim that by reissuing § 173.-115(a) under the authority of the HMTA, the Bureau proposes to classify polyester resin as a flammable liquid without having made the statutorily required finding that it poses a threat to life or property. They assert that such action is in violation of section 104 of the HMTA which reads in part as follows:

> Upon a finding by the Secretary, in his discretion, that the transportation of a particular quantity and form of material in commerce *may* pose an unreasonable risk to health and safety or property, he shall designate such quantity and form of material * * * as a hazardous material (emphasis supplied).

The Bureau takes this opportunity to point out that section 104 permits the Secretary to designate a material as hazardous if it *may* pose an unreasonable risk to health and safety or property. The section does not require the Secretary to go beyond a finding that the material is capable of posing such a risk. The merits of the previous rulemaking with respect to the flammable liquid definition have been discussed at length in Docket HM–102 and are summarized in the discussion which follows. Although nearly all of the significant activity in Docket HM–102 predated the HMTA, the procedures used to reach the conclusions of that rulemaking are in full accord with the new requirements of section 104.

These same commentors also assert that the reissuance of § 173.115(a) violates section 105(a) of the HMTA, in that the Bureau did not provide "an opportunity for informal, oral presentation" on the proposal. It was under Docket HM–102 that the Hazardous Materials Regulations Board (predecessor of the MTB) published the currently applicable definition of flammable liquids found in 49 CFR 173.115 (4 CFR 22263, May 22, 1975). A historic review of the efforts that lead to that publication will also lead to a better understanding of the Bureau's reaction to this assertion with regard to section 105(a) of the HMTA.

The first notice of proposed rulemaking relative to Docket HM–102 appeared in the FEDERAL REGISTER on February 27, 1968 under Docket HM–3 (33 FR 3382). Subsequent to that notice meetings were held with industry and trade associations such as Manufacturing Chemists Association, the National Fire Protection Association, the National Paints and Coatings Association, the American Petroleum Institute, the Society of the Plastics Industries, Inc., and the American Society for Testing and Materials. Of concern was the appropriate definition for flammable liquids considering the transportation environment, and the need for compatibility with the flammable liquid definitions of other government agencies. The recommended test method specified for evaluating the flammability hazard of liquids was discussed extensively with these groups.

In 1969, a contract (DOT–OS–00007) was established with the Bureau of Mines for an evaluation of the Department's hazard classification system and test methods. This resulted in the publication of a report in April 1970 titled, "Recommendation of Flash Point Method for Evaluation of Flammability Hazard in the Transportation of Flammable Liquids." The report contained an analysis of the flammability hazard presented in transportation; and recommended a definition for flammable liquids, and a method of test as a criterion for this definition. An additional contract (DOT–OS–00038) was let in 1969 for the study of the transportation environment. An extensive report was published under this contract in October 1971 by the General American Transportation Corporation titled, "A Survey of Environmental Conditions Incident to the Transportation of Materials." Much of this study was devoted to the temperature environment to be encountered in transportation. Based on these two studies, the proposed definition of a flammable liquid was considered to be somewhat conservative with respect to the maximum temperature limit to be encountered in transportation.

Representatives of the Consumer Product Safety Commission, and the Department of Labor's Occupational Safety and Health Administration (OSHA) were specifically asked to participate in the discussions and evaluation of the classification problem. On May 29, 1971, OSHA published its regulations for Flammable and Combustible Liquids (29 CFR 1910.106 effective date August 31, 1971). They specify a definition for flammable liquids identical with the definition proposed by this Department. A public hearing was held by OSHA concerning this standard at which time the desirability of uniformity of definition between the Department of Labor and Department of Transportation was discussed.

As a result of these many efforts, modifications of the proposed amendment were made at various times. The more important modifications included:

1. Deletion of the open cup as an alternate test method. [HM–67 (35 FR 18534), December 5, 1970]
2. Additional requirements for combustible liquids and the addition of certain exemptions for flammable liquids newly regulated under this amendment. [HM–102 (39 FR 2768), January 24, 1974]
3. Addition of a Setaflash tester as an alternate test method and additional exemptions for certain specific commodities. [HM–102 (40 FR 22263), May 22, 1975]

Four additional notices appeared in the FEDERAL REGISTER during this time period. These were concerned primarily with an extension of the time period for consideration of this rulemaking. Extensive files on this subject are open to the public. The Bureau maintains a public reading room and welcomes visits by any interested party.

Regardless of the statutory authority for a particular proposed regulation, when the Bureau issues a notice of proposed rulemaking, it schedules a public hearing on its own motion if it believes that the rulemaking is likely to be materially advanced by supplementing the written comments with oral presentations. In the case of proposed hazardous materials regulations under section 105 (a) of the Hazardous Materials Transportation Act, the Bureau is fully cognizant of the "opportunity for informal, oral presentation" provision which distinguishes that section. We do not, how-

ever, subscribe to the view that "a hearing is now guaranteed by law." We perceive the true state of the law on this matter to be somewhat less absolute. Even where a statute goes further than section 105(a) and states in unqualified terms that a hearing shall be held, a hearing is not required if the only reasons asserted for holding it are legally insufficient. *Dyestuffs and Chemicals, Inc.* v. *Flemming*, 271 F. 2d 281 (8th Cir. 1959), cert. denied, 362 U.S. 911 (1960). In accord is the § 102.27(a) provision of the Bureau's procedural regulations which provides that a petition for a hearing will be granted only if the petitioner shows good cause for the hearing.

While the Bureau routinely schedules one or more informal public hearings on all of its significant hazardous materials rule-making proposals, as it did in HM–102 which resulted in the change to the definition of "flammable liquid", there is no compelling legal or policy reason for the Bureau to hold hearings on those occasions when there is nothing material to be heard.

CLARIFICATION OF AMBIGUITIES IN REGULATIONS BEING MADE APPLICABLE TO MANUFACTURERS

Several comments on the proposed reissuance received from container manufacturers and associations representing these manufacturers asserted that reissuance of 49 CFR Part 178 should be deferred until certain clarifications are made to the provisions of that Part.

Prior to the enactment of the HMTA, the DOT lacked any direct jurisdiction over manufacturers of packages and containers that are used for transporting hazardous materials in commerce. Therefore, detailed regulations spelling out the requirements for containers were necessarily addressed to a class of persons subject to DOT jurisdiction (i.e. shippers). Congress saw this as a serious weakness that frustrated the DOT's efforts to adequately regulate for the safe transportation of hazardous materials. Congress cured this weakness by vesting in the Secretary of Transportation, under various provisions of the HMTA, regulatory and enforcement authority over those manufacturers. One goal of this reissuance is to implement that new authority, therefore, necessitating certain changes to Parts 178 and 179 to delineate the new responsibilities of container manufacturers resulting from the reissuance of those parts under the HMTA.

To accomplish that purpose, Parts 178 and 179 have been amended to provide that any person performing a function prescribed by either part must perform that function in accordance with the applicable part. The Bureau is specifically requiring that the manufacturer mark the packaging or container with the DOT specification. That mark will be understood to certify compliance by the manufacturer, that the functions performed by the manufacturer, have been performed in compliance with the applicable part.

Because of the DOT's historical lack of direct jurisdiction over container manufacturers, Parts 178 and 179 presently prescribe many functions with regard to packagings and containers that are, by their nature, performed after the package or container has left the control of the manufacturer. To insure that a packaging or container meets all the applicable specification requirements when ultimately used in the transport of hazardous materials, new § 178.0–2 asks that the manufacturer of a packaging or container inform each person to whom that packaging or container is transferred of any specification requirements which have not been met at the time of transfer. In addition, § 173.22(a) has been revised to clarify the shipper's responsibility for compliance with packaging and container specifications. The revised paragraph requires that when a shipper performs a function covered by, or having an effect on a specification requirement of Part 178 or 179, the shipper must perform that function in accordance with the specification. (This revision to § 173.22 was proposed under Docket HM–117 published on June 14, 1974 (39 FR 20805).)

As a result of market forces, i.e. shippers required by regulation to transport hazardous materials in containers meeting the specifications of Parts 178 and 179, container manufacturers have produced their product in compliance with those specifications. One commenter stated, "we manufacture our [container] according to DOT specification * * * or exemption. All tests are also performed to the same specification."

Thus, while proclaiming past voluntary compliance with DOT container manufacture and testing specifications, these manufacturers are now heard to say that the same specifications are so vague and questionable that proposed reissuance would put a very unfair burden on them by imposing the risk of civil penalties and criminal prosecution. They assert that such burdens should not be placed on the manufacturer until the vagueness and ambiguity are removed from the specifications.

The Bureau is not persuaded by these comments to defer reissuance of 49 CFR Parts 178 and 179 under the authority of the HMTA. Several reasons lead to this conclusion:

Container manufacturers' own past practices under the "shipper" regulations with regard to manufacture and testing provide guidance as to the purpose and meaning of the regulations governing the design and construction of containers;

Container manufacturers' long exposure to the past practices of the DOT with regard to the interpretation and enforcement of manufacture and testing specifications with respect to shippers also provide guidance as to future DOT practices with regard to manufacturers;

As in the case of any Federal compliance or enforcement action, any container manufacturer who may be accused of non-conforming to a regulation which he considers vague or ambiguous is entitled to assert that as a defense; and

Container manufacturers have the same rights and opportunities to request interpretations of and changes to the regulations as are currently exercised with great frequency by the shippers and carriers who have long been directly subject to the Federal hazardous materials transportation regulations.

In consideration of the foregoing 49 CFR Parts 171, 172, 173, 174, 175, 176, 177, 178, and 179 are amended as follows:

1. In Part 171, the authority citation following the table of contents is revised to read as follows:

PART 171—GENERAL INFORMATION, REGULATIONS, AND DEFINITIONS

* * * * *

AUTHORITY: 49 U.S.C. 1804, 1808; 49 CFR 1.53(e), unless otherwise noted.

* * * * *

2. In § 171.2, a new paragraph (c) is added to read as follows:

§ 171.2 General transportation requirements.

* * * * *

(c) No person may represent, mark, certify, or sell a packaging or container as meeting the requirements of this subchapter governing the use of that packaging or container in the transportation in commerce of a hazardous material unless the packaging or container is manufactured, fabricated, marked, maintained, reconditioned, or repaired, as the case may be, in accordance with this subchapter.

3. In § 171.8, a definition for "United States" is added alphabetically to read as follows:

§ 171.8 Definitions and abbreviations.

* * * * *

"United States" means the fifty States, the District of Columbia, the Commonwealth of Puerto Rico, the Virgin Islands, American Samoa, or Guam.

* * * * *

4. In Part 172, the authority citation following the table of contents is revised to read as follows:

PART 172—HAZARDOUS MATERIALS TABLE AND HAZARDOUS MATERIALS COMMUNICATION REGULATIONS

* * * * *

AUTHORITY: 49 U.S.C. 1803, 1804; 49 CFR 1.53(e), unless otherwise noted.

* * * * *

5. In § 172.3, a new paragraph (b) is added to read as follows:

§ 172.3 Applicability.

* * * * *

(b) When a person, other than one of those provided for in paragraph (a) of this section, performs a packaging labeling or marking function required by this part, that person shall perform the function in accordance with this part.

6. In Part 173, the authority citation following the table of contents is revised to read as follows:

PART 173—SHIPPERS—GENERAL REQUIREMENTS FOR SHIPMENTS AND PACKAGINGS

* * * * *

AUTHORITY: 49 U.S.C. 1803, 1804, 1808; 49 CFR 1.53(e), unless otherwise noted.

* * * * *

7. In § 173.1, a new paragraph (c) is added to read as follows:

§ 173.1 Purpose and scope.

* * * * *

(c) When a person other than the person preparing a hazardous material for shipment performs a function required by this part, that person shall perform the function in accordance with this part. are made in containers which, unless otherwise provided in this part, have been made, assembled with all parts or fittings in their proper place and properly secured, and marked in compliance with applicable specifications prescribed in Parts 178 and 179 of this subchapter or with specifications of the Department in effect at date of manufacture of container. The shipper may accept the manufacturer's certification or specification marking to determine that specification containers were manufactured in accordance with applicable specifications (see § 178.0–2 of this subchapter). When a shipper performs a function covered by, or having an effect on a specification requirement of Part 178 or Part 179, the shipper must perform that function in accordance with the specification.

* * * * *

8. In § 173.22, paragraph (a) is revised to read as follows:

§ 173.22 Shipper's responsibility.

(a) When a container is supplied by the shipper, the shipper shall be responsible to determine that shipments of hazardous materials.

* * * * *

9. In § 173.24, paragraph (c)(1) is revised to read as follows:

§ 173.24 Standard requirements for all packages.

* * * * *

(c) * * *

(1) Each specification container must be marked as follows:

(i) In an unobstructued area with letters and numerals identifying the container specification (e.g., DOT–1A, DOT–17E–304HT, DOT–23G40). See § 178.0–2 of this subchapter.

(ii) The name and adress or symbol of person making the mark specified in paragraph (c)(1)(i) of this section. Symbol letters, if used, must be registered with the Bureau of Explosives. Duplicate symbols are not authorized.

(iii) The markings must be stamped, embossed, burned, printed, or otherwise marked on the packaging to provide adequate accessibility, premanency, and contrast so as to be readily apparent and understood.

(iv) Unless otherwise specified, letters and numerals must be at least ½ inch high.

(v) Packaging which does not comply with the applicable specification listed in Parts 178 and 179 of this subchapter must not be marked to indicate such compliance (see § 178.0–2 and § 179.1 of this subchapter).

10. In Part 174, the authority citation following the table of contents is revised to read as follows:

PART 174—CARRIAGE BY RAIL

* * * * *

AUTHORITY: 49 U.S.C. 1803, 1804, 1808; 49 CFR 1.53(e), unless otherwise noted.

* * * * *

11. In Part 175, the authority citation following the table of contents is revised to read as follows:

PART 175—CARRIAGE BY AIRCRAFT

* * * * *

AUTHORITY: 49 U.S.C. 1803, 1804, 1808; 49 CFR 1.53(e), unless otherwise noted.

* * * * *

12. In Part 176, the authority citation following the table of contents is revised to read as follows:

PART 176—CARRIAGE BY VESSEL

* * * * *

AUTHORITY: 46 U.S.C. 170(7) (a–c); 49 U.S.C. 1803, 1804, 1808; 49 CFR 1.53 (e), (f), unless otherwise noted.

* * * * *

13. In Part 177, the authority citation following the table of contents is revised to read as follows:

PART 177—CARRIAGE BY PUBLIC HIGHWAY

* * * * *

AUTHORITY: 49 U.S.C. 1803, 1804, 1808; 49 CFR 1.53(e), unless otherwise noted.

* * * * *

14. In Part 178, the authority citation following the table of contents is revised to read as follows:

PART 178—SHIPPING CONTAINER SPECIFICATIONS

* * * * *

AUTHORITY: 49 U.S.C. 1804, 1808; 49 CFR 1.53(e), unless otherwise noted.

15. In Part 178, new §§ 178.0, 178.0–1, and 178.0–2 are added immediately preceding Subpart A to read as follows:

§ 178.0 Purpose, scope, and applicability.

§ 178.0–1 Purpose and scope.

This part prescribes the manufacturing and testing specifications for packaging and containers used for the transportation of hazardous materials in commerce.

§ 178.0–2 Applicability.

(a) Any person who performs a function prescribed in this part, shall perform that function in accordance with this part.

(b) When this part requires (either expressly or by reference to § 173.24 of this subchapter) a packaging or container to be marked with a DOT specification (for example, DOT–1A, DOT–17E–304HT, DOT–23G40), compliance with that requirement is the responsibility of the packaging or container manufacturer. Marking the packaging or container with the DOT specification shall be understood to certify compliance by the manufacturer, that the functions performed by the manufacturer, as prescribed in this part, have been performed in compliance with this part. (See also § 173.28 "Reuse of containers." That section envisions the marking of containers to be performed by a person other than the original manufacturer.)

(c) Except as specifically provided in § 178.340, the manufacturer of a packaging or container should inform each person to whom that packaging or container is transferred of any specification requirements which have not been met at time of transfer.

16. In §§ 178.1–8, 178.2–6, 178.3–8, 178.4–7, 178.5–7, 178.6–8, 178.7–7, 178.8–7, 178.9–7, 178.12–9, 178.13–5, 178.14–7, 178.182–4, 178.198–4, and 178.218–10, the second sentence in paragraph (a)(1) is deleted; and paragraph (a)(2) is revised to read as follows:

(a) * * *

(2) Name or symbol of person making the mark specified in paragraph (a)(1) of this section and located just above or below that mark. Symbol, if used, must be registered with the Bureau of Explosives.

* * * * *

17. In § 178.15–7, paragraph (b) is revised to read as follows:

§ 178.15–7 Marking.

* * * * *

(b) Each container must also be marked with the name or symbol of person making the mark specified in paragraph (a) of this section. Symbol, if used, must be registered with the Bureau of Explosives.

18. Section 178.18 is revised to read as follows:

§ 178.18–8 Marking on each container.

(a) Marking on top head plainly and permanently as follows:

(1) DOT–43A.

(2) Name or symbol of person making the mark specified in paragraph (a)(1) of this section and located just above, below, or following that mark. Symbol, if used, must be registered with the Bureau of Explosives.

(3) Rated gallonage and year of manufacture (for example, 5–50).

19. § 178.19–6 is revised to read as follows:

§ 178.19–6 Marking.

(a) Each container must be permanently marked by embossment in letters and figures at least ½ inch in size as follows:

(1) DOT–34**; stars to be replaced by the rated capacity of the container (for example, DOT–34–5).

(2) Month and year of manufacture. For example, DOT–34–5–6/65 to indicate a container of 5 gallons capacity made in June 1965.

(3) Name or symbol of person making the marks specified in paragraphs (a) (1) and (a) (2) of this section and located just above or below those marks. Symbol, if used, must be registered with the Bureau of Explosives.

20. In § 178.20–1, a new paragraph (e) is added to read as follows:

§ 178.20–1 Capacity, thickness of metal, test and closure.

* * * * *

(e) "Marking." Each container must be marked as prescribed in § 173.24 of this subchapter.

21. Section 178.21–2 is revised to read as follows:

§ 178.21–2 Capacity and marking of container.

(a) Containers of 5 to 13 gallons capacity are covered by this specification. Actual capacity of the container must be the marked capacity plus 5 percent minimum.

(b) Each container must be permanently marked with figures and letters at least ¼ inch high to show:

(1) DOT–2T.

(2) Name or symbol of person making the mark specified in paragraph (b) (1) of this section. Symbol, if used, must be registered with the Bureau of Explosives.

(3) Month and year of manufacture.

§ 178.315–5 Marking.

§ 178.318–3 Marking.

22. Part 178 is amended by adding new §§ 178.315–5 and 178.318–3 to read as follows:

Each container must be marked as prescribed in § 173.24 of this subchapter.

23. Section 178.24–5 is revised to read as follows:

§ 178.24–5 Marking.

(a) Each container must be permanently marked by embossment in figures and letters at least ¼ inch in size to show:

(1) DOT–2U.

(2) Name or symbol of person making the mark specified in paragraph (a) (1) of this section. Symbol, if used, must be registered with the Bureau of Explosives.

(3) Month and year of manufacture.

(4) Rated capacity.

§ 178.24–6 [Amended]

24. In § 178.24–6, paragraph (a) is amended by changing the word "chapter" to read "subchapter."

25. In § 178.27–2, paragraph (c) is revised to read as follows:

§ 178.27–2 Construction, capacity and marking.

* * * * *

(c) Marking: Each container must be permanently marked in figures and letters at least ¼ inch in size to show:

(1) DOT–2TL.

(2) Name or symbol of person making the mark specified in paragraph (c) (1) of this section. Symbol, if used, must be registered with the Bureau of Explosives.

(3) Month and year of manufacture.

(4) Rated (marked) capacity.

26. Section 178.33–9 is revised to read as follows:

§ 178.33–9 Marking.

(a) By means of printing, lithographing, embossing, or stamping, each container must be marked to show:

(1) DOT–2P.

(2) Name or symbol of person making the mark specified in paragraph (a) (1) of this section. Symbol, if used, must be registered with the Bureau of Explosives.

27. Section 178.33a–9 is revised to read as follows:

§ 178.33a–9 Marking.

(a) By means of printing, lithographing, embossing, or stamping, each container must be marked to show:

(1) DOT–2Q.

(2) Name or symbol of person making the mark specified in paragraph (a) (1) of this section. Symbol, if used, must be registered with the Bureau of Explosives.

28. In § 178.35–3, paragraph (b) is revised to read as follows:

§ 178.35–3 Construction, capacity and marking.

* * * * *

(b) Marking: Each container must be permanently marked with figures and letters at least ¼ inch in size to show:

(1) DOT–2S.

(2) Name or symbol of person making the mark specified in paragraph (b) (1) of this section. Symbol, if used, must be registered with the Bureau of Explosives.

(3) Month and year of manufacture.

(4) Minimum capacity.

* * * * *

29. In § 178.35a–2, paragraph (c) is revised to read as follows:

§ 178.35a–2 Construction, capacity and marking.

* * * * *

(c) Markings: Each container must be permanently marked with figures and letters at least ¼ inch in size to show:

(1) DOT–2SL.

(2) Name or symbol of person making the mark specified in paragraph (c) (1) of this section. Symbol, if used, must be registered with the Bureau of Explosives.

(3) Month and year of manufacture.

(4) Minimum capacity.

* * * * *

30. In §§ 178.38–20, 178.39–19, 178.40–20, 178.41–19, 178.42–14, 178.43–20, 178.44–23, 178.47–21, 178.48–19, 178.49–19, 178.50–19, 178.52–19, 178.53–18, 178.54–20, 178.55–20, 178.58–21, 178.59–18, 178.60–22, and 178.68–19, the second sentence in paragraph (a) (2) is revised and in §§ 178.36–20, 178.37–20, and 178.57–20, the second sentence in paragraph (a) (3) is revised to read as follows:

The symbol and numbers must be those of person making DOT mark.

§§ 178.51–19, 178.56–19, 178.61–20 [Amended]

31. In §§ 178.51–19, 178.56–19, and 178.61–20, the first sentence in paragraph (a) (2) is revised to read as follows:

The serial number and identifying symbol of person making DOT mark.

32. In § 178.65–14, paragraph (b) (8) is revised to read as follows:

§ 178.65–14 Marking.

* * * * *

(b) * * *

(8) The following statement: Federal law forbids transportation if refilled—penalty up to $25,000 fine and 5 years imprisonment (49 U.S.C. 1809).

* * * * *

33. In §§ 178.80–11, 178.81–11, 178.82–11, 178.83–11, 178.84–11, 178.87–11, 178.88–10, 178.89–9, 178.90–10, 178.91–11, 178.92–12, 178.97–9, 178.98–9, 178.99–9, 178.100–9, 178.101–9, 178.102–4, 178.110–8, 178.115–10, 178.116–10, 178.117–11, 178.118–10, 178.119–10, 178.130–8, 178.133–9, and 178.134–4, the last sentence in paragraph (a) (1) is deleted and paragraph (a) (2) is revised, and in §§ 178.103–6, 178.131–9, 178.132–9, and 178.135–8, the last sentence in paragraph (a) (1) is deleted and paragraph (a) (3) is revised to read as follows:

Name or symbol of person making the marks specified in paragraph (a) (1) of this section. Symbol, if used, must be registered with the Bureau of Explosives.

34. Section 178.85–10 is revised to read as follows:

§ 178.85–10 Marking.

(a) Marking on each container by embossing on head with raised marks, or by embossing or die stamping on footring on drums equipped with footrings, or on metal plates securely attached to drum by brazing or welding not less than 20 percent of the plates perimeter, as follows:

(1) DOT–5F.

(2) Name or symbol of person making the mark specified in paragraph (a) (1) of this section. Symbol, if used, must be registered with the Bureau of Explosives.

(3) Serial number and name or symbol of company or person for whose use the container is made.

(4) Gauge of metal in thinnest part, rated capacity in gallons, and year of manufacture (for example 14–11–50). When gauge of metal in body differs from that in head, both must be indicated with slanting line between and with gauge of body indicated first (for example, 14/12–11–50 for body 14 gauge and head 12 gauge).

35. In §§ 178.107–9, 178.108–9, 178.109–9, 178.111–8, 178.112–10, 178.136–9, 178.146–15, 178.147–15, 178.148–5, 178.149–7, 178.155–12, 178.156–12, 178.157–12, 178.160–9, 178.161–9, 178.190–9, 178.191–9, 178.193–6, 178.196–15, and 178.197–14, the second sentence in paragraph (a) (1) is deleted and paragraph (a) (2) is revised to read as follows:

Name or symbol of person making the mark specified in paragraph (a) (1) of this section and located just above, below, or following that mark. Symbol, if used,

must be registered with the Bureau of Explosives.

36. Section 178.140–6 is revised to read as follows:

§ 178.140–6 Marking.

(a) Marking on each container by embossing on head with raised marks as follows:

(1) DOT–13.

(2) Name or symbol of person making the mark specified in paragraph (a)(1) of this section. Symbol, if used, must be registered with the Bureau of Explosives.

37. Section 178.141–7 is revised to read as follows:

§ 178.141–7 Marking.

(a) Marking on each container by embossing on head with raised marks as follows:

(1) DOT–13A.

(2) Name or symbol of person making the mark specified in paragraph (a)(1) of this section. Symbol, if used, must be registered with the Bureau of Explosives.

(3) Size of markings (minimum): 5/16 inch high.

38. Section 178.150–7 is revised to read as follows:

§ 178.150–7 Marking.

(a) Each container must be marked as follows:

(1) DOT–33A.

(2) The letters "NRC", located just above or below the DOT mark, to indicate a nonreusable container.

(3) Name or symbol of person making the other marks specified in this section and located on the same face as those other marks. Symbol, if used, must be registered with the Bureau of Explosives.

(4) Size of markings: Specification markings prescribed in this section must be at least ¼ inch high. All markings must be legible.

39. In §§ 178.165–13, 178.176–6, 178.177–6, and 178.171–11, paragraph (a)(1) is deleted and a new paragraph (b) is added to read as follows:

Each box must also be marked with the name or symbol of person making the mark specified in paragraph (a) of this section. Symbol, if used, must be registered with the Bureau of Explosives.

40. In §§ 178.168–18, 178.169–18, 178.170–17, and 178.171–17, the second sentence in paragraph (a)(1) is deleted and a new paragraph (d) is added to read as follows:

Each box must also be marked with the name or symbol of person making the other marks specified in this section. Symbol, if used, must be registered with the Bureau of Explosives.

§ 178.172–19 [Amended]

41. In § 178.172–19, the second sentence in paragraph (a)(1) is deleted and a new paragraph (b) is added to read as follows:

Each box must also be marked with the name or symbol of person making the mark specified in paragraph (a) of this section. Symbol, if used, must be registered with the Bureau of Explosives.

§§ 178.185–19, 178.186–19 [Amended]

42. In §§ 178.185–19 and 178.186–19, the second sentence in paragraph (a)(1) is deleted and paragraph (b) is revised to read as follows:

The name or symbol of person making the marks specified in paragraph (a) of this section must be located just above, below, or following those marks. Symbol, if used, must be registered with the Bureau of Explosives.

§ 178.185–22 [Amended]

43. In § 178.185–22, paragraph (c)(3) is deleted and paragraph (c)(2) is revised to read as follows:

§ 178.185–22 Special box authorized only when used in conjunction with inside spec. 2U (§ 178.24 of this chapter) polyethylene 5- and 15-gallon cubical containers.

* * * * *

(c) * * *

(2) The name or symbol of person making the mark specified in paragraph (c)(1) of this section and located just just above, below, or following that mark. Symbol, if used, must be registered with the Bureau of Explosives.

44. In § 178.187–5, paragraph (c) is deleted and paragraph (b) is revised to read as follows:

§ 178.187–5 Marking authorized.

* * * * *

(b) The name or symbol of person making the mark specified in paragraph (a) of this section must be located just above, below, or following that mark. Symbol, if used, must be registered with the Bureau of Explosives.

45. In § 178.194–6, the existing text is designated paragraph (a) and a new paragraph (b) is added to read as follows:

§ 178.194–6 Marking.

* * * * *

(b) Each jacket must also be marked with the name or symbol of person making the marks specified in paragraph (a) of this section. Symbol, if used, must be registered with the Bureau of Explosives.

46. In §§ 178.205–18, 178.206–18, 178.207–18, 178.209–13, 178.214–17, and 178.219–3, the second sentence in paragraph (a)(1) is deleted and paragraph (a)(2) is revised to read as follows:

Name and address or symbol of person making the mark specified in paragraph (a)(1) of this section and located just above or below that mark. Symbol, if used, must be registered with the Bureau of Explosives.

47. Section 178.208–12 is revised to read as follows:

§ 178.208–12 Marking.

(a) Each box must be marked as follows:

(1) DOT–12E110.

(i) This marking shall be enclosed by a rectangle.

(2) Name and address or symbol of person making the mark specified in paragraph (a)(1) of this section and located just above or below that mark. Symbol, if used, must be registered with the Bureau of Explosives.

(3) When metal straps are prescribed, boxes must be marked "____ (number) Metal Straps Required" just above or below the mark specified in paragraph (a)(1) of this section.

(4) Size of markings: Specification markings specified in paragraph (a)(1) of this section must be at least ½ inch high. All markings must be legible.

§§ 178.210–12, 178.211–6 [Amended]

48. In §§ 178.210–12 and 178.211–6, the last sentence in paragraph (a)(1) is deleted and paragraph (a)(2) is revised to read as follows:

Name and address or symbol of person making the marks specified in paragraph (a)(1) of this section and located just above or below those marks. Symbol, if used, must be registered with the Bureau of Explosives.

§ 178.212–8 [Amended]

49. In § 178.212–8, the last sentence in paragraph (a)(1) is deleted and paragraph (a)(2) is revised to read as follows:

Name or symbol of person making the other marks specified in this section and located on the same face as those other marks. Symbol, if used, must be registered with the Bureau of Explosives.

* * * * *

50. In § 178.224–4, paragraph (a)(3) is deleted and paragraph (a)(2) is revised to read as follows:

§ 178.224–4 Marking.

(a) * * *

(1) * * *

(2) Name or symbol of person making the marks specified in paragraph (a)(1) of this section and located just above, below, or following those marks. Symbol, if used, must be registered with the Bureau of Explosives.

§ 178.225–3 [Amended]

51. In § 178.225–3, the last sentence in paragraph (a)(1)(i) is deleted.

52. Section 178.226–4 is revised to read as follows:

§ 178.226–4 Marking.

(a) Each container must be marked to show:

(1) DOT–29.

(2) The name or symbol of person making the mark specified in paragraph (a)(1) of this section. Symbol, if used, must be registered with the Bureau of Explosives.

53. In §§ 178.230–8, 178.233–9, 178.234–9, and 178.240–10, the semicolon and text following the DOT specification (for example, DOT–36A) in paragraph (a)(1) is deleted and paragraph (a)(2) is revised to read as follows:

Name and address or symbol of person making the mark specified in paragraph (a)(1) of this section and located just above or below that mark. Symbol, if used, must be registered with the Bureau of Explosives.

54. In §§ 178.236–7, 178.237–7, 178.238–7, and 178.239–7, paragraphs (a)(1) and

(a) (2) are deleted and a new paragraph (b) is added to read as follows:

Each bag must also be marked with the name and address or symbol of the person making the mark specified in paragraph (a) of this section and be located just above or below that mark. Symbol, if used, must be registered with the Bureau of Explosives.

55. Section 178.241–5 is revised to read as follows:

§ 178.241–5 Marking.

(a) Each bag must be marked with letters and figures at least ½ inch high in rectangle as follows:

(1) DOT–44P.

(2) This marking shall be enclosed by a rectangle.

(b) Each bag must also be marked with the name and address or symbol of the person making the mark specified in paragraph (a) of this section and be located just above or below that mark. Symbol, if used, must be registered with the Bureau of Explosives.

56. In § 178.350–3, paragraph (b) is revised to read as follows:

§ 178.350–3 Marking.

* * * * *

(b) The letter and number size and additional marking requirements of § 173.24 of this subchapter must be complied with.

PART 179—SPECIFICATIONS FOR TANK CARS

57. In Part 179, the authority citation following the table of contents is revised to read as follows:

* * * * *

AUTHORITY: 49 U.S.C. 1804, 1808; 49 CFR 1.53(e), unless otherwise noted.

* * * * *

58. Section 179.1 is revised to read as follows:

§ 179.1 General.

(a) This part prescribes the specifications for tanks that are to be mounted on or form part of a tank car and which are used for the transportation of hazardous materials in commerce.

(b) Except as provided in paragraph (c) of this section, tanks to which this part is applicable, must be built to the specifications prescribed in this part.

(c) Tanks built to specifications predating those in this part may continue in use as provided in § 173.31 of this subchapter.

(d) Any person who performs a function prescribed in this part, shall perform that function in accordance with this part.

(e) When this part requires a tank to be marked with a DOT specification (for example, DOT–105A100W), compliance with that requirement is the responsibility of the tank builder. Marking the tank with the DOT specification shall be understood to certify compliance by the builder that the functions performed by the builder, as prescribed in this part, have been performed in compliance with this part.

(f) The tank builder should inform each person to whom that tank is transferred of any specification requirements which have not been met at time of transfer.

Effective date: This amendment is effective on January 3, 1977.

(49 U.S.C. 1803, 1804, 1808 and 49 CFR 1.53 (e).)

Issued in Washington, D.C. on August 31, 1976.

JAMES T. CURTIS, Jr.,
Director, Materials Transportation Bureau.

[FR Doc.76–26376 Filed 9–8–76;8:45 am]

CHAPTER X—INTERSTATE COMMERCE COMMISSION

SUBCHAPTER A—GENERAL RULES AND REGULATIONS

PART 1033—CAR SERVICE

[Fifth Revised S.O. No. 1234]

Distribution of Freight Cars

SEPTEMBER 3, 1976.

At a Session of the Interstate Commerce Commission, Railroad Service Board, held in Washington, D.C., on the 2nd day of September, 1976.

It appearing, That there is an acute shortage of freight cars for transporting shipments of fertilizer, [1] phosphate, (dried or ground, treated or untreated fish meal, grain, grain products, soybeans or [1] soybean products; that certain tariff provisions require the use of cars of specified cubic or weight carrying capacities; that the carriers are unable to furnish sufficient such cars to transport shipments of such weights; that cars of lesser capacity are available; that such cars cannot be used because of certain tariff provisions; that there is immediate need to use every available car for transportation of fertilizer and grain; that the inability of the carriers to furnish sufficient fertilizer and grain cars results in great economic loss; and that present regulations and practices with respect to the use, supply, control, movement, and distribution of fertilizer and grain cars are ineffective. It is the opinion of the Commission that an emergency exists requiring immediate action to promote car service in the interest of the public and the commerce of the people. Accordingly, the Commission finds that notice and public procedure are impracticable and contrary to the public interest, and that good cause exists for making this order effective upon less than thirty days' notice.

It is ordered, That:

§ 1033.1234 Distribution of freight cars.

(a) Subject to the concurrence of the shipper, carriers may substitute a sufficient number of smaller cars for larger cars ordered to transport shipments of fertilizer, [1] phosphate, (dried or ground, treated or untreated), fish meal, grain, grain products, soybeans or [1] soybean products regardless of tariff requirements specifying minimum cubic or weight carrying capacity. (See exceptions (b) and (c).)

(b) *Exception.* This order shall not apply to shipments subject to tariff provisions requiring the use of twenty-five or more cars per shipment.

(c) *Exception.* This order shall not apply to shipments subject to tariff provisions which require that cars be furnished by the shipper.

(d) *Rates and minimum weights applicable.* The rates to be applied and the minimum weights applicable to shipments for which cars smaller than those ordered have been furnished and loaded as authorized by Section (a) of this order shall be the rates and minimum weights applicable to the larger cars ordered.

(e) *Billing to be endorsed.* The carrier substituting smaller cars for larger cars as authorized by Section (a) of this order shall place the following endorsement on the bill of lading and on the waybills authorizing movement of the car:

"Car of (_____) cu. ft. and of (_____) lbs. or greater capacity ordered. Smaller cars furnished authority Fifth Revised ICC Service Order No. 1234."

(f) *Concurrence of shipper required.* Smaller cars shall not be furnished in lieu of cars of greater capacity without the consent of the shipper.

(g) *Exceptions.* Exceptions to this order may be authorized to railroads by the Railroad Service Board, Washington, D.C., 20423. Requests for such exception must be submitted in writing, or confirmed in writing, and must clearly state the points at which such exceptions are requested and the reason therefor.

(h) *Rules and regulations suspended.* The operation of all rules, regulations, or tariff provisions is suspended insofar as they conflict with the provisions of this order.

(i) *Application.* The provisions of this order shall apply to intrastate, interstate, and foreign commerce.

(j) *Effective date.* This order shall become effective at 12:01 a.m., September 3, 1976.

(k) *Expiration date.* This order shall expire at 11:59 p.m., October 31, 1976, unless otherwise modified, changed, or suspended by order of this Commission.

(Secs. 1, 12, 15, and 17(2), 24 Stat. 379, 383, 384, as amended; 49 U.S.C. 1, 12, 15, and 17(2). Interprets or applies Secs. 1(10–17), 15(4), and 17(2), 40 Stat. 101, as amended, 54 Stat. 911; 49 U.S.C. 1(10–17), 15(4) and 17(2).)

It is further ordered, That a copy of this order and direction shall be served upon the Association of American Railroads, Car Service Division, as agent of all railroads subscribing to the car service and car hire agreement under the terms of that agreement, and upon the American Short Line Railroad Association; and that notice of this order be given to the general public by depositing a copy in the Office of the Secretary of the Commission at Washington, D.C., and by filing it with the Director, Office of the Federal Register.

By the Commission, Railroad Service Board, members Lewis R. Teeple, Thomas

[1] Phosphate, (dried or ground, treated or untreated), and soybean products added.

J. Byrne, and William J. Love. Member Lewis R. Teeple not participating.

H. GORDON HOMME, Jr.,
Acting Secretary.

[FR Doc.76-26393 Filed 9-8-76;8:45 am]

Title 50—Wildlife and Fisheries

CHAPTER I—U.S. FISH AND WILDLIFE SERVICE, DEPARTMENT OF THE INTERIOR

PART 32—HUNTING

Cabeza Prieta National Wildlife Refuge, Arizona

The following special regulations are issued and are effective on September 1, 1976.

§ 32.32 Special regulations; big game; for individual wildlife refuge areas.

ARIZONA

CABEZA PRIETA NATIONAL WILDLIFE REFUGE

The public hunting of bighorn sheep on the Cabeza Prieta National Wildlife Refuge, Arizona, is permitted except in those areas designated by signs as closed to hunting. The bighorn sheep season extends from December 4 through December 19, 1976, inclusive. The open bighorn sheep area, comprising 641,420 acres, is delineated on maps available at refuge headquarters, Yuma, Arizona, and from the Regional Director, U.S. Fish and Wildlife Service, P.O. Box 1306, Albuquerque, New Mexico 87103. Hunting shall be in accordance with all applicable State regulations covering the hunting of bighorn sheep subject to the following special conditions:

(1) Bighorn sheep limited to 4 permits issued by the Arizona Game and Fish Department.

(2) Bighorn sheep hunters may hunt in those areas designated on their permits.

(3) Possession or transportation of any loaded firearm or strung bow within or on any motorized vehicle or its attachments is prohibited. A loaded firearm shall mean any firearm containing any cartridge or ammunition in its chamber, magazine or clip.

(4) Possession or transportation of any uncased firearm within or on any motorized vehicle or its attachments is prohibited. An uncased firearm shall mean any firearm not encased in any holster, scabbard, or gun case (soft or hard).

(5) Travel by vehicle is restricted to those roads and trails designated by the Refuge Manager. Maps showing these designated routes of travel are available to holders of Arizona Game and Fish Department permits to hunt sheep in this area.

The provisions of this special regulation supplement the regulations which govern hunting on wildlife refuge areas generally which are set forth in Title 50, Code of Federal Regulations, Part 32, and are effective through December 19, 1976.

HAVASU NATIONAL WILDLIFE REFUGE

The public hunting of bighorn sheep on the Havasu National Wildlife Refuge, Arizona, is permitted from December 4 through December 19, 1976, inclusive, but only in the Arizona (Unit 16A) portion designated by signs as open to hunting. This open area, comprising 18,600 acres, is delineated on maps available at refuge headquarters, Needles, California, and from the Regional Director, U.S. Fish and Wildlife Service, P.O. Box 1306, Albuquerque, New Mexico 87103. Hunting shall be in accordance with all applicable State regulations covering the hunting of bighorn sheep subject to the following special conditions:

(1) Only the person holding the permit issued by the Arizona Game and Fish Department to hunt desert bighorn sheep in Unit 16A will be permitted to hunt on the refuge.

(2) Hunting is prohibited within one-fourth mile of any occupied dwelling or concession operation.

The provisions of this special regulation supplement the regulations which govern hunting on wildlife refuge areas generally which are set forth in Title 50, Code of Federal Regulations, Part 32, and are effective through December 19, 1976.

KOFA GAME RANGE

The public hunting of bighorn sheep and deer on the Kofa Game Range, Arizona, is permitted except in those areas designated by signs as closed to hunting. The bighorn sheep season extends from December 4 through December 19, 1976, inclusive; the deer season extends from October 22 through November 7, 1976, inclusive, and from November 12 through November 21, 1976, inclusive. These open areas, comprising 660,000 acres, are delineated on maps available at refuge headquarters, Yuma, Arizona and from the Regional Director, U.S. Fish and Wildlife Service, P.O. Box 1306, Albuquerque, New Mexico 87103. Hunting shall be in accordance with all applicable State regulations covering the hunting of bighorn sheep and deer subject to the following special conditions:

(1) Bighorn sheep limited to 9 permits issued by the Arizona Game and Fish Department.

(2) Bighorn sheep hunters may hunt only in those areas designated on their permits.

(3) Deer limited to 700 permits issued by the Arizona Game and Fish Department.

(4) Possession or transportation of any loaded firearm or strung bow within or on any motorized vehicle or its attachments is prohibited. A loaded firearm shall mean any firearm containing any cartridge or ammunition in its chamber or magazine.

(5) Possession or transportation of any uncased firearm within or on any motorized vehicle or its attachments is prohibited. An uncased firearm shall mean any firearm not encased in any holster, scabbard or gun case (soft or hard).

The provisions of this special regulation supplement the regulations which govern hunting on wildlife refuge areas generally which are set forth in Title 50, Code of Federal Regulations, Part 32, and are effective through December 19, 1976.

ARIZONA AND CALIFORNIA

IMPERIAL NATIONAL WILDLIFE REFUGE

The public hunting of deer on the Imperial National Wildlife Refuge, Arizona and California, is permitted only on the area designated by signs as open to hunting. This open area, comprising 7,000 acres, is delineated on maps available at refuge headquarters, Martinez Lake, Arizona, and from the Regional Director, U.S. Fish and Wildlife Service, P.O. Box 1306, Albuquerque, New Mexico 87103. Hunting seasons are as follows: Arizona—from November 12 through November 21, 1976, inclusive; California—from September 25 through November 7, 1976, inclusive. Hunting shall be in accordance with all applicable State regulations covering the hunting of deer subject to the following special condition:

(1) Except as provided under the special regulations covering the hunting of small game, doves and migratory waterfowl on the Imperial National Wildlife Refuge, possession of any firearms other than a legal deer hunting firearm, as defined by State hunting regulations, is prohibited.

The provisions of this special regulation supplement the regulations which govern hunting on wildlife refuge areas generally which are set forth in Title 50, Code of Federal Regulations, Part 32, and are effective through November 21, 1976.

NEW MEXICO

BOSQUE DEL APACHE NATIONAL WILDLIFE REFUGE

The public hunting of deer on the Bosque del Apache National Wildlife Refuge, New Mexico, is permitted only on the area designated by signs as open to hunting. This open area, comprising 20,200 acres, is delineated on maps available at refuge headquarters, San Antonio, New Mexico, and from the Regional Director, U.S. Fish and Wildlife Service, P.O. Box 1306, Albuquerque, New Mexico 87103. Hunting shall be in accordance with all applicable State regulations covering the hunting of deer subject to the following special conditions:

(1) The open season for hunting deer on the refuge is November 6 and 7, 1976, and from November 9 through November 21, 1976, inclusive.

(2) Bag limit is 1 antlered deer per season.

(3) All hunters must leave the refuge by 1 hour after sunset.

(4) Overnight camping is prohibited.

(5) Only center-fire rifles chambered for cartridges meeting the legal requirements of the State of New Mexico are legal weapons for the hunt.

(6) Vehicular travel is restricted to designated roads only.

(7) Hunting and retrieval of kills must be by foot. Horses are prohibited.

(8) Fires are prohibited.

The provisions of this special regulation supplement the regulations which govern hunting on wildlife refuge areas generally which are set forth in Title 50, Code of Federal Regulations, Part 32,

and are effective through November 21, 1976.

SAN ANDRES NATIONAL WILDLIFE REFUGE

The public hunting of deer (either sex) on the San Andres National Wildlife Refuge, New Mexico, is permitted from October 30 through October 31, 1976, inclusive, but only on the area designated by signs as open to hunting. This open area, comprising 57,215 acres, is delineated on maps available from the Refuge Manager, Bosque del Apache National Wildlife Refuge, P.O. Box 278, San Antonio, New Mexico 87832, and from the Regional Director, U.S. Fish and Wildlife Service, P.O. Box 1306, Albuquerque, New Mexico 87103. Hunting shall be in accordance with all applicable State, Federal and military regulations subject to the following special conditions:

(1) Hunters must check in and out in person at the check station located on the Jornada road near U.S. 70. The check station will be open 24 hours a day. Hunters may check in during the afternoon of October 29, 1976. Time of entry into the hunting area will be at the discretion of the officers in charge. Any entry permits required by the military authorities will be available at the check station. All hunters must check out no later than 10:00 p.m., October 31, 1976.

(2) No entry into the hunting area from the west will be permitted north of the Rope Springs road. Hunters will not be permitted to enter the hunting area from the east side of the San Andres Range except at the discretion of the officers in charge.

(3) The officers in charge may restrict the number of hunters entering any one area. If required by the firing schedule, hunters will be cleared from all areas where their safety is endangered.

(4) Camping will be permitted only at designated campsites, which includes a quarter-mile radius from each campsite sign.

(5) No open fires are permitted.

(6) Vehicles are restricted to established roads.

The provisions of this special regulation supplement the regulations which govern hunting on wildlife refuge areas generally which are set forth in Title 50, Code of Federal Regulations, Part 32, and are effective through October 31, 1976.

The public hunting of desert bighorn sheep on the San Andres National Wildlife Refuge, New Mexico, is permitted from October 2 through October 10, 1976, inclusive, but only on the area designated by signs as open to hunting. This open area, comprising 57,215 acres, is delineated on maps available from the Refuge Manager, Bosque del Apache National Wildlife Refuge, P.O. Box 278, San Antonio, New Mexico 87832, and from the Regional Director, U.S. Fish and Wildlife Service, P.O. Box 1306, Albuquerque, New Mexico 87103. Hunting shall be in accordance with all applicable State regulations covering the hunting of desert bighorn sheep.

The provisions of this special regulation supplement the regulations which govern hunting on wildlife refuge areas generally which are set forth in Title 50, Code of Federal Regulations, Part 32, and are effective through October 10, 1976.

W. O. NELSON, Jr.,
Regional Director,
Albuquerque, New Mexico.

AUGUST 31, 1976.

[FR Doc.76-26331 Filed 9-8-76;8:45 am]

PART 32—HUNTING

Fish Springs National Wildlife Refuge, Utah

The following special regulation is issued and is effective September 9, 1976.

§ 32.12 **Special regulations; migratory game birds, for individual wildlife refuge areas.**

UTAH

FISH SPRINGS NATIONAL WILDLIFE REFUGE

The public hunting of ducks, coots, and mergansers on the Fish Springs National Wildlife Refuge, Utah, is permitted from October 2, 1976 through January 2, 1977, inclusive, but only on the area designated by signs as open to hunting. This open area comprises 6,773 acres and is delineated on maps available at refuge headquarters, 66 miles southwest of Dugway, Utah 84022, and from the Area Manager, U.S. Fish and Wildlife Service, Federal Bldg., 125 South States Street, Salt Lake City, Utah 84111. Hunting shall be in accordance with all State and Federal regulations covering the hunting of ducks, coots, and mergansers, subject to the following special conditions:

(1) All hunters must register at the Visitor Information Station prior to hunting each day, and check out at the end of each day.

(2) Shooting from, upon, or across dikes or roads is prohibited.

(3) The use of small boats, canoes, etc. is permitted during the hunting season, but outboard motors or air thrust boats are prohibited.

(4) Dogs may be used for hunting, but are to be kept under control at all times.

The provisions of these special regulations supplement the regulations that govern hunting on wildlife refuge areas generally that are set forth in Title 50, Code of Federal Regulations, Part 32, and are effective through January 2, 1977.

ROLF H. KRAFT,
Refuge Manager, Fish Springs
National Wildlife Refuge.

AUGUST 31, 1976.

[FR Doc.76-26332 Filed 9-8-76;8:45 am]

PART 32—HUNTING

Certain National Wildlife Refuges in California

The following regulations will be effective October 9, 1976. These regulations apply to public hunting on portions of certain national wildlife refuges in California.

GENERAL CONDITIONS: Hunting shall be in accordance with applicable State and Federal regulations. Portions of refuges which are open to hunting are designated by signs and/or delineated on maps. Special conditions applying to individual refuges are listed on the reverse side of maps available at the refuge headquarters and from the office of the Regional Director, Fish and Wildlife Service, P.O. Box 3737, Portland, Oregon 97208.

§ 32.12 **Special regulations; migratory game birds; for individual wildlife refuge areas.**

Migratory game birds, except snipe and pigeons and doves, may be hunted on the following refuge areas:

CALIFORNIA

Salton Sea National Wildlife Refuge, P.O. Box 247, Calipatria, California 92233.

Kern National Wildlife Refuge, P.O. Box 219, Delano, California 93215.

Special condition: Due to a lack of water, Kern may not have a hunting program this year. Hunters are advised to contact the Refuge Manager or offices of the California Fish and Game Department for up to date information on water and hunting conditions.

Merced National Wildlife Refuge, (Headquarters: San Luis National Wildlife Refuge, P.O. Box 2176, Los Banos, California 93635).

Migratory game birds, except pigeons and doves, may be hunted on the following refuge areas:

Sacramento National Wildlife Refuge, Route 1, Box 311, Willows, California 95988.

Colusa National Wildlife Refuge, Route 1, Box 311, Willows, California 95988.

Delevan National Wildlife Refuge, Route 1, Box 311, Willows, California 95988.

Sutter National Wildlife Refuge, Route 1, Box 311, Willows, California 95988.

Kesterson National Wildlife Refuge, P.O. Box 2176, Los Banos, California 93635.

San Luis National Wildlife Refuge, P.O. Box 2176, Los Banos, California 93635.

Clear Lake National Wildlife Refuge, (Headquarters: Klamath Basin National Wildlife Refuges, Route 1, Box 74, Tulelake, California 96134).

Special conditions: 1. Boats with or without motors are permitted. Air-thrust and inboard water-thrust boats are prohibited.

2. All decoys, boats, and other personal property must be removed from the refuge at the close of each day.

Lower Klamath National Wildlife Refuge, (Headquarters: Klamath Basin National Wildlife Refuges, Route 1, Box 74, Tulelake, California 96134).

Special conditions: 1. During the first two days of waterfowl season, all hunters 16 years of age and older must have in their possession an entry permit for the controlled hunting unit in which they are hunting.

2. Posted retrieving zones are established on certain hunting units. Possession of firearms in these retrieving zones is prohibited, except, unloaded firearms may be taken through these zones when necessary to reach or leave hunting areas. Decoys may not be set in retrieving zones.

3. Boats with or without motors are permitted. Air-thrust and inboard water-thrust boats are prohibited.

4. All decoys, boats, and other personal property must be removed from the refuge at the close of each day.

5. Bow hunters must follow the same regulations as firearm hunters. The use of long bow is permitted.

6. Legal waterfowl shooting hours shall be from one-half hour before sunrise to 1:00 p.m. daily on all California portions of the refuge.

Tule Lake National Wildlife Refuge, (Headquarters: Klamath Basin National Wildlife Refuges, Route 1, Box 74, Tulelake, California 96134).

Special conditions: 1. During the first two days of waterfowl season, all hunters 16 years of age and older must have in their possession an entry permit for the controlled hunting unit in which they are hunting.

2. Posted retrieving zones are established on certain hunting units. Possession of firearms in these retrieving zones is prohibited except, unloaded firearms may be taken through these zones when necessary to reach or leave hunting areas. Decoys may not be set in retrieving zones.

3. Boats with or without motors are permitted. Air-thrust and inboard water-thrust boats are prohibited.

4. All decoys, boats, and other personal property must be removed from the refuge at the close of each day.

5. In designated spaced blind areas, hunters may not possess any loaded firearm further than 100 feet from the established blind stakes. Hunters will select blind sites by lottery at the beginning of each day's hunt. Hunters may shoot only from within their assigned blind sites.

6. The use of long bow is permitted. Bow hunters must follow the same regulations as firearm hunters.

7. Legal waterfowl shooting hours shall be from one-half hour before sunrise to 1:00 p.m. daily.

Modoc National Wildlife Refuge, P.O. Box 1610, Alturas, California 96101.

Special conditions: 1. First weekend only, entry permits are required to enter the hunting area for every individual with the exception of persons under 16 years of age.

2. After first weekend, hunting permitted on Tuesdays, Thursday, and Saturdays during authorized seasons.

3. Hunters are required to enter hunting area via designated parking sites.

4. Hunting area is open for access from 90 minutes prior to legal shooting hours until 90 minutes after sunset on days hunting is permitted.

§ 32.22 Special regulations; upland game; for individual wildlife refuge areas.

Ring-necked pheasant only may be hunted on the following refuge areas:

CALIFORNIA

Colusa National Wildlife Refuge, Route 1, Box 311, Willows, California 95988.

Delevan National Wildlife Refuge, Route 1, Box 311, Willows, California 95988.

Kern National Wildlife Refuge, P.O. Box 219, Delano, California 93215.

Special condition: Due to a lack of water, Kern may not have a hunting program this year. Hunters are advised to contact the Refuge Manager or offices of the California Fish and Game Department for up to date information on water and hunting conditions.

Merced National Wildlife Refuge, P.O. Box 2176, Los Banos, California 93635.

Sacramento National Wildlife Refuge, Route 1, Box 311, Willows, California 95988.

Sutter National Wildlife Refuge, Route 1, Box 311, Willows, California 95988.

Lower Klamath National Wildlife Refuge, (Headquarters: Klamath Basin National Wildlife Refuges, Route 1, Box 74, Tulelake, California 96134).

Special conditions: 1. Additional refuge area designated by special posting will be open to a special 4-day pheasant hunt.

2. Pheasants may not be hunted in retrieving zones.

3. Daily limit is two male pheasants during The Special Hunt.

Tule Lake National Wildlife Refuge, (Headquarters: Klamath Basin National Wildlife Refuges, Route 1, Box 74, Tulelake, California 96134.)

Special conditions: 1. Additional refuge area designated by special posting will be open to a special 4-day pheasant hunt.

2. Pheasants may not be hunted in retrieving zones.

3. Daily limit is two male pheasants during The Special Hunt.

The provisions of these special regulations supplement the regulations which govern hunting on wildlife refuge areas generally and which are set forth in Title 50, Code of Federal Regulations, Part 32, and are effective through June 30, 1977.

JAMES W. TEETER,
Regional Director,
Fish and Wildlife Service.

[FR Doc.76-26290 Filed 9-8-76;8:45 am]

proposed rules

This section of the FEDERAL REGISTER contains notices to the public of the proposed issuance of rules and regulations. The purpose of these notices is to give interested persons an opportunity to participate in the rule making prior to the adoption of the final rules.

DEPARTMENT OF THE TREASURY

Customs Service

[19 CFR Part 6]

AIR COMMERCE REGULATIONS

Landing Requirements for Private Aircraft Arriving From Areas South of the United States

In order to provide better Customs service to private aircraft arriving from certain areas south of the United States, it is considered desirable to add the Presidio-Lely International Airport, Presidio, Texas, to the list of designated airports set forth in § 6.14(e) of the Customs Regulations (19 CFR 6.14(e)).

Accordingly, notice is hereby given that under the authority of R.S. 251, as amended (19 U.S.C. 66), section 624, 46 Stat. 759 (19 U.S.C. 1624), and section 1109, 72 Stat. 799, as amended (49 U.S.C. 1509), it is proposed to amend § 6.14(e) of the Customs Regulations (19 CFR 6.14(e)) by adding the Presidio-Lely International Airport, Presidio, Texas, to the list of designated airports for private aircraft arriving from certain areas south of the United States.

Prior to the adoption of the foregoing proposal, consideration will be given to any relevant data, views, or arguments which are submitted in writing to the Commissioner of Customs, Attention: Regulations Division, Washington, D.C. 20229, and received not later than September 24, 1976.

Written material and suggestions submitted will be available for public inspection in accordance with section 103.8 (b) of the Customs Regulations (19 CFR 103.8(b)), at the Regulations Division, Headquarters, United States Customs Service, Washington, D.C., during regular business hours.

VERNON D. ACREE,
Commissioner of Customs.

Approved: September 1, 1976.

DAVID R. MACDONALD,
Assistant Secretary of the Treasury.

[FR Doc.76-26367 Filed 9-8-76;8:45 am]

Office of the Secretary

[31 CFR Part 1]

DISCLOSURE OF RECORDS

Fees for Services

The Department of the Treasury proposes to amend its regulations at 31 CFR Part 1, governing fees for services rendered in connection with the disclosure of records. The proposed amendments are to the regulations issued pursuant to 5 U.S.C. 552, as amended (the Freedom of Information Act); however, pursuant to 31 CFR 1.26, the amendments would also affect the fees to be charged for requests made under the Privacy Act of 1974. The purposes of the amendments are: To more closely conform to the Freedom of Information Act, by eliminating minimum fees; to raise the fee charged for locating records under FOIA to a level which more closely approximates the cost of the service rendered and to eliminate the imposition and collection of fees when the charges would be minimal.

Accordingly, notice is hereby given pursuant to 5 U.S.C. 553 that the Department of the Treasury proposes, pursuant to the authority of 5 U.S.C. 552(a)(4)(A) and 31 U.S.C. 483a, to adopt the following amendments to Part 1, Subtitle A of Title 31 of the Code of Federal Regulations:

§ 1.6 [Amended]

1. Revise § 1.6(g)(1)(i) and (g)(3)(i) to read:

* * * * *

(g) * * *

(i) Photocopies, per page up to 8½" x 14", $0.10 each, except that no charge shall be imposed for copying 10 pages or less.

* * * * *

(i) The fee charged for services of personnel involved in locating records shall be $5.00 for each hour or fraction thereof, except that no charge shall be imposed for a search consuming one hour or less.

2. Amend 1.6(g)(3)(ii) by changing "$3.50" to read "$5.00."

Interested persons are invited to submit written comments, suggestions or objections regarding the above amendments to Richard R. Albrecht, General Counsel, Room 3000, Department of the Treasury, Washington, D.C. 20220, on or before October 12, 1976. Comments submitted in response to this Notice will be available to the public upon request therefor.

Dated: September 3, 1976.

RICHARD R. ALBRECHT,
General Counsel.

[FR Doc.76-26321 Filed 9-8-76;8:45 am]

DEPARTMENT OF AGRICULTURE

Agricultural Marketing Service

[7 CFR Part 982]

FILBERTS GROWN IN OREGON AND WASHINGTON

Proposed Grade Regulations for Shelled Filberts

Notice is given of proposals to (1) establish minimum grade regulations for shelled filberts, (2) change the grade requirement prescribed for shelled filberts declared and withheld in lieu of merchantable filberts in satisfaction of a restricted obligation, and (3) make a minor conforming change in the administrative rules and regulations. This action is pursuant to the marketing agreement, as amended, and Order No. 982, as amended (7 CFR Part 982; 40 FR 53226, 55829), regulating the handling of filberts grown in Oregon and Washington (hereinafter collectively referred to as the "order"). The order is effective under the Agricultural Marketing Agreement Act of 1937, as amended (7 U.S.C. 601–674).

Section 982.45(a) of the order provides, in part, that no handler shall handle any shelled filberts unless they meet such minimum standards as are established by the Secretary on the basis of a recommendation of the Filbert Control Board. The Board has now recommended that shelled filberts be required to meet the standards for Oregon No. 1 whole and broken grade for shelled filberts contained in the Oregon Grade Standards for Filbert (Hazelnut) Kernels.

It is necessary to establish these standards because of the continuing importance of the shelled filbert market. Mandatory inspection and certification of filbert kernels would tend to promote orderly marketing because only acceptable quality kernels could be handled, and consumers and users could depend on the quality of each shipment.

This proposal would also necessitate a change in the standards applied to shelled filberts declared and withheld by a handler in lieu of merchantable filberts in satisfaction of a restricted obligation pursuant to §§ 982.50(a) and 982.51(b). Section 982.50(a) currently provides that these shelled filberts should meet the standards in effect for Oregon No. 1 grade for shelled filberts as contained in Oregon Grade Standards for Filbert (Hazelnut) Kernels, or such other standards as may be recommended by the Board and established by the Secretary. Because of its recommendation to establish minimum grade regulations for shelled filberts on the basis of Oregon No. 1 whole and broken grade, the Board also recommended, as a conforming change, the establishment of this grade for shelled filberts declared and withheld in lieu of merchantable filberts in satisfaction of a restricted obligation.

Both proposals would be included in § 982.101 of a new subpart entitled Subpart—Grade and Size Regulation.

It is also proposed that the reference to "Oregon Grades and Standards for Walnuts and Filberts" in § 982.453 of Subpart—Administrative Rules and Regulations (7 CFR 982.432–982.471) be changed to "Oregon Grade Standards

Filberts In Shell." This is a conforming change to recognize a change in the title of the standards applicable under the order to inshell filberts.

Consideration will be given to any written data, views, or arguments pertaining to the proposal which are received by the Hearing Clerk, U.S. Department of Agriculture, Room 112, Administration Building, Washington, D.C. 20250, not later than September 22, 1976. All written submissions made pursuant to this notice should be in quadruplicate and will be made available for public inspection at the office of the Hearing Clerk during official hours of business (7 CFR 1.27(b)).

The proposals follow:

Subpart—Grade and Size Regulation

1. Add a new subpart entitled Subpart—Grade and Size Regulation and include a § 982.101 in that subpart reading as follows:

§ 982.101 Minimum grade standards for shelled filberts.

(a) Pursuant to § 982.50(a), no handler shall handle any shelled filberts unless such filberts meet the requirements for Oergon No. 1 whole and broken grade for shelled filberts as contained in Oregon Grade Standards for Filbert (Hazelnut) Kernels.

(b) Pursuant to §§ 982.50(a) and 982.51 (b), a handler may declare and withhold shelled filberts in lieu of merchantable filberts in satisfaction of his restricted obligation. Shelled filberts so declared and withheld shall, in lieu of the standards prescribed pursuant to § 982.50(a) (3), meet the standards in effect for Oregon No. 1 whole and broken grade for shelled filberts as contained in Oregon Grade Standards for Filbert (Hazelnut) Kernels.

2. In § 982.453 of Subpart—Administrative Rules and Regulations (7 CFR 982.432–982.471), "Oregon Grades and Standards for Walnuts and Filberts" is revised to read "Oregon Grade Standards Filberts In Shell".

Dated: September 2, 1976.

CHARLES R. BRADER,
Deputy Director,
Fruit and Vegetable Division.

[FR Doc.76-26311 Filed 9-8-76;8:45 am]

EDUCATION, AND WELFARE DEPARTMENT OF HEALTH,

Food and Drug Administration

[21 CFR Part 201]

[Docket No. 76N-0207]

EPINEPHRINE INHALATION PREPARATIONS; PRESCRIPTION DISPENSING AND WARNINGS

Withdrawal of Proposal and Termination of Rulemaking Proceeding

The Food and Drug Administration (FDA) is withdrawing the proposal (published in the FEDERAL REGISTER of April 15, 1972 (37 FR 7519)) to amend § 3.67 (now § 201.305 (21 CFR 201.305) pursuant to recodification published in the FEDERAL REGISTER of March 27, 1975 (40 FR 13996)) and terminating the rule making proceeding initiated by that proposal. The proposal, if adopted, would have limited epinephrine inhalation preparations to prescription dispensing and required that specified warnings be added to their labeling.

After considering the comments received in response to the proposal, the Commissioner of Food and Drugs concluded that the matter should be reviewed by the Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products Panel who would advise him on the safety, effectiveness, and adequacy of labeling of these over-the-counter (OTC) bronchodilator drug products. That review is now completed, and the proposed monograph including the panel's conclusions and recommendations to the Commission is published elsewhere in this issue of the FEDERAL REGISTER. The panel recommended that epinephrine inhalation drug products continue to be dispensed over-the-counter but with certain labeling changes. Interested persons will have an opportunity to comment on both the proposed monograph and the tentative final monograph, which the Commissioner will issue at a later date.

Accordingly, the Commissioner finds that the April 15, 1972 proposal is now superseded; however, the requirements in § 201.305 (21 CFR 201.305) (formerly § 3.67) governing isoproterinol inhalation preparations are not affected by this section.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 502 503 (b), 505, 701(a), 52 Stat. 1050–1053 as amended, 1055 (21 U.S.C. 352, 353(b), 355, 371(a))) and under authority delegated to him (21 CFR 2.120), the Commissioner hereby withdraws the proposed amendment to § 3.67 published in the FEDERAL REGISTER of April 15, 1972 (37 FR 7519) and terminates the rulemaking proceeding initiated by that proposal.

Dated: July 30, 1976.

SHERWIN GARDNER,
Acting Commissioner
of Food and Drugs.

[FR Doc.76-26174 Filed 9-8-76;8:45 am]

DEPARTMENT OF HOUSING AND URBAN DEVELOPMENT

Federal Insurance Administration

[24 CFR Part 1917]

[Docket No. FI 2296]

APPEALS FROM FLOOD ELEVATION DETERMINATION AND JUDICIAL REVIEW

Proposed Flood Elevation Determinations for the City of Livermore, California

The Federal Insurance Administrator, in accordance with section 110 of the Floor Disaster Protection Act of 1973 (Pub. L. 93–234), 87 Stat. 980, which added section 1363 to the National Flood Insurance Act of 1968 (Title XIII of the Housing and Urban Development Act of 1968 Pub. L. 90–448), 42 U.S.C. 4001–4128, and 24 CFR Part 1917 (§ 1917.4(a)), hereby gives notice of his proposed determinations of flood elevations for the City of Livermore, California.

Under these Acts, the Administrator, to whom the Secretary has delegated the statutory authority, must develop criteria for flood plain management in identified flood hazard areas. In order to participate in the National Flood Insurance Program, the City of Livermore must adopt sound flood plain management measures that are consistent with the flood elevations determined by the Secretary.

Proposed flood elevations (100-year flood) are listed below for selected locations. Maps and other information showing the detailed outlines of the flood-prone areas and the proposed flood elevations are available for review at City Hall, 2250 First Street, Livermore, California 94550.

Any person having knowledge, information, or wishing to make a comment on these determinations should immediately notify Mayor Helen Tirsell, City Hall, 2250 First Street, Livermore, California 94550. The period for comment will be ninety days following the second publication of this notice in a newspaper of local circulation in the above-named community.

The proposed 100-year Flood Elevations are:

Source of flooding	Location	Elevation in feet above mean sea level	Width from shoreline or bank of stream (facing downstream) to 100-yr flood boundary (feet)	
			Right	Left
Arroyo Mocho	Southern Pacific RR	450	40	40
	South edge of Stanley Blvd	452	1,670	50
	West edge of Holmes St	472	60	0
Arroyo Las Positas	West side of Airway Blvd	381	50	800
	West edge of Bluebell Dr	501	30	35
	West edge of Heather Lane	512	190	30
	Along north edge of Frontage Rd	535	70	580
Altamont Creek	Along north edge of Bluebell Dr	500	880	150
	West edge of Vasco Rd	526	910	40
Arroyo Seco	South side Highway 50	506	90	90
	Lucille St	551	0	0

(National Flood Insurance Act of 1968 (Title XIII of Housing and Urban Development Act of 1968), effective January 28, 1969 (33 FR 17804, November 28, 1968), as amended; 42 U.S.C. 4001–4128; and Secretary's delegation of authority to Federal Insurance Administrator 34 F.R. 2680, February 27, 1969, as amended by 39 FR 2787, January 24, 1974.)

Issued: August 24, 1976.

J. ROBERT HUNTER,
Acting Federal
Insurance Administrator.

[FR Doc.76-26365 Filed 9-8-76;8:45 am]

[24 CFR Part 1917]

[Docket No. FI-2295]

APPEALS FROM FLOOD ELEVATION DETERMINATION AND JUDICIAL REVIEW

Proposed Flood Elevation Determinations for the City of Riverside, Missouri

The Federal Insurance Administrator, in accordance with section 110 of the Flood Disaster Protection Act of 1973 (Pub. L. 93-234), 87 Stat. 980, which added section 1363 to the National Flood Insurance Act of 1968 (Title XIII of the Housing and Urban Development Act of 1968 Pub. L. 90-448), 42 U.S.C. 4001-4128, and 24 CFR Part 1917 (§ 1917.4 (a)), hereby gives notice of his proposed determinations of flood elevations for the City of Riverside, Missouri.

Under these Acts, the Administrator, to whom the Secretary has delegated the statutory authority, must develop criteria for flood plain management in identified flood hazard areas. In order to participate in the National Flood Insurance Program, the City of Riverside must adopt sound flood plain management measures that are consistent with the flood elevations determined by the Secretary.

Proposed flood elevations (100-year flood) are listed below for selected locations. Maps and other information showing the detailed outlines of the flood-prone areas and the proposed flood elevations are available for review at City Hall, Riverside, Missouri 64168.

Any person having knowledge, information, or wishing to make a comment on these determinations should immediately notify Mayor E. H. Young, City Hall, P.O. Box 9135, Riverside, Missouri 64168. The period for comment will be ninety days following the second publication of this notice in a newspaper or local circulation in the above-named community.

The proposed 100-year Flood Elevations are:

Source of flooding	Location	Elevation in feet above mean sea level	Width from shoreline or bank of stream (facing downstream) to 100-yr flood boundary (feet)	
			Right	Left
Burlington Creek	Paradise Valley Rd	764	240	440
	M-9	764	[1] 2,940	[1] 14,500
	Burlington Northern Inc	764	[1] 2,460	[1] 15,280
East Creek	U.S. Highway 69	771	160	[1] 40
	Railroad bridge	767	80	60
Missouri River	I-635	759	[2]	1,070
	Fairfax Bridge	758	[2]	960
Line Creek	U.S. Highway 69	766	230	510
	Bridge No. 71	761	240	120
	Northwest Platte Rd	757	600	[1] 4,640
Jumping Branch	50th St	770	150	150
	U.S. Highway 69	760	100	200

[1] Extends to corporate limits.
[2] Bank outside corporate limits.

(National Flood Insurance Act of 1968 (Title XIII of Housing and Urban Development Act of 1968), effective January 28, 1969 (33 FR 17804, November 28, 1968), as amended; 42 U.S.C. 4001-4128; and Secretary's delegation of authority to Federal Insurance Administrator 34 FR 2680, February 27, 1969, as amended by 39 FR 2787, January 24, 1974.)

Issued: Aug. 24, 1976.

J. ROBERT HUNTER,
Acting Federal Insurance Administrator.

[FR Doc.76-26366 Filed 9-8-76;8:45 am]

DEPARTMENT OF TRANSPORTATION

National Highway Traffic Safety Administration

[49 CFR Part 571]

[Docket No. 1-22; Notice 03]

VEHICLE IDENTIFICATION NUMBER

Advance Notice of Proposed Rulemaking

This is an advance notice of proposed rulemaking to advise the public that the National Highway Traffic Safety Administration (NHTSA) has tentatively concluded that further specificity is desirable in the elements of Standard No. 115, *Vehicle Identification Number*, to reduce errors in and simplify data processing for programs such as safety defect recall, accident investigation studies, vehicle theft, certification, registration, titling, insurance, and inspection. Extension of the standard's applicability to all types of motor vehicles is also being considered. No rule will be issued without further notice and opportunity for comment.

The Vehicle Identification Number (VIN) is a number assigned to passenger cars by a manufacturer in accordance with Standard No. 115, and is unique as to that manufacturer's passenger car products for a 10-year period. Its purpose, in meeting the need for motor vehicle safety, is to make more difficult the unauthorized use of automobiles that contributes to hazardous highway conditions. Additionally, motor vehicle certification, compliance and safety defect recall, accident investigation studies and other research, are all aided by the requirement that passenger cars be identified by a virtually unique number. The NHTSA has stated its opinion that all aspects of the VIN are covered by Standard No. 115, and that any State or local requirements of general applicability that impose requirements beyond those set forth in the standard would be in violation of section 103(d) of the National Traffic and Motor Vehicle Safety Act (15 U.S.C. 1392(d)).

Besides the VIN's use in reducing the incidence of unauthorized use of automobiles, it is important to State Motor Vehicle Administrators, automobile theft bureaus, the International Association of Chiefs of Police, the International Association of Auto Theft Investigators, and numerous other local, state, and international law enforcement agencies. The Federal Interagency Committee on Auto Theft Prevention regards the VIN as an an important tool in solving the stolen vehicle problem. This Committee, headed jointly by the Secretary of Transportation and the Attorney General, includes representatives of the Departments of State, Commerce, Treasury and Office of Management and Budget.

Volkswagen of American, Inc., and the Motor Vehicle Manufacturers Association (MVMA) have recently petitioned for the assignment of meaning to the VIN's characters and their arrangement, in order to convey detailed information about the vehicle's manufacture and description in addition to assigning it a unique identifier. In addition to containing information valuable to accident causation research and safety defect and compliance investigations, a uniform structure of the VIN presumably would provide a basis for compatible interconnection of electronic data files, and would reduce the number of errors attributable to manual transcription.

At least four systems for assigning meaning to the characters and arrangement of the VIN have been developed. It is anticipation of the difficulties in using these incompatible systems that prompts the two petitions and the agency's tentative conclusion that further specification of the elements in the VIN would contribute to motor vehicle safety. Under the agency's opinion that existing Standard No. 115 covers all aspects of the VIN, other regulatory bodies are prevented from establishing any further specificity in the VIN within the United States.

The agency also concludes that the same considerations underlying the value of the VIN for passenger cars may justify extension of the standard's applicability to all types of motor vehicles.

Through consultation with and participation in several standards setting organizations, the agency has selected the systems of the Vehicle Equipment Safety Commission (VESC) and the International Standards Organization (ISO) for consideration as the basis for standardization. Although the systems are identical in most respects, the VESC requires a vehicle descriptor with a fixed field of four characters, while the ISO requires a 12- to 17-character variable-length vehicle descriptor. Vehicle manufactures prefer the variable field's adaptability to existing VIN systems and the differing needs of each manufacturer. State motor vehicle administrations, the insurance companies, and others that use the VIN prefer a fixed field so that transcription is more accurate and electronic storage costs are minimized.

The agency sees the merits of both points of view. International harmonization of standards, the competing needs for flexibility and accuracy, and the costs of electronic storage are all relevant considerations in choosing a system.

It is the agency's present view that aspects of each system can be adapted to serve the needs of all VIN users. Specifically, the NHTSA is considering a vehicle descriptor composed of a fixed field of six characters, with the manufacturer option to fill each position in the field with a character that has meaning or with a character that indicates that the position is blank. In this way, a fixed-length VIN is achieved in the interests of transcription accuracy. The agency believes that transcription accuracy will contribute to motor vehicle safety by aiding research in motor vehicle accident causation and the recall of defective or noncomplying vehicles. At the same time, manufacturers would retain flexibility in the number of meaningful characters they wish to utilize, permitting the continued use of existing codes and computer capacity.

The one-time costs of adopting any standardized system are solicited as the grounds for an agency decision on the reasonableness of proposing this change. Particular costs or complexity associated with extending the standard's applicability to all types of motor vehicles (i.e., trucks, buses, multipurpose passenger vehicles, trailers, and motorcycles) should be noted. Comments on anticipated leadtimes are also requested.

The views of all interested parties, particularly vehicle manufacturers, component suppliers, data processing specialists, vehicle administrators, insurance companies, and law enforcement officials, are solicited. It is anticipated that a public meeting to consider all issues raised by this notice will take place shortly after the comment closing date. To assist in the development of written and oral comments, a summary of the ISO and VESC systems follows.

The ISO VIN has a variable length of 12 to 17 alpha/numeric characters (except the last four must be numeric) and must not be identical to another VIN assigned within 30 years.

The ISO VIN consists of three sections:

1. The World Manufacturer Identifier (WMI)—three characters to identify continent, country and manufacturer.

2. The Vehicle Descriptor Section (VDS)—one to six characters to identify the general attributes of the vehicle.

3. The Vehicle Indicator Section (VIS)—eight characters to identify the year and plant of manufacture, and to provide for assignment of a sequential number.

The VESC VIN consists of two regulations published in 1976 to establish a system for passenger cars and non-motive powered recreational vehicles. This VIN specifies a fixed length of 15 characters. The informational content and type of each character is specified, except that the make and year characters may be roman letters or arabic numerals.

The format of the VESC VIN consists of two sections:

1. Vehicle Descriptor Section (VDS)—seven characters to describe the vehicle. For passenger cars this is a three character make identifier followed by car line, series, body type and engine type identifiers.

2. Vehicle Indicator Section (VIS)—eight characters to indicate model year, manufacturing plant and to provide for assignment of sequential number. The manufacturer identifier of the ISO System and the make identifier of the VESC system are the same for the United States.

The VESC system is consistent with the ISO system except that it requires the descripter section to be four alpha characters. The ISO requires at least one and permits up to six alpha or numeric characters in its descriptor section. Comments are requested concerning possible ways of resolving the differences between the two systems.

It is noted that the Volkswagen and MVMA petitions, which both request adoption of standardization in accordance with the ISO standard, will be granted or denied on the basis of the agency's future decision on a specific course of action.

Interested persons are invited to submit information, views, and arguments on the areas described and on the general subject of VIN standardization. Comments should refer to the docket number and be submitted to: Docket Section, National Highway Traffic Safety Administration, Room 5108, 400 Seventh Street, SW., Washington, D.C. 20590. It is requested but not required that 10 copies be submitted.

All comments received before the close of business on the comment closing date indicated below will be considered, and will be available for examination in the docket at the above address both before and after that date. The NHTSA will continue to file relevant material as it becomes available in the docket after the closing date, and it is recommended that interested persons continue to examine the docket for new material.

(Sec. 103, 112, 119, Pub. L. 89-563, 80 Stat. 718 (15 U.S.C. 1392, 1401, 1407); delegations of authority at 49 CFR 1.50 and 49 CFR 501.8.)

Comment closing date: October 26, 1976.

Issued: September 3, 1976.

ROBERT L. CARTER,
Associate Administrator,
Motor Vehicle Programs.

[FR Doc.76—26333 Filed 9-3-76;2:25 pm]

ENVIRONMENTAL PROTECTION AGENCY

[40 CFR Part 52]

[FRL 613-1]

APPROVAL AND PROMULGATION OF IMPLEMENTATION PLANS

Plan Revisions—Montana

On May 5, September 4, and December 1, 1975, the Governor of Montana submitted proposed revisions to the Montana State Implementation Plan (SIP). These revisions amend regulations applicable to incinerators, industrial processes, the storage of petroleum products, the control of odors, and aluminum reduction facilities (Anaconda Aluminum Company); and provides for new procedures relating to violations of emission standards caused by malfunctions. Additionally, the revisions adopted several Federal new source performance standards as State regulations.

REVISIONS APPLICABLE TO ANACONDA ALUMINUM

On May 5, 1975, the Governor of Montana submitted regulation 16-2.14(1)-S14080 of the Montana Administrative Code to clarify the particulate matter control strategy as it applies to Anaconda. Specifically, the regulation limits particulate matter emissions to 0.33 pounds per hour per reduction cell or 9.4 pounds per ton of aluminum produced per 24 hours, whichever is less.

Previously the only emission limitation applicable to this source was regulation 16-2.14(1)-S1430, a general regulation for industrial processes, which relates allowable emissions to the process weight. Because of the difficulty in defining actual process weight for aluminum reduction facilities, this provision was rendered unenforceable as a practical matter against this source.

On December 1, 1975, the Governor of Montana completed the May 5, 1975 SIP package by submitting a compliance schedule setting forth a timetable by which Anaconda will come into compliance with regulation S14080. The schedule includes incremental steps toward compliance with the emission limitation. The Anaconda Aluminum Company shall be in full compliance by June 1, 1979, with all applicable Montana laws and regulations on fluoride and particulate emissions from the company's aluminum reduction plant at Columbia Falls, Montana. The final control plan is designated to provide for attainment of the national ambient air quality standards for particulate matter as expeditiously as practicable in the vicinity of the aluminum reduction plant.

MISCELLANEOUS REVISIONS

On September 4, 1975, the Governor of Montana submitted various revisions to the SIP. The revisions consist of the following changes to the presently approved SIP:

Industrial Processes (16-2.14(1)-S1430): This revision indicates that reduction cells of a primary aluminum reduction plant and sources subject to the New Source Performance Standards listed in Montana Administrative Code regulation 16-2.14(1)-S14082 will not be subject to regulation *16-2.14(1)-S1430, Particulate Matter, Industrial Processes* since specific state regulations are in effect for these facilities.

Incinerators (16-2.14(1)-S1420: The presently approved SIP requires all incinerators to limit particulate matter emissions to 0.2 grains per standard cubic foot of dry flue gas.

The proposed revision requires all new incinerators (constructed or modified after September 5, 1975) to limit particulate matter emissions to 0.10 grains per standard cubic foot of dry flue gas, ex-

cept that all new incinerators subject to the New Source Performance Standards set forth at 40 CFR Part 60 shall meet those Federal standards. Additionally, all existing incinerators must meet a particulate matter emission standard of 0.10 grains per standard cubic foot of dry gas by September 30, 1977. Further, all incinerators must comply with a 10 percent opacity limitation. These provisions would reduce overall particulate emissions from incinerators.

Storage of Petroleum Products (16–2.14(1)–S14070): The proposed revision adds crude oil to the list of petroleum products which are subject to the storage requirements. The proposed revision also exempts from the regulation existing refineries which normally process less than 7000 barrels per day of crude oil. In addition, the proposed revision extends the date for final compliance with the storage requirements from June 30, 1972 to January 1, 1977 for those refineries which normally process 7000 barrels per day or more of crude oil. These provisions would not result in an increase in emissions from existing facilities.

Control of Odors (16–2.14(1)–S1480): The proposed revision no longer exempts equipment used to process food for human consumption in food service establishments from the odor regulation. Since odors are not a criteria pollutant under the Clean Air Act, this provision would not be considered a part of the SIP.

Malfunction Regulation (16–2.14(1)–S14000): So called malfunction regulations are interpretations of an emission limitation in that they signify how the limitation will be enforced. Therefore, this State malfunction regulation advises the sources of the manner in which the State may exercise its discretion in enforcing the applicable emission limitation.

The proposed revision provides that when a malfunction of equipment causes an increase in emissions which would continue for four (4) hours, the owner or operator must notify the State agency. Application may be made by the owner or operator to continue operation for an extended period under malfunction conditions. In addition, the State agency may require the owner or operator to submit a written report of the malfunction. The regulation further provides that a source shall be considered in violation of the applicable emission limitation unless the appropriate procedures are followed and enforcement discretion is exercised.

The previously approved provision provided only for reporting of a malfunction that extended eight (8) hours.

Standards for New Sources (16–2.14(1)–S14082): This regulation incorporates the Federal New Source Performance Standards (40 CFR Part 60) as State Standards for the following source categories: Fossil fuel-fired steam generators, incinerators, portland cement plants, nitric acid plants, sulfuric acid plants, asphalt concrete plants, petroleum refineries, storage vessels for petroleum liquids, secondary lead smelters, secondary brass and bronze ingot plants, iron and steel plants, and sewage treatment plants.

Preliminary review indicates that EPA intends to approve all the revisions as submitted by Montana. The proposed revisions are available for public inspection at the office of the State agency and at the offices of the Environmental Protection Agency listed below.

Department of Health and Environmental Sciences, Environmental Sciences Division, Air Quality Bureau, Cogswell Building, Helena, Montana 59601.
Environmental Protection Agency, Region VIII, Office of Public Affairs, Suite 900, 1860 Lincoln Street, Denver, Colorado 80203.
Environmental Protection Agency, Room 329, 401 M Street, S.W., Washington, D.C. 20460.

Interested persons are encouraged to submit written comments on any of the proposed revisions. Such comments will be accepted for consideration until October 12, 1976. Comments should be addressed to the Office of Regional Counsel, Environmental Protection Agency, Region VIII, Suite 900, 1860 Lincoln Street, Denver, Colorado 80203. All comments will be available for public inspection during normal business hours at the offices of the Environmental Protection Agency noted above.

(Sec. 110, Clean Air Act (42 U.S.C. 1857c–5); 39 FR 18805.)

Dated: August 18, 1976.

JOHN A. GREEN,
Regional Administrator.

It is proposed to amend Part 52 of Chapter I, Title 40 of the Code of Federal Regulations as follows:

Subpart BB—Montana

1. In § 52.1383, the table is amended as follows:

§ 52.1383 Compliance schedules.

* * * * *

Source	Location	Date of State order	Regulation involved	Date of adoption	Effective date	Final compliance date
*	*	*	*	*	*	*
Anaconda Aluminum.	Columbia Falls.	Nov. 21, 1975	S. 14080...	Nov. 21, 1975	Immediate....	June 1, 1979

[FR Doc.76–26287 Filed 9–8–76;8:45 am]

[40 CFR Part 55]

[FRL 612–8]

ENERGY RELATED AUTHORITY UNDER SECTION 119 OF THE CLEAN AIR ACT

Withdrawal of Proposed Compliance Date Extension for Niagara Mohawk Power Corporation, New York State

The purpose of this FEDERAL REGISTER notice is for the Environmental Protection Agency (EPA) to announce withdrawal of its proposed compliance date extension for the Niagara Mohawk Power Corporation, Albany Station, Units 1, 2, 3 and 4. This regulatory action was proposed by EPA under the authority of section 119 of the Clean Air Act on March 30, 1976 (41 FR 13371) and revised on June 14, 1976 (41 FR 23979).

Section 2 of the Energy Supply and Environmental Coordination Act of 1974 (ESECA), as amended by the Energy Policy and Conservation Act, authorizes the Administrator of the Federal Energy Administration (FEA) to issue orders to certain powerplants and major fuel burning installations prohibiting such facilities from burning natural gas or petroleum products as their primary energy source. Section 3 of ESECA added a new Section 119 to the Clean Air Act which requires the Administrator of the EPA to issue compliance date extensions for meeting certain air pollution requirements to facilities issued FEA prohibition orders whenever certain eligibility criteria are satisfied.

One such eligibility criterion is the requirement of section 119(c)(2)(C) of the Clean Air Act that facilities receiving compliance date extensions must achieve the most stringent degree of emission reduction required under an applicable implementation plan as soon as practicable, but no later than December 31, 1978. In addition, section 2 of ESECA and section 119(d)(1)(B) of the Clean Air Act require the EPA Administrator to notify the FEA whether a facility that has been issued an FEA prohibition order will be able to burn coal and comply with all applicable air pollution requirements without an EPA compliance date extension.

If compliance without an extension is not possible, the prohibition on oil and natural gas use contained in an FEA prohibition order may not become effective any earlier than either:

(a) The date EPA certifies to FEA as the earliest date that certain conditions and limitations on the EPA compliance date extension can be met, or

(b) For facilities which are ineligible for compliance date extensions, the earliest date on which the facility will be able to burn coal in compliance with all applicable air pollution requirements.

FEA plans to make its prohibition orders effective, after receipt of EPA's notifications or certifications, by service of Notices of Effectiveness which will set forth the dates after which burning of natural gas or petroleum products as a primary energy source will be prohibited.

On June 30, 1975 FEA issued prohibition orders Nos. OFU–056, 057, 058 and 059 to Niagara Mohawk Power Corporation, Albany Station, Units 1, 2, 3 and 4. On March 30, 1976 at 41 FR 13371 EPA proposed to issue a compliance date extension under Section 119 of the Clean Air Act to this facility which was revised on June 14, 1976 at 41 FR 23979. That proposal reflected EPA's finding that final compliance with the New York State Implementation Plan requirements for control of particulate matter and sulfur dioxide emissions while burning coal at these Units will take 30 months from the date of service by FEA of the Notices of Effectiveness of its prohibition orders.

A schedule based on this time frame was proposed as part of the March 30, 1976 proposed EPA compliance date extension for the subject facility. Since the date of that proposal, FEA has advised EPA that FEA's Notices of Effectiveness for Niagara Mohawk Power Corporation, Albany Station, Units 1, 2, 3 and 4 will not be issued by a date 30 months before December 31, 1978. This will result in the proposed EPA compliance schedule extending past December 31, 1978, thereby making this facility ineligible for a compliance date extension under Section 119 of the Clean Air Act.

Therefore, EPA is rescinding its proposed compliance date extension for Niagara Mohawk Power Corporation, Albany Station, Units 1, 2, 3 and 4. To discharge its responsibilities under section 119(d)(1)(B) of the Clean Air Act, EPA will certify to FEA the earliest date at which this facility will be able to burn coal and comply with all applicable air pollution requirements. The prohibition contained in FEA's order may not become effective any earlier than the date so certified by EPA.

The FEA prohibition orders issued to Niagara Mohawk Power Corporation, Albany Station, Units 1, 2, 3 and 4 are not affected by this action except insofar as the projected date of effectiveness of the prohibition contained in the FEA orders may be adjusted to take account of the time needed for achieving compliance with all applicable air pollution requirements at this facility.

In addition, this action does not affect any authority which FEA may have to impose specified schedules for achieving compliance with applicable air pollution requirements in connection with the FEA prohibition orders or Notices of Effectiveness to the facility in question.

Dated: August 19, 1976.

MEYER SCOLNICK,
Acting Regional Administrator.

[FR Doc.76-26286 Filed 9-8-76;8:45 am]

FEDERAL COMMUNICATIONS COMMISSION

[47 CFR Part 21]

[Docket No. 20870]

DOMESTIC PUBLIC LAND MOBILE RADIO SERVICE

Order and Public Notice

Adopted: August 27, 1976.

Released: August 31, 1976.

In the Matter of Regulatory Policies and Procedures For the Domestic Public Land Mobile Radio Service.

By the Chief, Common Carrier Bureau:

1. Presently before us for consideration is the request of the National Association of Radiotelephone Systems (NARS) for an extension of time for filing comments and reply comments in the above-captioned proceeding. A notice of inquiry and notice of proposed rulemaking in this matter was adopted by the Commission on July 7, 1976 and was released on July 15, 1976 [41 CFR 29432, July 16, 1976].

2. NARS states that the broad scope of this proceeding, which is intended in part to formulate "objective" standards for licensing new or additional DPLMRS facilities, necessitates a comprehensive economic investigation of the radio common carrier industry together with a complete reevaluation of the substantive and procedural licensing policies of the Commission. Moreover, NARS states the Commission has imposed stringent pleading burdens on those parties who challenge the premises and conclusions expressed or implicit in the notice. Expressing a desire to assist the Commission in its examination of the issues in a systematic and comprehensive fashion, NARS insists that absent and adequate existing data base nor an in-house staff capable of conducting a major inquiry, additional time is required so that NARS might sponsor a study of the industry so as to obtain sufficient specific factual data which would enable NARS to prepare its comments.

3. We have considered all the matters advanced by NARS and agree that the public interest would be served by granting parties additional time in which to file comments in this proceeding. Although we do not agree with NARS that a six-month extension of time is necessary, we will extend for two months the filing dates as specified in the original notice.

4. Accordingly, pursuant to Section 0.303(c) of the Commission's rules, *it is ordered*, That, to the extent indicated above, the request of the National Association of Radiotelephone Systems, is granted, and the time for filing comments in this proceeding is extended from September 3 to November 5, 1976, and the time for filing reply comments is extended from October 1 to December 3, 1976; and that, in all other respects, this request is denied.

FEDERAL COMMUNICATIONS COMMISSION,
JOSEPH A. MARINO,
Deputy Chief,
Common Carrier Bureau.

[FR Doc.76-26354 Filed 9-8-76;8:45 am]

[Docket No. 20811 RM-2681]

[47 CFR Part 73]

TABLE OF ASSIGNMENTS, FM BROADCAST STATIONS (BILLINGS, MONTANA)

Extending Time for Filing Comments and Reply Comments

Adopted: September 1, 1976.

Released: September 2, 1976.

1. On May 13, 1976, the Commission adopted a notice of proposed rule making, 41 FR 21363, proposing the assignment of Channel 223 to Billings, Montana. The present dates, as previously extended, for filing comments and reply comments are September 2 and September 22, 1976, respectively.

2. On August 31, 1976, counsel for petitioner, Radio Billings, Inc., filed a request for a further extension of time and a waiver of § 1.46(b) of the Commission's rules which requires that such requests be filed at least 7 days before the filing date. Counsel states that due to recent personnel changes in the Broadcast Division of the parent corporation and the fact that a permanent director of that division has only been appointed within the last few weeks, the short additional time requested is needed to allow the parent corporation to further assess what action it wishes to take in this docket proceeding. It further states that in view of the fact that this proceeding was initiated by Radio Billings, Inc., grant of this extension request will not have any adverse impact on any other party in interest and feels that this short extension will not unduly delay action in this docket.

3. It appears that the requested waiver of § 1.46(b) and extension of time is warranted. Accordingly, *It is ordered*, That the dates for filing comments and reply comments are extended to and including September 23 and October 13, 1976, respectively. However, in view of the almost three months that have been allowed for the filing of initial comments herein, it is not contemplated that any further extension requests will be granted.

4. This action is taken pursuant to authority found in sections 4(i), 5(d)(1) and 303(r) of the Communications Act of 1934, as amended, and § 0.281 of the Commission's rules.

FEDERAL COMMUNICATIONS COMMISSION,
[SEAL] WALLACE E. JOHNSON,
Chief, Broadcast Bureau.

[FR Doc.76-26352 Filed 9-8-76;8:45 am]

notices

This section of the FEDERAL REGISTER contains documents other than rules or proposed rules that are applicable to the public. Notices of hearings and investigations, committee meetings, agency decisions and rulings, delegations of authority, filing of petitions and applications and agency statements of organization and functions are examples of documents appearing in this section.

DEPARTMENT OF DEFENSE

ARMED FORCES INSTITUTE OF PATHOLOGY SCIENTIFIC ADVISORY BOARD

Cancellation Meeting

AUGUST 30, 1976.

Notice of the meeting of the Armed Forces Institute of Pathology's Scientific Advisory Board, announced in Volume 41, Federal Register, No. 163, on 20 August 1976, at page 35201, scheduled for 16–17 September, 1976, at 0830 hours in the Director's Conference Room, Armed Forces Institute of Pathology, Washington, D.C., is hereby cancelled.

Dated: September 2, 1976.

By authority of the Secretary of the Army.

R. S. SEEBERG,
LTC, U.S. Army Acting Director, Admin. Mgt. Directorate TAGCEN.

[FR Doc.76–26325 Filed 9–8–76;8:45 am]

SPECIAL COMMISSION ON THE UNITED STATES MILITARY ACADEMY

Establishment

In accordance with the provisions of Public Law 92–463, Federal Advisory Committee Act, notice was given on Friday, 3 September 1976, 41 FR 37352, that the Department of the Army would establish the Special Commission on the United States Military Academy. The Office of Management and Budget concurred in its establshment and in the publication of the above stated notice.

The Office of Management and Budget at the request of the Department of Defense has further reviewed the purpose for which the Special Commission on the United States Military Academy is being established and has determined that it is in the best interest of the public that this Commission be established at the earliest possible date. Therefore, the Office of Management and Budget agreed to waive its requirement that the above referenced notice appear in the FEDERAL REGISTER at least 15 days prior to the filing of the Committee's Charter with the appropriate standing Committee's of the Senate and the House of Representatives of the United States Congress. Accordingly, the Committee Management Secretariat of the Office of Management and Budget has authorized the Department of Defense to file the Charter for the Special Commission on the United States Military Academy this date with the Armed Services Committee of the United States Senate, the Armed Services Committee of the United States House of Representatives and the Library of Congress.

MAURICE W. ROCHE,
Directorate for Correspondence and Directives, OASD (Comptroller).

SEPTEMBER 7, 1976.

[FR Doc.76–26474 Filed 9–8–76;8:45 am]

Office of the Secretary

DEFENSE SCIENCE BOARD TASK FORCE ON PATRIOT VULNERABILITY

Meeting

The Defense Science Board Task Force on PATRIOT Vulnerability will meet in closed session on 28, 29, and 30 September 1976, in the Pentagon, Washington, D.C.

The mission of the Defense Science Board is to advise the Secretary of Defense and the Director of Defense Research and Engineering on overall research and engineering and to provide long-range guidance in these areas to the Department of Defense.

The task force will provide an analysis of the PATRIOT vulnerability to current and projected threats and provide related guidance and advice regarding R&D action considered appropriate within the Department of Defense.

In accordance with Section 10(d) of Appendix I, Title 5, United States Code, it has been determined that this task force meeting concerns matters listed in Section 552(b) of Title 5 of the United States Code, specifically subparagraph (1) thereof, and that accordingly this meeting will be closed to the public.

MAURICE W. ROCHE,
Director, Correspondence and Directives, OASD (Comptroller).

SEPTEMBER 3, 1976.

[FR Doc.76–26306 Filed 9–8–76;8:45 am]

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

MANUFACTURE OF CONTROLLED SUBSTANCES

Application

Section 303(a)(1) of the Comprehensive Drug Abuse Prevention and Control Act of 1970 (21 U.S.C. 823(a)(1)) states:

"The Attorney General shall register an applicant to manufacture controlled substances in schedule I or II if he determines that such registration is consistent with the public interest and with United States obligations under international treaties, conventions, or protocols in effect on the effective date of this part. In determining the public interest, the following factors shall be considered:

(1) maintenance of effective controls against diversion of particular controlled substances and any controlled substance in schedule I or II compounded therefrom into other than legitimate medical, scientific, research, or industrial channels, by limiting the importation and bulk manufacture of such controlled substances to a number of establishments which can produce an adequate and uninterrupted supply of these substances under adequately competitive conditions for legitimate medical, scientific, research, and industrial purposes;"

Pursuant to Section 1301.43 of Title 21 of the Code of Federal Regulations (CFR), notice is hereby given that on July 30, 1976, Endo Laboratories, Inc., 1000 Stewart Avenue, Garden City, NY 11430, made application to the Drug Enforcement Administration to be registered as a bulk manufacturer of the basic class of controlled substances listed below:

Drug:	Schedule
Hydrocodone	II
Oxycodone	II
Oxymorphone	II

Pursuant to Section 301 of the Controlled Substances Act (21 U.S.C. 821), and in accordance with 21 CFR 1301.43 (a), notice is hereby given that the above firm has made application to the Drug Enforcement Administration to be registered as a bulk manufacturer of the basic class of controlled substances indicated, and any other such person, and any existing registered bulk manufacturer of the above substances may file written comments on or objections to the issuance of such registration and may, at the same time, file a written request for a hearing on the application in accordance with 21 CFR 1301.54 in such form as prescribed by 21 CFR 1316.47. Such comments, objections and requests for a hearing may be filed no later than October 14, 1976.

Comments and objections may be addressed to the DEA Federal Register Representative, Office of Chief Counsel, Drug Enforcement Administration, Room 1203, 1405 Eye Street, NW., Washington, D.C. 20537.

Dated: August 30, 1976.

JERRY N. JENSON,
Deputy Administrator, Drug Enforcement Administration.

[FR Doc.76–26313 Filed 9–8–76;8:45 am]

MANUFACTURE OF CONTROLLED SUBSTANCES

Application

Section 303(a)(1) of the Comprehensive Drug Abuse Prevention and Control Act of 1970 (21 U.S.C. 823(a)(1)) states:

"The Attorney General shall register an applicant to manufacture controlled substances in schedule I or II if he determines that such registration is consistent with the public interest and with United States obligations under international treaties, conventions, or protocols in effect on the effective date of this part. In determining the public interest, the following factors shall be considered:

(1) maintenance of effective controls against diversion of particular controlled substances and any controlled substance in schedule I or II compounded therefrom into other than legitimate medical, scientific, research, or industrial channels, by limiting the importation and bulk manufacture of such controlled substances to a number of establishments which can produce an adequate and uninterrupted supply of these substances under adequately competitive conditions for legitimate medical, scientific, research, and industrial purposes;"

Pursuant to Section 1301.43 of Title 21 of the Code of Federal Regulations (CFR), notice is hereby given that the following manufacturers made application to the Drug Enforcement Administration to be registered as bulk manufacturers of the basic class of controlled substances listed below:

Eli Lilly & Company Mfg., Tippecanoe Laboratory, Box 685 Lilly Road, Lafayette, IN 47902 (undated):

Drug:	Schedule
Methadone	II
Methadone-intermediate	II

Eli Lilly & Co., 1249 South White River Parkway, East Drive, Building 80, Indianapolis, IN 46225 (undated):

Drug:	Schedule
Opium powders	II
Secobarbital	II
Amobarbital	II

Pursuant to Section 301 of the Controlled Substances Act (21 U.S.C. 821), and in accordance with 21 CFR 1301.43 (a), notice is hereby given that the above firms have made application to the Drug Enforcement Administration to be registered as bulk manufacturers of the basic class of controlled substances indicated, and any other such person, and any existing registered bulk manufacturer of any of the above basic class of controlled substances, may file written comments on or objections to the issuance of such registrations and may at the same time, file a written request for a hearing on the applications in accordance with 21 CFR 1301.54 in such form as prescribed by 21 CFR 1316.47. Such comments, objections and requests for a hearing may be filed no later than October 14, 1976.

Comments and objections may be addressed to the DEA Federal Register Representative, Office of Chief Counsel, Drug Enforcement Administration, Room 1203, 1405 Eye Street, NW., Washington, D.C. 20537.

Dated: August 30, 1976.

JERRY N. JENSON,
Deputy Administrator,
Drug Enforcement Administration.

[FR Doc.76-26314 Filed 9-8-76;8:45 am]

MANUFACTURE OF CONTROLLED SUBSTANCES

Application

Section 303(a)(1) of the Comprehensive Drug Abuse Prevention and Control Act of 1970 (21 U.S.C. 823(a)(1)) states:

The Attorney General shall register an applicant to manufacture controlled substances in schedule I or II if he determines that such registration is consistent with the public interest and with United States obligations under international treaties, conventions, or protocols in effect on the effective date of this part. In determining the public interest, the following factors shall be considered:

(1) maintenance of effective controls against diversion of particular controlled substances and any controlled substance in schedule I or II compounded therefrom into other than legitimate medical, scientific, research, or industrial channels, by limiting the importation and bulk manufacture of such controlled substances to a number of establishments which can produce an adequate and uninterrupted supply of these substances under adequately competitive conditions for legitimate medical, scientific, research, and industrial purposes";

Pursuant to Section 1301.43 of Title 21 of the Code of Federal Regulations (CFR), notice is hereby given that on August 18, 1976, Pharmaceuticals Division, Ciba-Geigy Corp., 556 Morris Avenue, Summit, NJ 07901, made application to the Drug Enforcement Administration to be registered as a bulk manufacturer of methylphenidate, a basic class of controlled substance in schedule II.

Pursuant to Section 301 of the Controlled Substances Act (21 U.S.C. 821), and in accordance with 21 CFR 1301.43 (a), notice is hereby given that the above firm has made application to the Drug Enforcement Administration to be registered as a bulk manufacturer of the basic class of controlled substance indicated, and any other such person, and any existing registered bulk manufacturer of methylphenidate, may file written comments on or objections to the issuance of such registration and may, at the same time, file a written request for a hearing on the application in accordance with 21 CFR 1301.54 in such form as prescribed by 21 CFR 1316.47. Such comments, objections and requests for a hearing may be filed no later than October 14, 1976.

Comments and objections may be addressed to the DEA Federal Register Representative, Office of Chief Counsel, Drug Enforcement Administration, Room 1203, 1405 Eye Street, NW., Washington, D.C. 20537.

Dated: August 30, 1976.

JERRY N. JENSON,
Deputy Administrator,
Drug Enforcement Administration.

[FR Doc.76-26315 Filed 9-8-76;8:45 am]

DEPARTMENT OF THE INTERIOR

Bureau of Land Management

[NM 28549]

NEW MEXICO

Notice of Application

AUGUST 31, 1976.

Notice is hereby given that, pursuant to Section 28 of the Mineral Leasing Act of 1920 (30 U.S.C. 185), as amended by the Act of November 16, 1973 (87 Stat. 576), Gas Company of New Mexico, a division of Southern Union Company, has applied for two 6 and 8½-inch natural gas pipelines and a 1-acre compressor station site right-of-way across the following lands:

NEW MEXICO PRINCIPAL MERIDIAN,
NEW MEXICO

T. 18 N., R. 5 W.,
Sec. 3, lot 2, SW¼NE¼, E½SW¼, SW¼SW¼ and NW¼SE¼;
Sec. 4, SE¼SE¼;
Sec. 9, NE¼SW¼, S½SW¼ and NW¼SE¼;
Sec. 17, SE¼NE¼, NE¼SE¼ and S½SE¼;
Sec. 19, lot 4, E½SW¼ and N½SE¼;
Sec. 20, NW¼NE¼, E½NW¼ and N½SW¼;
Sec. 30, lots 1, 2, 3 and 4.
T. 19 N., R. 5 W.,
Sec. 15, SW¼SE¼ and E½SE¼;
Sec. 22, N½NE¼, SW¼NE¼ and W½SE¼;
Sec. 27, W½E½;
Sec. 34, W½E½.
T. 16 N., R. 8 W.,
Sec. 10, NE¼NW¼ and W½NW¼.
T. 15 N., R. 9 W.,
Sec. 8, E½SE¼;
Sec. 18, SE¼SE¼;
Sec. 30, W½NE¼, E½SW¼ and NW¼SE¼.
T. 11 N., R. 10 W.,
Sec. 14, NW¼NE¼, S½NE¼ and NE¼SE¼;
Sec. 24, E½NW¼ (lots 7 and 8).
T. 14 N., R. 10 W.,
Sec. 12, NE¼NW¼ and W½NW¼;
Sec. 22, within M.S. 2251.
T. 14 N., R. 11 W.,
Sec. 22, N½S½ and SE¼SE¼;
Sec. 24, S½S½.
T. 15 N., R. 17 W.,
Sec. 18, S½NE¼.

These pipelines will convey natural gas across 16.072 miles of national resource lands in McKinley and Valencia Counties, New Mexico.

The purpose of this notice is to inform the public that the Bureau will be proceeding with consideration of whether the application should be approved, and if so, under what terms and conditions.

Interested persons desiring to express their views should promptly send their name and address to the District Manager, Bureau of Land Management, P.O.

Box 6770, Albuquerque, New Mexico 87107.

FRED E. PADILLA,
Chief, Branch of Lands and Minerals Operations.

[FR Doc.76-26329 Filed 9-8-76;8:45 am]

Geological Survey

UTAH

Known Geothermal Resources Area

Pursuant to the authority vested in the Secretary of the Interior by Sec. 21(a) of the Geothermal Steam Act of 1970 (84 Stat. 1566, 1572; 30 U.S.C. 1020), and delegations of authority in 220 Departmental Manual 4.1 H, Geological Survey Manual 220.2.3, and Conservation Division Supplement (Geological Survey Manual) 220.2.1 G, the following described lands are hereby defined as a known geothermal resources area, effective February 1, 1976:

(44) UTAH

NEWCASTLE KNOWN GEOTHERMAL RESOURCES AREA

SALT LAKE MERIDIAN

T. 36 S., R. 15 W.,
Secs. 20, 21, 29, and 30.

The area described aggregates 1,067 ha (2,636 acres) more or less.

Dated: August 25, 1976.

GEORGE H. HORN,
Conservation Manager, Central Region.

[FR Doc.76-26330 Filed 9-8-76;8:45 am]

Fish and Wildlife Service

SEA WORLD, INC.

Issuance of Permit for Marine Mammals

On March 10, 1976, a notice was published in the FEDERAL REGISTER (41 FR 10239-41) that an application had been filed with the Fish and Wildlife Service by Sea World, Inc., San Diego, California (L. H. Cornell, D.V.M.) for a permit to take three (3) Sea Otters (*Enhydra lutris*), for the purpose of scientific research and public display.

Notice is hereby given that on September 2, 1976, as authorized by the provisions of the Marine Mammal Protection Act of 1972 (16 U.S.C. 1361-1407), the Fish and Wildlife Service issued a permit to Sea World, Inc., subject to certain conditions set forth therein.

The permit is available for public inspection during normal business hours at the Fish and Wildlife Service's office in Suite 600, 1612 K Street NW., Washington, D.C.

Dated: September 3, 1976.

C. R. BAVIN,
Chief, Division of Law Enforcement, U.S. Fish and Wildlife Service.

[FR Doc.76-26401 Filed 9-8-76;8:45 am]

Bureau of Reclamation

[INT FES 76-47]

PROPOSED EASTERN NEW MEXICO WATER SUPPLY PROJECT, NEW MEXICO

Notice of Availability of Final Environmental Statement

Pursuant to Section 102(2)(C) of the National Environmental Policy Act of 1969, the Department of the Interior has prepared a final environmental statement for the proposed Eastern New Mexico Water Supply Project, New Mexico.

The environmental statement concerns a proposed 248-mile aqueduct to deliver municipal and industrial water from Ute Reservoir to nine project cities in Eastern New Mexico.

Copies are available for inspection at the following locations:

Office of Assistant to the Commissioner—Ecology, Room 7626, Bureau of Reclamation, Department of the Interior, Washington, D.C. 20240, telephone (202) 343-4991.

Division of Engineering Support, Technical Services Branch, E&R Center, Denver Federal Center, Denver, Colorado 80225, telephone (303) 234-3022.

Office of the Regional Director, Bureau of Reclamation, Herring Plaza Box H-4377, Amarillo, Texas 79101, telephone (806) 376-2404.

Albuquerque Planning Office, Bureau of Reclamation, Post Office Box 252, Albuquerque, New Mexico 87103, telephone (505) 766-2272.

Single copies of the final statement may be obtained on request to the Commissioner of Reclamation, Regional Director, or Albuquerque Planning Officer. Please refer to the statement number above.

Dated: September 3, 1976.

RONALD G. COLEMAN,
Assistant Secretary of the Interior.

[FR Doc.76-26341 Filed 9-8-76;8:45 am]

DEPARTMENT OF AGRICULTURE

Farmers Home Administration

[Notice of Designation No. A370]

FLORIDA

Designation of Emergency Areas

The Secretary of Agriculture has determined that farming, ranching, or aquaculture operations have been substantially affected in Sumter County, Florida, as a result of excessive rainfall May 15 through June 15, 1976.

Therefore, the Secretary has designated this area as eligible for emergency loans pursuant to the provisions of the Consolidated Farm and Rural Development Act, as amended by Public Law 94-68, and the provisions of 7 CFR 1832.-3(b) including the recommendation of Governor Reubin O'D. Askew that such designation be made.

Applications for emergency loans must be received by this Department no later than October 26, 1976, for physical losses and May 27, 1977, for production losses, except that qualified borrowers who receive initial loans pursuant to this designation may be eligible for subsequent loans. The urgency of the need for loans in the designated area makes it impracticable and contrary to the public interest to give advance notice of proposed rulemaking and invite public participation.

Done at Washington, D.C., this 1st day of September, 1976.

JOSEPH R. HANSON,
Acting Administrator, Farmers Home Administration.

[FR Doc.76-26309 Filed 9-8-76;8:45 am]

[Notice of Designation No. A369]

TEXAS

Designation of Emergency Areas

The Secretary of Agriculture has determined that farming, ranching, or aquaculture operations have been substantially affected in Young County, Texas, as a result of prolonged drought beginning August 1, 1975, through May 24, 1976.

Therefore, the Secretary has designated this area as eligible for emergency loans pursuant to the provisions of the Consolidated Farm and Rural Development Act, as amended by Public Law 94-68, and the provisions of 7 CFR 1832.3(b) including the recommendation of Governor Dolph Briscoe that such designation be made.

Applications for emergency loans must be received by this Department no later than October 26, 1976, for physical losses and May 27, 1977, for production losses, except that qualified borrowers who receive initial loans pursuant to this designation may be eligible for subsequent loans. The urgency of the need for loans in the designated area makes it impracticable and contrary to the public interest to give advance notice of proposed rulemaking and invite public participation.

Done at Washington, DC, this 1st day of September, 1976.

JOSEPH R. HANSON,
Acting Administrator, Farmers Home Administration.

[FR Doc.76-26310 Filed 9-8-76;8:45 am]

Forest Service

PROPOSED ADDITION TO THE TETON WILDERNESS

Notice of Availability of Draft Environmental Statement

Pursuant to Section 102(2)(C) of the National Environmental Policy Act of 1969, the Forest Service, Department of Agriculture, has prepared a draft environmental statement for the proposed addition to the Teton Wilderness, Bridger-Teton National Forest, Wyoming. The Forest Service report number is USDA-FS-DES (Leg) 76-09.

The environmental statement evaluates the proposal to increase the Teton Wilderness from 557,311 to 585,629 acres by moving the present boundary

westward to the border of the John D. Rockefeller, Jr. Memorial Parkway and Grand Teton National Park.

The proposed area is completely surrounded by classified wilderness and two popular National Parks. Present management has been limited to non-consumptive uses, chiefly recreation and watershed protection. The area is similar in character to the adjoining Teton Wilderness. Its location, in the heart of a very large area dedicated to recreation and preservation of natural ecosystems, makes the area highly sensitive to any management which would sharply conflict with the goals and philosophy of the surrounding areas.

This proposed addition of 28,318 acres to the existing Teton Wilderness would be administered by the U.S. Forest Service, in accordance with the provisions of the Wilderness Act, Public Law 88–577, dated September 3, 1964, and the Regulations of the Secretary of Agriculture, Title 36 C.F.R. 243.1.

This draft environmental statement was transmitted to CEQ on September 2, 1976.

Copies are available for inspection during regular working hours at the following locations:

USDA, Forest Service, South Agriculture Building, Room 3230, 12th & Independence Ave., SW., Washington, D.C. 20250.
Regional Planning Office, USDA, Forest Service, Federal Building, Room 4408, 324 25th Street, Ogden, Utah 84401.
Forest Supervisor, Bridger-Teton National Forest, Forest Service Building, P.O. Box 1888, Jackson, Wyoming 83001.

A limited number of single copies are available upon request to John R. McGuire, Chief, Forest Service, South Agriculture Building, 12th and Independence Avenue, SW., Washington, D.C. 20250 and/or H. Reid Jackson, Forest Supervisor, Forest Service Building, P.O. Box 1888, Jackson, Wyoming 83001.

Copies of the environmental statement have been sent to various Federal, State, and local agencies as outlined in the CEQ guidelines.

Comments are invited from the public and from State and local agencies which are authorized to develop and enforce environmental standards and from Federal agencies having jurisdiction by law or special expertise with respect to any environmental impact involved for which comments have not been requested specifically.

Comments concerning the proposed action and requests for additional information should be addressed to Forest Supervisor H. Reid Jackson, Forest Service Building, P.O. Box 1888, Jackson, Wyoming 83001. Comments must be received by November 2, 1976 in order to be considered in the preparation of the final environmental statement.

Dated: September 2, 1976.

EINAR L. ROGET,
Associate Deputy Chief.

[FR Doc.76–26308 Filed 9–8–76;8:45 am]

Soil Conservation Service

WATKINS GLEN RESOURCE CONSERVATION AND DEVELOPMENT (RC&D) MEASURE, N.Y.

Availability of Negative Declaration of Environmental Statement

Pursuant to Section 102(2)(C) of the National Environmental Policy Act of 1969; Part 1500.6(e) of the Council on Environmental Quality Guidelines (38 FR 20550), August 1, 1973; and Part 650.8(b)(3) of the Soil Conservation Service Guidelines (39 FR 19651), June 3, 1974; the Soil Conservation Service, U.S. Department of Agriculture, gives notice that an environmental impact statement is not being prepared for the Watkins Glen RC&D Measure, Schuyler County, New York.

The environmental assessment of this Federal action indicates that the measure will not create significant adverse local, regional, or national impacts on the environment and that no significant controversy is associated with the measure. As a result of these findings, Mr. Robert L. Hilliard, State Conservationist, Soil Conservation Service, USDA, U.S. Courthouse and Federal Building, 100 S. Clinton Street, Room 771, Syracuse, New York 13202, has determined that the preparation and review of an environmental impact statement is not needed for this measure.

The measure concerns a plan for flood prevention. The planned works of improvement include a floodwater diversion and the alteration of streets in the village of Watkins Glen.

The environmental assessment file is available for inspection during regular working hours at the following location:

Soil Conservation Service, USDA, U.S. Courthouse & Federal Building, 100 S. Clinton Street, Room 771, Syracuse, New York 13202.

The negative declaration is available for single copy requests at the above location.

No administrative action on implementation of the proposal will be taken until September 24, 1976.

(Catalog of Federal Domestic Assistance Program No. 10.901, National Archives Reference Services.)

VICTOR H. BARRY, Jr.,
Deputy Administrator for Field Services, Soil Conservation Service.

AUGUST 30, 1976.

[FR Doc.76–26289 Filed 9–8–76;8:45 am]

DEPARTMENT OF COMMERCE

Domestic and International Business Administration

BRIGHAM YOUNG UNIV.

Notice of Decision on Application for Duty-Free Entry of Scientific Article

The following is a decision on an application for duty-free entry of a scientific article pursuant to Section 6(c) of the Educational, Scientific, and Cultural Materials Importation Act of 1966 (Pub. L. 89–651, 80 Stat. 897) and the regulations issued thereunder as amended (15 CFR 301).

A copy of the record pertaining to this decision is available for public review during ordinary business hours of the Department of Commerce, at the Office of Import Programs, Department of Commerce, Washington, D.C. 20230.

Docket Number: 76–00402. Applicant: Brigham Young University, Purchasing Department, Provo, Utah 84601. Article: Electron Microscope, Model EM 400 with an eucentric goniometer stage (high tilt). Manufacturer: Philips Electronics Instruments, NVD, The Netherlands. Intended use of article: The article is intended to examine materials at low, intermediate and high magnifications, to investigate freeze-etch replicas at various magnifications, to examine thick specimens, to examine stereo pairs of various kinds of tissue with both freeze-etch and thin section preparations, for various applications of histochemistry at various magnifications, to examine thick specimens, and to apply analytical electron microscopy to various tissue systems and in particulate investigations. Specific projects include the following:

Elemental Analysis of Teliospors of Smut Fungi.

Investigations of stereo pairs of biological materials.

Recombination of particles which constitute the photosynthetic apparatus.

Intracellular distribution of trace metals in higher plants.

Analysis of air particulates.

In addition, the article will be used for educational purposes in the following courses:

621 Electron Microscopy—to teach students principles of specimen preparation and handling and electron optics.
622 Electron Microscopy Laboratory—practical application of principles learned in 621.
526 Cell Biology—to teach principles of molecular physiology and ultrastructure of cells, with emphasis upon eucaryotic organisms.

Comments: No comments have been received with respect to this application. Decision: Application approved. No instrument or apparatus of equivalent scientific value to the foreign article, for such purposes as this article is intended to be used, is being manufactured in the United States.

Reasons: The foreign article is equipped with an eucentric goniometer stage which has a ±60 degree tilt. At the time the foreign article was ordered the most closely comparable domestic instrument was the Model EMU–4C available from the Adam David Company. The Department of Health, Education, and Welfare (HEW) advised in its memorandum dated August 17, 1976 that the eucentric goniometer stage of the article is pertinent to the applicant's intended purposes. HEW further advises that the

EMU-4C does not have a scientifically equivalent eucentric goniometer stage. We, therefore, find that EMU-4C is not of equivalent scientific value to the foreign article for such purposes as this article is intended to be used.

The Department of Commerce knows of no other instrument or apparatus of equivalent scientific value to the foreign article, for such purposes as this article is intended to be used, which is being manufactured in the United States.

(Catalog of Federal Domestic Assistance Program No. 11.105, Importation of Duty-Free Educational and Scientific Materials.)

RICHARD M. SEPPA,
Director,
Special Import Program Division.

[FR Doc.76-26300 Filed 9-8-76;8:45 am]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, ET AL.

Notice of Applications for Duty-Free Entry of Scientific Articles

The following are notices of the receipt of applications for duty-free entry of scientific articles pursuant to Section 6(c) of the Educational, Scientific, and Cultural Materials Importation Act of 1966 (Public Law 89-651; 80 Stat. 897). Interested persons may present their views with respect to the question of whether an instrument or apparatus of equivalent scientific value for the purposes for which the article is intended to be used is being manufactured in the United States. Such comments must be filed in triplicate with the Director, Special Import Programs Division, Office of Import Programs, Washington, D.C. 20230, within 20 calendar days after the date on which this notice of application is published in the FEDERAL REGISTER.

Amended regulations issued under cited Act (15 CFR 301) prescribe the requirements applicable to comments.

A copy of each application is on file, and may be examined during ordinary Commerce Department business hours at the Special Import Programs Division, Department of Commerce, Washington, D.C. 20230.

Docket Number: 76-00508. Applicant: DHEW, National Institutes of Health, Laboratory of Biophysics, IRP, NINCDS, Marine Biological Laboratory, L-320, Woods Hole, MA 02543. Article: Ultramicrotome, Model LKB 8800A with Cryokit, Model 14800-1 and accessories. Manufacturer: LKB Produkter AB, Sweden. Intended use of article: The article is intended to be used for studies of the nervous system of several species of invertebrates and vertebrates. Special attention will be given to histochemistry with frozen sections. Investigators will study the subcellular localization of enzymes especially those involved with neurotransmitters metabolism. The distribution of diffusible substances within the cell after being taken up by the cell will also be investigated. Tracing specific synapses and other cell to cell contact with membrane specialization will be conducted after intracellular injection of markers to identified cells. Changes in intracellular spaces and in membrane structure or in membrane interaction between two neighboring cells induced by changes in their biochemical and biophysical environments will also be studied. Application received by Commissioner of Customs: August 12, 1976.

Docket Number: 76-00509. Applicant: Washington State University, Division of Purchasing, Pullman, Washington 99162. Article: Combination PZ 8 Flaker and a PSKM 8 Double Stream Mill (Ring Refiner). Manufacturer: L. Pallman KG, West Germany. Intended use of article: The article is intended to be used in composition board research to prepare particles from various species of wood, types of raw material (chips, shavings, hog trim, sawdust, plywood trim). The objective of this research is to produce 4 times as much product from the same forest base now available. The article will also be used in MSE 550, Parameters for Synthesis of Wood Composition Materials, a course for graduates students covering the theory and practice of wood composite materials and development. Application received by Commissioner of Customs: August 16, 1976.

Docket Number: 76-00510. Applicant: Cornell University Medical College, 525 East 68 Street, New York, New York 10021. Article: Blood Gas Electrode Meter Type D 22- modified for 110 V, 60C current. Manufacturer: L. Escheweiler & Co., West Germany. Intended use of article: The article is a replacement part for an existing blood gas instrument being used for investigation of oxygen and carbon dioxide tension in blood and cerebral spinal fluid. Application received by Commissioner of Customs: August 16, 1976.

Docket Number: 76-00511. Applicant: The University of Iowa, College of Medicine, Department of Physiology & Biophysics, Iowa City, Iowa 52240. Article: Flow scintillation counting system and accessories. Manufacturer: Berthold Instruments, West Germany. Intended use of article: The article is intended to be used for the study of peptide hormones and blood factors. Specifically, the article will be used for determination of the primary sequence of Somantomedian C isolated from human blood plasma which would allow synthesis of large quantities for clinical treatment of patients having growth hormone deficiencies. Application received by Commissioner of Customs: August 18, 1976.

Docket Number: 76-00512. Applicant: State University of New York, Downstate Medical Center, 450 Clarkson Ave., Brooklyn, New York 11203. Article: Superconductive Solenoid, Room Temperature Shim System and Programmed Energization/SC Shim Power Supply. Manufacturer: Canada Superconductor and Cryogenics Company Ltd., Canada. Intended use of article: The article is intended to be used for experiments aimed at detecting internal tumors in the monkey. The objective of this research is to develop a nmr technique that will ultimately detect and non-invasively localize internal tumors in man. Both high resolution nmr experiments utilizing p^{31} as the probe nucleus and relaxation measurements using P^{31}, K^{39}, Na^{23} and H^1 are planned. Application received by Commissioner of Customs: August 18, 1976.

Docket Number: 76-00513. Applicant: University of Georgia—Institute for Natural Products Research, Athens, Georgia 30602. Article: Fourier Transformation NMR Spectrometer System, Model JNM/FX60. Manufacturer: JEOL Ltd., Japan. Intended use of article: The article is intended to be used for the following research projects for which ^1H and ^{13}C nuclear magnetic resonance spectra are of vital significance:

(a) Structure determinations of naturally occurring diterpenoid alkaloids.

(b) Stereochemical assignments in alkaloids.

(c) Structural determinations of di-, sesqui-, and triterpenes.

(d) Structural studies on resin acid degradation products.

(e) Structural studies on pharmacologically active constituents of marsh and beach plants of Georgia and the Southeast.

(f) Synthetic studies on complex alkaloids and terpenes.

(g) Identification and synthesis of theoretically significant naturally occurring substances.

(h) Studies on bis-diterpenoid alkaloids.

(i) Studies on the biogenesis of diterpene alkaloids.

The experiments to be performed with the article all involve pulse (Fourier transform) NMR spectroscopy on proton and carbon nuclei. In addition to recording spectra for determination of structures of natural products and synthetic intermediates, chemical shifts, and homo- and heteronuclear coupling constants, experiments will include the determination of positions and amounts of isotopic labelling (carbon 13), conformational free energies, and occasionally the quantitative analysis of mixtures for determination of optical purities. The educational purposes of the article involve the training of graduate students and postdoctoral associates in the use and applications of ^1H and ^{13}C NMR spectroscopy to chemical problems under study. Application received by Commissioner of Customs: August 18, 1976.

Docket Number: 76-00514. Applicant: Duke University, Department of Chemistry, Durham, North Carolina 27706. Article: Fourier Transformation Nuclear Magnetic Resonance Spectrometer System, Model JNM/FX-60. Manufacturer: JEOL Ltd., Japan. Intended use of article: The article is intended to be used for a broad range of research programs which involve the acquisition of nmr spectra of hydrogen, carbon-13, fluorine and phosphorus nuclei. The materials derived for this study will originate from research programs being conducted in the areas of inorganic, organic physical, analytical and biological chemistry. These research projects will include the following:

(a) Structural Studies of Alkaloids.

(b) Conformational Characteristics of Cyclic Nitrogen and Oxygen Heterocycles.

(c) Biosyntheses of Plant and Fungal Metabolites Using ^{13}C-enriched Precursors.

(d) Synthesis and Stereochemistry of Cyclohexylflurophosphoranes.

(e) Synthesis and Stereochemistry of Silylaminoboranes.

(f) Nuclear Relaxation Studies of Substrate Binding to Cobalt (II) Metalloenzymes.

(g) Development of a-Formyl Ketone Photochemical Annelation. Techniques in Natural Product Synthesis.

(h) Total Synthesis of Tetracyclic Sesquiterpenes.

(i) Total Synthesis of the Alkaloids Derived from *Gelsemien* Species.

(j) Low-temperature ^{13}C-Spectra of Organo-Zinc Compounds.

(k) Correlation of ^{13}C Chemical Shifts with Reaction Rates.

(l) Synthesis and Characterization of Cyano Cobaloximes and Cyanobridged Dicobaloximes.

(m) Structure and Isomerism in Phosphine Complexes of Nickel (II).

(n) Conformational Analysis of Crown Ethers and Their Complexes with Representative and Transition Metal Ions.

(o) Synthesis and Stereochemistry of 14 - and 17 - Phosphasteroids.

(p) Synthesis and Stereochemistry of 7-10 Membered Rings Containing Phosphorous.

(q) Synthesis of Phospholonaphthalenes, Phospholophenanthrenes, Phospholoquinolines, and Selected Heterocyclic Systems.

(r) Phospholane Derivatives with Epoxy and Aziridino Groups for Anticancer Testing.

(s) New Method for Constructing Multicyclic Phosphorus Compounds From 3-Monoalkylamino-2-phospholene Sulfides.

(t) Experimental and Theoretical Investigations of ^{31}P NMR Phenomena.

(u) McCormack Cycloadditions to Variously Substituted 1-Vinyl-cycloalkenes; Effects of Ring-biasing on the Stereochemistry of the Cycloaddition.

(v) Synthesis of Pyrethroids for Agricultural Purposes.

(w) ^{13}C and ^{1}H CIDNP Studies from Radical Pair Reactions.

(x) ^{13}C Studies of Cyclic Peroxides and Hydroperoxides Related to Prostaglandin Endoperoxides.

(y) ^{13}C Studies of Hydrocarbons Formed From Radical Cyclizations.

(z) ^{13}C Studies of Oxidized Phospholipids and Steroids.

The article will also be used for educational purposes in the following courses: (a) Spectral and Structural Study of Organic Compounds—to teach the practical application of various techniques in elucidating molecular structure and (b) Independent Study in Chemistry—to introduce undergraduate students to independent research in chemistry. Application received by Commissioner of Customs: August 18, 1976.

(Catalog of Federal Domestic Assistance Program No. 11.105, Importation of Duty-Free Educational and Scientific Materials.)

RICHARD M. SEPPA,
Director,
Special Import Programs Division.

[FR Doc.76-26304 Filed 9-8-76;8:45 am]

NAVAL REGIONAL MEDICAL CENTER

Notice of Decision on Application for Duty-Free Entry of Scientific Article

The following is a decision on an application for duty-free entry of a scientific article pursuant to Section 6(c) of the Educational, Scientific, and Cultural Materials Importation Act of 1966 (Pub. L. 89-651, 80 Stat. 897) and the regulations issued thereunder as amended (15 CFR 301).

A copy of the record pertaining to this decision is available for public review during ordinary business hours of the Department of Commerce, at the Office of Import Programs, Department of Commerce, Washington, D.C. 20230.

Docket Number: 76-00409. Applicant: Naval Regional Medical Center, Portsmouth, Virginia 23708. Article: Electron Microscope, Model EM 9S-2, and accessories. Manufacturer: Carl Zeiss, West Germany. Intended use of article: The article is intended to be used in conducting the following experiments:

(a) A study of neonatal neural tissue with regard to viral inclusions.

(b) A morphologic study of the development of muscle cells.

(c) "The Origin of Islet-cells in the Pancreas, A Possible Neural Crest Derivative."

(d) "The Nature of the Proliferative Response in Experimental Glomerulonephritis."

(e) "The Occurrence of Nucleolar Caps in Malignant Tumors in Man."

(f) "Classification of Human Leukemias and Lymphomas by Ultrastructural and Immunologic Features."

(g) "An ultrastructural study of the cardiac conducting System in Myocardial Disease."

All of these research projects involve the use of transmission electron microscopy to examine epon-embedded tissue sectioned on an ultramicrotome. The article will also be used for educational purposes in the course Residency in Anatomic and Clinical Pathology in which residents will learn basic EM preparation techniques of biological materials.

Comments: No comments have been received with respect to this application.

Decision: Application approved. No instrument or apparatus of equivalent scientific value to the foreign article, for such purposes as this article is intended to be used, was being manufactured in the United States at the time Customs received the application (May 4, 1976).

Reasons: The foreign article is a relatively simple, easy to operate, medium resolution electron microscope designed for confident use by beginning students with a minimum of detailed programing. The article provides 7 Angstroms point to point resolution, an accelerating voltage of 60 kilovolts (KV), and low distortion magnifications from 140–60,000 × (Magnifications of 140 to 1000 × are within the normal, light microscopic range). Thus the article covers the range of light and electron microscopy. The domestic instrument available at the time Customs received the application was Adam David Company's (AD) Model EMU-4C, a more complex instrument vis a vis the article which provides low distortion magnification at 500 × and higher. The Department of Health, Education, and Welfare (HEW) advises in its memorandum dated August 17, 1976 that quality low magnification performance of the article as well as its simplicity and ease of operation are pertinent to the purposes for which the foreign article is intended to be used. HEW also advises that the EMU-4C is too complex for the applicant's program and does not provide equivalent low magnification performance. Furthermore, HEW advises that AD's Model PA-1 was in a development stage at the time Customs received the application. In this regard, it is noted that a prototype of the PA-1 was first shown by AD in November, 1974. Neither the Department of Commerce nor its consultants have been able to determine or verify the capabilities of the PA-1 as of the date of this decision. Thus, the Department does not have a sufficient basis for ruling that AD was able to supply the PA-1 within a normal delivery time at the time Customs received the application.

We, therefore, find that the Model EMU-4C was not of equivalent scientific value to the foreign article for such purposes as this article is intended to be used at the time Customs received the application.

The Department of Commerce knows of no other instrument or apparatus of equivalent scientific value to the foreign article for such purposes as this article is intended to be used, which was being manufactured in the United States at the time Customs received the application.

RICHARD M. SEPPA,
Director,
Special Import Programs Division.

(Catalog of Federal Domestic Assistance Program No. 11.105, Importation of Duty-Free Educational and Scientific Materials.)

[FR Doc.76-26302 Filed 9-8-76;8:45 am]

STANFORD UNIV.

Notice of Decision on Application for Duty-Free Entry of Scientific Article

The following is a decision on an application for duty-free entry of a scientific article pursuant to Section 6(c) of the Educational, Scientific, and Cultural Materials Importation Act of 1966 (Pub. L. 89-651, 80 Stat. 897) and the regulations issued thereunder as amended (15 CFR 301).

A copy of the record pertaining to this decision is available for public review during ordinary business hours of the

Department of Commerce, at the Office of Import Programs, Department of Commerce, Washington, D.C. 20230.

Docket Number: 76–00404. Applicant: Stanford University, School of Medicine, Room S142, Stanford, California 94305. Article: Nikon Model M inverted microscope and accessories. Manufacturer: Nikon Optical Co., Japan. Intended Use of article: The article is intended to be used for the study of the parasitic disease of man, schistosomiasis to obtain an understanding of the basic mechanisms of host-parasite interactions between the immature stages of the parasites and the fresh-water snails in which they develop. The article will also be used directly in the advanced training of postdoctoral fellows and other students.

Comments: No comments have been received with respect to this application.

Decision: Application approved. No instrument or apparatus of equivalent scientific value to the foreign article, for such purposes as this article is intended to be used, is being manufactured in the United States.

Reasons: The article provides an integrated system for cinephotomicrography. The Department of Health, Education, and Welfare (HEW) advises in its memorandum dated August 17, 1976 that the capability of the article described above is pertinent to the applicant's intended use. HEW also advises that it knows of no domestic instrument which provides the pertinent capability.

The Department of Commerce knows of no other instrument or apparatus of equivalent scientific value to the foreign article, for such purposes as this article is intended to be used, which is being manufactured in the United States.

(Catalog of Federal Domestic Assistance Program No. 11.105, Importation of Duty-Free Educational and Scientific Materials.)

RICHARD M. SEPPA,
Director,
Special Import Programs Division.

[FR Doc.76–26303 Filed 9–8–76;8:45 am]

Economic Development Administration

LOCAL PUBLIC WORKS CAPITAL DEVELOPMENT AND INVESTMENT PROGRAM

Availability of Application Forms

Notice is hereby given that, pursuant to authority contained in section 107 of Title I of the Public Works Employment Act of 1976 (42 USC 6701 *et seq.*), application forms for assistance under the Local Public Works Capital Development and Investment Act of 1976 are now available.

The application forms may be obtained from the Economic Development Administration's (EDA) Regional Offices. The following is a list of EDA Regional Offices.

Atlantic Regional Office, William J. Green, Jr., Federal Building, 600 Arch Street, Room 10424, Philadelphia, Pennsylvania 19106.
Southeastern Regional Office, 1365 Peachtree Street NE., Suite 700, Atlanta, Georgia 30309.
Midwestern Regional Office, 32 West Randolph Street, Room 1025, Chicago, Illinois 60601.
Southwestern Regional Office, 221 West Sixth Street, Suite 600, Austin, Texas 78701.
Rocky Mountain Regional Office, 909 17th Street, Suite 505, Denver, Colorado 80202.
Western Regional Office, 1700 West Lake Avenue, North, Suite 500, Seattle, Washington 98109.

No applications for financial assistance will be accepted until funds to implement the Local Public Works Capital Development and Investment Program have actually been appropriated and apportioned to and made available for use by EDA. EDA will publish notice in the FEDERAL REGISTER in advance of the date on which applications will be accepted.

Dated: September 1, 1976.

J. W. EDEN,
Assistant Secretary
for Economic Development.

[FR Doc.76–26334 Filed 9–8–76;8:45 am]

ELFSKIN CORP.

Petition for a Determination of Eligibility

A petition by Elfskin Corporation, Cherry Valley, Worcester, Massachusetts 01611, a producer of fabric linings and coated materials, was accepted for filing on September 2, 1976, under Section 251 of the Trade Act of 1974 (Pub. L. 93–618). Consequently, the United States Department of Commerce has initiated an investigation to determine whether increased imports into the United States of articles like or directly competitive with those produced by the firm contributed importantly to total or partial separation of the firm's workers, or threat thereof, and to a decrease in sales or production of the petitioning firm.

Any party having a substantial interest in the proceedings may request a public hearing on the matter. A request for a hearing must be received by the Chief, Trade Act Certification Division, Economic Development Administration, U.S. Department of Commerce, Washington, D.C. 20230, no later than the close of business of the tenth calendar day following the publication of this notice.

JACK W. OSBURN,
Chief, Trade Act Certification
Division, Office of Planning
and Program Support.

[FR Doc.76–26335 Filed 9–8–76;8:45 am]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Office of Education

ADVISORY COUNCIL ON FINANCIAL AID TO STUDENTS

Meeting

Notice is hereby given, pursuant to Section 10(a)(2) of the Federal Advisory Committee Act (P.L. 92–463), that the next meeting of the Advisory Council on Financial Aid to Students will be held on September 29 and 30, 1976, from 9:00 a.m. to 5:00 p.m. at the Hyatt Regency Hotel, Washington, D.C.

The Advisory Council on Financial Aid to Students is established under Section 499(a) of the Higher Education Act of 1965, as amended (20 U.S.C. 1089). The Committee shall advise the Commissioner on matters of general policy arising in the administration by the Commissioner of programs relating to financial assistance to students and on the evaluation of the effectiveness of these programs.

The meeting of the Committee shall be open to the public. The proposed agenda includes:

Assignment of work papers to be prepared by Council members on selected topics related to student financial aid. These papers will serve as basis for deliberation during the following meetings of the Council, preparatory to publishing its Third Annual Report to the Commissioner and to Congress.

Records shall be kept of all Committee Proceedings and shall be available for public inspection at the Council's Office located in Room 4931, Regional Office Building No. 3, 7th and D Streets, SW., Washington, D.C. 20202.

Signed in Washington, D.C., on September 2, 1976.

WARREN T. TROUTMAN,
OE Delegate.

[FR Doc.76–26293 Filed 9–8–76;8:45 am]

Office of the Secretary

ASSISTANT SECRETARY FOR ADMINISTRATION AND MANAGEMENT

Statement of Organization, Functions and Delegations of Authority

Part 1 of the Statement of Organization, Functions, and Delegations of Authority of the Department of Health, Education, and Welfare, Office of the Secretary, Office of the Assistant Secretary for Administration and Management, is amended to revise Chapter 1T30, Office of Administration (40 FR 11622), to combine into a single OS headquarters Equal Employment Opportunity Office the responsibilities for all OS headquarters equal employment opportunity programs. The revised Chapter reads as follows:

Section 1T30.10 Organization. Delete: OS Equal Employment Opportunity Staff; OS Federal Women's Program Staff; OS Spanish-Speaking Program Staff.

Add: OS Office of Equal Employment Opportunity.

Section 1T30.20 Functions. Delete: G. OS Equal Employment Opportunity Staff; H. OS Federal Women's Program Staff; I. OS Spanish-Speaking Program Staff and substitute the following new paragraph G, OS Office of Equal Employment Opportunity as follows:

G. *OS Office of Equal Employment Opportunity:* Carries out equal employment opportunity activities within OS headquarters, particularly as they relate to special focus minority groups and women as mandated by Executive Order 11478 and as amended by Pub. L. 92–261 (42

USC 2000 e16), Departmental and Civil Service Commission Regulations which require the establishment and maintenance of a positive program of nondiscrimination in employment based on race, color, religion, sex and national origin. The major functions of the Office (including provisions which focus on the Federal Women's Program and the Spanish-Speaking Program) are:

1. Provide direction and guidance on the EEO system to OS managers and employees at headquarters through development and issuance of directives, instructions, and guidelines.

2. Coordinate and formulate the OS headquarters Affirmative Action Plan; monitor and evaluate efficiency and effectiveness of the Plan.

3. Manages the OS headquarters EEO complaint system and prepares proposed dispositions on all formal complaints; ensures adequacy of counselors and advisors, as well as investigators through training and assignment. Processes discrimination complaints based on age (P.L. 93-259) under Section 713 of the Civil Service Commission's EEO provisions.

4. Maintains surveillance over minority employment data and provides for the analysis and issuance of manpower information relevant to minority, female, and Spanish-Speaking employment profiles through the OS automatic data systems.

5. Develops recommendations of policies and provides direction and guidance on activities related to the status of minorities, women, and Spanish-Speaking persons employed by Office of the Secretary headquarters.

6. Develops and issues guidelines providing technical advice in assuring understanding and positive attitudes toward equal employment opportunities for minorities, women, and Spanish-Speaking persons to OS headquarters managers and employees.

7. Coordinates and provides liaison functions for OS headquarters with organizations at the Departmental level and with other Federal and private agencies having to do with minority group, national women's, and Spanish-Speaking programs to develop awareness of the needs and attitudes of these special focus groups as affected by OS programs and to provide leadership in the creation of quality programs.

8. Analyzes the employment status of minorities, women, and Spanish-Speaking persons at OS headquarters and prepares reports evaluating the effectiveness of the OS Federal Women's and Spanish-Speaking Programs, identifying problems and recommending alternatives.

9. Advises OS headquarters managers in implementing special focus group employment programs, providing guidance in recruitment, training, upward mobility, and career counseling.

10. Counsels minorities, women, and Spanish-Speaking employees in all areas related to their employment and represents the OS headquarters at meetings affecting these groups.

Dated: August 30, 1976.

JOHN OTTINA,
Assistant Secretary for Administration and Management.

[FR Doc.76-26339 Filed 9-8-76;8:45 am]

DEPARTMENT OF HOUSING AND URBAN DEVELOPMENT

Office of Interstate Land Sales Registration

[Docket No. N-76-627]

SWANSBORO COUNTRY

Hearing

In the matter of: Swansboro Country, Richard H. Dyer, President, W & D Investment Company, Inc., OILSR No. 0-4335-04-791, Docket No. 76-207-IS.

Pursuant to 15 U.S.C. 1706(d) and 24 CFR 1720.160(b).

Notice is hereby given that: 1. Swansboro Country, Richard H. Dyer, President, W & D Investment Company, authorized agent and officers, hereinafter referred to as "Respondent," being subject to the provisions of the Interstate Land Sales Full Disclosure Act (Pub. 9-448) (15 U.S.C. 1701 *et seq.*) received a Notice of Proceedings and Opportunity for Hearing issued July 27, 1976, which was sent to the developer pursuant to 15 U.S.C. 1706(d), 24 C.F.R. 1710.45 (b)(1) and 1720.125 informing the developer of information obtained by the Office of Interstate Land Sales Registration alleging that the Statement of Record and Property Report for Swansboro Country, located in El Dorado County, California, contain untrue statements of material fact or omit to state material facts required to be stated therein or necessary to make the statements therein not misleading.

2. The Respondent filed an Answer received August 12, 1976, in response to the Notice of Proceedings and Opportunity for Hearing.

3. In said Answer the Respondent requested a hearing on the allegations contained in the Notice of Proceedings and Opportunity for Hearing.

4. Therefore, pursuant to the provisions of 15 U.S.C. 1706(d) and 24 CFR 1720.160(d), *it is hereby ordered,* That a public hearing for the purpose of taking evidence on the questions set forth in the Notice of Proceedings and Opportunity for Hearing will be held before Judge James W. Mast, in Northern California, at a place to be determined, on October 6, 1976 at 10:00 a.m.

5. The following time and procedure is applicable to such hearing: All affidavits and a list of all witnesses are requested to be filed with the Hearing Clerk, HUD Building, Room 10150, Washington, D.C., 20410 on or before September 8, 1976.

6. The Respondent is hereby notified that failure to appear at the above scheduled hearing shall be deemed a default and the proceedings shall be determined against Respondent, the allegations of which shall be deemed to be true, and an order Suspending the Statement of Record, herein identified, shall be issued pursuant to 24 CFR 1710.45(b)(1).

This Notice shall be served upon the Respondent forthwith pursuant to 24 CFR 1720.440.

By the Secretary.

Dated: August 20, 1976.

JAMES W. MAST,
Administrative Law Judge.

[FR Doc.76-26357 Filed 9-8-76;8:45 am]

Office of Assistant Secretary for Housing Management

[Docket No. D-76-456]

REGIONAL ADMINISTRATORS ET AL.

Redelegation of Authority With Respect to Loan and Contract Servicing

The Redelegation of Authority to Regional Administrators et al. with respect to Loan and Contract Servicing published at 35 FR 16104, October 14, 1970, as amended, is further amended as follows:

In section A, paragraph 2 is revised to read as follows:

"2. Each Regional Administrator, Deputy Regional Administrator, Area Director, Deputy Area Director, Insuring Office Director, and Insuring Office Deputy Director is authorized to approve the deferment of principal for insured project mortgages subsequent to final endorsement and to endorse that approval on modification agreements by the mortgagor and mortgagee."

(Secretary's delegation of authority to redelegate published at 36 FR 5005, March 16, 1971.)

Effective date. This amendment to redelegation of authority is effective on September 9, 1976.

JAMES L. YOUNG,
Assistant Secretary for Housing-Federal Housing Commissioner.

[FR Doc.76-26356 Filed 9-8-76;8:45 am]

DEPARTMENT OF TRANSPORTATION

Federal Aviation Administration

AIR TRAFFIC PROCEDURES ADVISORY COMMITTEE

Meeting

Pursuant to section 10(a)(2) of the Federal Advisory Committee Act (Pub. L. 93-463; 5 U.S.C. App. I) notice is hereby given of a meeting of the Federal Aviation Administration Air Traffic Procedures Advisory Committee to be held October 12 through October 15, 1976, from 9 a.m. E.D.T. to 4 p.m. daily, except for the last day which will terminate at 1 p.m., in conference rooms 7A and B at FAA Headquarters, 800 Independence Ave., SW., Washington, D.C.

The agenda for this meeting is as follows: A continuation of the Committee's

review of present air traffic control procedures and practices for standardization, clarification, and upgrading of terminology and procedures.

Attendance is open to the interested public but limited to the space available. With the approval of the Chairman, members of the public may present oral statements at the meeting. Persons wishing to attend and persons wishing to present oral statements should notify, not later than the day before the meeting, and information may be obtained from, Mr. Franklin L. Cunningham, Executive Director, Air Traffic Procedures Advisory Committee, Air Traffic Service, AAT-300, 800 Independence Ave., SW., Washington, D.C. 20591, telephone (202) 426-3725.

Any member of the public may present a written statement to the Committee at any time.

Issued in Washington, D.C., on August 27, 1976.

F. L. CUNNINGHAM,
Executive Director, ATPAC.

[FR Doc.76-26292 Filed 9-8-76;8:45 am]

Federal Aviation Administration

RADIO TECHNICAL COMMISSION FOR AERONAUTICS (RTCA) EXECUTIVE COMMITTEE

Meeting

Pursuant to section 10(a)(2) of the Federal Advisory Committee Act (Pub. L. 92-463; 5 U.S.C. App. I) notice is hereby given of a meeting of the RTCA Executive Committee to be held September 24, 1976, RTCA Conference Room 261, 1717 H Street, N.W., Washington, D.C., 20006, commencing at 9:30 a.m. The agenda for this meeting is as follows: (1) Approval of Minutes of 7-23-1976 meeting; (2) Special Committee Activities Report for July-August 1976; (3) Chairman's Report of RTCA Administration and Activities; (4) Report of RTCA MOC/MPS Informal Review Group; (5) Consideration of establishing additional Special Committees.

Attendance is open to the interested public but limited to the space available. With the approval of the Chairman, members of the public pay present oral statements at the hearing. Persons wishing to attend and persons wishing to present oral statements should notify, not later than the day before the meeting, and information may be obtained from RTCA Secretariat, 1717 H Street, N.W., Washington, D.C. 20006; (202) 296-0484.

Any member of the public may present a written statement to the Committee at any time.

Issued in Washington, D.C., on August 23, 1976.

KARL F. BIERACH,
Designated Officer.

[FR Doc.76-26143 Filed 9-8-76;8:45 am]

Office of Hazardous Materials Operations

HAZARDOUS MATERIALS REGULATIONS EXEMPTIONS

Notice of Grants and Denials of Applications for Exemptions

In accordance with the procedures governing the application for, and the processing of, exemptions from the Department of Transportation's Hazardous Materials Regulations (49 CFR Part 107, Subpart B), notice is hereby given of the exemptions granted July 1976. The modes of transportation involved are identified by a number in the "Nature of Exemption Thereof" portion of the table below as follows: (1) Motor vehicle, (2) Rail freight, (3) Cargo vessel, (4) Cargo-only aircraft, (5) Passenger-carrying aircraft.

Application numbers prefixed by the letters EE represent applications for Emergency Exemptions.

Application No.	Exemption No.	Applicant	Regulation(s) affected	Nature of exemption thereof
		GRANTS		
4108-X	DOT-E 4108	Southern Oxygen Supply Co., Atlanta, Ga.	49 CFR 172.5, 173.315(a).	To become a party to exemption No. 4108. (See application No. 76-288.) (Mode 1.)
4666-X	DOT-E 4666	American Cyanamid Co., Wayne, N.J.	49 CFR 173.377(a)(1), 178.205-17.	To allow a net weight increase of a class B poison packed in inside DOT-2D bags overpacked in DOT-12B fiberboard boxes closed by tape not less than 2 inches wide. (Modes 1 and 2.)
5167-X	DOT-E 5167	Chemagro Agricultural Division, Mobay Chemical Corp., Kansas City, Mo.	49 CFR 173.377(b); 46 CFR 146.25-200.	To ship a poisonous solid, class B in various DOT-2D/12B combination packages. (Modes 1, 2, and 3.)
5662-X	DOT-E 5662	Great Lakes Chemical Co., El Dorado, Ark.	49 CFR 173.353(a), 173.401(a)(1); 46 CFR 146.25-200.	To become a party to exemption 5662. (See application No. 76-158.) (Modes 1, 2, and 3.)
75-160	DOT-E 5719	Platte Chemicals Co., Greeley, Colo.	49 CFR 173.377(i)(1); 46 CFR 146.25-200.	To become a party to exemption 5719. (See applications Nos. 76-221 and 76-349.) (Modes 1, 2, and 3.)
76-47	DOT-E 5854	Sea-Land Service, Inc., Elizabeth, N.J.	46 CFR 146.21-100, 146.26-100; 49 CFR pt. 173.	To ship flammable and combustible liquids in intermodal portable tanks complying with DOT specification MC-306 with certain exceptions. (Modes 1, 2, and 3.)
76-391	DOT-E 6039	Cosden Oil & Chemical Co., Calumet City, Ill.	49 CFR 172.5, 173.315(a).	To ship liquefied ethylene in a non-DOT specification insulated cargo tank. (Mode 1.)
6258-X, 76-249.	DOT-E 6258	Lehigh Valley Chemical Co., Easton, Pa.	49 CFR 173.119(a)(23).	To ship acetone in a DOT specification 12A fiberboard box with inside DOT-2E polyethylene bottles. (Modes 1 and 2.)
6258-P	DOT-E 6258	J. T. Baker Chemical Co., Phillipsburg, N.J.	49 CFR 173.119(a)(23).	To become a party to exemption 6258. (See applications Nos. 6258-X, 76-249, and 76-394.) (Modes 1 and 2.)
76-160	DOT-E 6464	American LNG Co., Oak Brook, Ill.	49 CFR 172.5, 173.315(a).	To ship LNG and liquefied ethylene in a non-DOT specification cargo tank. (Mode 1.)
75-328	DOT-E 6464	New Bedford Gas & Edison Light Co., New Bedford, Mass.		
76-316	DOT-E 6464	El Paso Products Co., Odessa, Tex.		
76-114	DOT-E 6464	James Russell Engineering Works, Inc., Boston, Mass.		
6498-X	DOT-E 6498	Luxfer USA Ltd., Riverside, Calif.	49 CFR 173.302(a)(1), 173.304(a)(1) and (d)(3), 173.336(a)(2), 173.337(a)(1).	To ship liquefied and nonliquefied compressed gases, and certain other hazardous materials in non-Dot specification seamless, high pressure aluminum cylinders. (Modes 1, 2, 3, and 4.)
6519-X	DOT-E 6519	Hercules, Inc., Wilmington, Del.	49 CFR 173.53(e)(4)	To ship a propellant explosive, liquid, class B in an insulated DOT specification MC-307 and MC-312 stainless steel cargo tanks. (Mode 1.)
6765-X	DOT-E 6765	Union Carbie Corp., Murray Hill, N.J.	46 CFR 146.24-100; 49 CFR 172.5, 173.315.	To become a party to exemption 6765. (See application No. 76-269.) (Modes 1 and 3.)
75-62	DOT-E 6787	Advanced Chemical Technology, City of Industry, Calif.	49 CFR 173.119 (a) and (b), 173.346(a), 173.357(b), 173.358(a), 173.359 (a) and (b); 46 CFR 146.21-100, 146.23-100, 146.25-200.	To authorize DOT-34 polyethylene containers for shipment of class B poisonous liquids, flammable liquids and corrosive liquids. (Modes 1, 2, and 3.)
76-162	DOT-E 6824	Bio-Lab, Inc., Decatur, Ga.	49 CFR 173.217(a)	To ship certain oxidizing materials in a specially designed polyethylene bottles overpacked in non-DOT specification fiberboard boxes. (Modes 1 and 2.)
7007-X	DOT-E 7007	Jones Chemicals, Inc., Caledonia, N.Y.; Allied Chlorine and Chemical Pro., Inc., Miami, Fla.; Dixie Chemical Co., Houston, Tex.	49 CFR 173.314(c); 46 CFR 146.24-100.	To ship chlorine in specially designed DOT specification 110A500W tanks for export only. (Modes 1 and 3.)

Application No.	Exemption No.	Applicant	Regulation(s) affected	Nature of exemption thereof
7025-P	DOT-E 7025	Air Products & Chemicals, Allentown, Pa.	49 CFR 172.5, 173.315(a)(1).	To become a party to exemption 7025. (See applications Nos. 76-355, 75-115.) (Mode 1.)
7060-X	DOT-E 7060	Federal Express Corp., Clarksville, Md.	49 CFR 103.19(b), 103.23.	To become a party to exemption 7060. (See application No. 76-293.) (Mode 4.)
7233-X	DOT-E 7233	TMT Trailer Ferry, Inc., Jacksonville, Fla.	46 CFR 146.27-30 (d)(2)(i), 146.27-30 (d)(2)(ii); 49 CFR 173.120.	To waive certain operational requirements pertaining to motor vehicles containing fuel on unmanned barges. (Mode 3.)
76-75	DOT-E 7277	Structural Composities Industries, Inc., Azusa, Calif.	49 CFR 173.302(a)(1)	To authorize shipment of compressed air in non-DOT specification filament-wound reinforced plastic (FRP) aluminum lined cylinders. (Modes 1, 2, 3, 4, and 5.)
76-371	DOT-E 7283	Shipley Co., Inc., Newton, Mass.	49 CFR 173.249(a)	To ship caustic soda, liquid in a DOT specification 57 portable tank. (Mode 1.)
76-369	DOT-E 7284	Virginia Chemical Co., Portsmouth, Va.	49 CFR 173.249(a)(6)	To ship alkaline corrosive liquids, n.o.s. in a DOT specification MC-303 cargo tank. (Mode 1.)
76-282	DOT-E 7287	Erco Inc. Ltd., Canada, (Breit & Garcia Naval Architects, New Orleans, La.).	46 CFR 146.22-100	To authorize stowage of drums of elemental phosphorus under deck. (Mode 3.)
7408-N	DOT-E 7408	Aerojet Solid Propulsion Co., Sacramento, Calif.	46 CFR 146.20-200	To authorize commercial shipment of rocket motors, class B explosives in non-DOT specification plywood boxes. (Mode 3.)
7428-N	DOT-E 7428	United States Steel Corp., McKeesport, Pa.	49 CFR 173.302(a)(3)	To authorize shipment of certain flammable and nonflammable compressed gases in 3 non-DOT specification seamless wire hoop-wrapped steel cylinders complying with DOT specification 3AAX1800 except for marking.
7436-N	DOT-E 7436	Hooker Chemicals & Plastics Corp., Niagara Falls, N.Y.	46 CFR 146.27-100	To ship ferrophosphorus in non-DOT specification fiber drums loaded in containers. (Mode 3.)
7443-N	DOT-E 7443	The Carborundum Co., Newark, N.J.	49 CFR 178.340-5	To ship waste corrosive liquids, n.o.s. in a non-DOT specification teflon-lined cargo tank conforming with DOT specification MC-312 except for head attachment. (Mode 1.)
7444-N	DOT-E 7444	El Paso Products Co., Odessa, Tex.; New Bedford Gas & Edison Light Co., New Bedford, Mass.; James Russell Engineering Works, Boston, Mass.	49 CFR 172.5, 173.315(a).	To ship certain flammable cryogenic liquids in a non-DOT specification cargo tank. (Mode 1.)
7460-N	DOT-E 7460	Fabricated Metals, Inc., San Leandro, Calif.; Boeing Aircraft Co., Seattle, Wash.	49 CFR 173.119	To ship methyl ethyl ketone and toluol in a DOT specification 57 portable tank. (Mode 1.)
7461-N	DOT-E 7461	Ethyl Corp., Baton Rouge, La.	49 CRF 172.5, 173.315(a).	To ship hydrogen chloride, anhydrous in a non-DOT specification cargo tank. (Mode 1.)

EMERGENCY EXEMPTION

EE7233	DOT-E 7233	TMT Trailer Ferry, Inc., Jacksonville, Fla.	46 CFR 146.27-30	To transport motor vehicles containing fuel on unmanned barges with certain operational requirements are waived. (Mode 3.)

DENIALS

76-112 Request by American Hoechst Corp., Sommerville, N.J.—To ship various hazardous materials in drums complying with DOT Specification 37A except for markings, denied July 12, 1976.

76-300 Request by BASF Wyandotte Corp., Parsippany, N.J.—To renew SP 6700 authorizing shipment of flammable liquids, n.o.s. in non-DOT specification drums, denied July 14, 1976.

76-372 Request by Bayvet Corporation, Shawnee Mission, Kan.—To ship a 52 percent concentration of organic phosphate compound dry in DOT Specification 21C fiber drums, described as "Drugs, Chemicals, Medical or Cosmetics, n.o.s., Solid," denied July 28, 1976.

76-387 Request by Beech Aircraft Corp., Wichita, Kan.—To transport nonspillable aircraft batteries in excess of fifty pounds in an inaccessible cargo pit of any aircraft, denied July 2, 1976.

76-396 Request by Mobil Chemical Company, Richmond, Va.—To amend U.S. Coast Guard SP 43-71 to allow carriage of phosphorus oxychloride in specially designed portable tanks, denied July 7, 1976.

7007-X Request by Trinity Industries, Inc., Dallas, Texas—To authorize domestic shipments of chlorine in DOT Specification 110A500W tanks, denied July 9, 1976.

7408-N Request by Aerojet Solid Propulsion Co., Sacramento, Calif.—For priority exemption to make commercial shipment of rocket motors Class B, explosives in military specification plywood boxes, denied June 24, 1976.

7484-X Request by Trans-World Airlines, Inc., Kansas City, Mo.—To renew FAA Exemption 2169 authorizing the transportation of non-spillable electric storage batteries in an inaccessible cargo pit or bin, denied July 15, 1976.

7485-N Request by Technicon Instruments Corp., Tarrytown, N.Y.—To comingle packages of poisons and corrosives in the same sea container, denied July 15, 1976.

7486-N Request by Browning Chemical Corp., New York, N.Y.—To ship calcium hypochlorite in foreign-made drums complying with DOT Specification 37A except for markings, denied July 8, 1976.

EE7488-N Request by Mr. Michael Goldhammer, Portland, Ore.—For an emergency exemption to carry as carry-on baggage, his battery-powered wheelchair aboard a passenger-carrying aircraft, denied July 16, 1976.

ALAN I. ROBERTS,
Director, Office of Hazardous Materials Operations.

[FR Doc.76-26378 Filed 9-8-76;8:45 am]

Office of Pipeline Safety Operations

[Docket No. 76-10W]

TRANS-ALASKA CRUDE OIL PIPELINE

Grant of Waiver

By letter dated March 19, 1976, the Alyeska Pipeline Service Company (Alyeska) requested a waiver from compliance with the welding requirement of 49 CFR 195.218 with respect to girth weld No. 49344T at the completed Jim River Crossing No. 2 on the Trans-Alaska crude oil pipeline. This girth weld serves to tie-in two sections of 48-inch concrete coated pipe in the 620-foot crossing. Section 195.218 requires that longitudinal weld seams on adjacent length of pipe must be offset. However, at weld No. 49344T, the seams on adjacent pipe lengths are abutting, not "offset" as required.

In requesting the waiver, Alyeska asserted that "there are no metallurgical or safety reasons for offsetting longitudinal seams on liquid pipelines." As further support for the waiver, Alyeska submitted that at the factory in Japan each seam had been ultrasonically inspected over its entire length and radiographed for a distance of eight inches from each end. Also, Alyeska said the girth weld was radiographically tested in the field and found acceptable under the standards of API Standard 1104 (1973 ed.), which are incorporated by reference in 49 CFR 195.228. Alyeska further stated that the entire crossing was hydrostatically tested to at least 1152 psi, or 92 percent of specified minimum yield strength (SMYS), and that the operating pressure at the weld is not to exceed 750 psi, or 60 percent of SMYS. (To meet the requirements of 49 CFR 195.302, the crossing must be tested again for 24 hours before being placed in operation.)

After reviewing the information and arguments presented by Alyeska, the Office of Pipeline Safety Operations (OPSO) denied the waiver request by letter dated August 6, 1976. The request was denied because Alyeska did not convincingly demonstrate that offseting of seams is not necessary for safety at weld No. 49344T. OPSO stated that even though the pressure and weld test data indicate an absence of unacceptable defects, "the data do not demonstrate that the concentration of stresses at the intersection of welds would not eventually be detrimental to the (girth) weld strength, which is what Section 195.218 is intended to prevent." Nevertheless, Alyeska was afforded an opportunity to submit a petition for reconsideration based on additional information about the safety of the girth weld and reasons

why compliance with Section 195.218 would not be in the public interest.

On August 12, 1976, Alyeska submitted a petition for reconsideration. In its petition, Alyeska argues that because of the excellent notch toughness properties of the pipe and girth weld materials at weld No. 49344T, even the presence of surface flaws would not be a problem at the intersection of welds and thus a fracture would not result from the cyclic loading to which the pipe and girth weld materials will be subject. Alyeska further argues that the very small difference between material properties of the girth weld metal and pipe metal minimizes the opportunity for stress concentrations in the weld or heat affected zone, and that any strain in these areas would be accommodated by the ductility of the surrounding material.

In addition, Alyeska alleges that compliance with Section 195.218 would not be in the public interest because of the environmental disturbances that would occur if the weld must be replaced. Alyeska states that replacement would entail excavation to at least 30 feet below the water table with consequent silting and adverse effects on stream flow. According to Alyeska, the results would be harmful to the eggs and fry of the large fish population of the Jim River and to the river's use as a fishery.

On August 13, 1976, OPSO asked Alyeska to supplement its petition with data on the mechanical properties of the girth weld and pipe materials. The requested data indicates that the mechanical properties of elongation, hardness, and fracture toughness (as evidenced by high Charpy V-Notch energy levels at low temperatures) greatly exceed the pipeline's specifications for sound ductile welds. The data further indicates that the pipe and girth weld materials have similar tensile and notch toughness properties.

Additionally, OPSO discussed the welding problem with welding engineering experts outside the Government. In the opinion of these experts, the strength of the weld would not be reduced by the abutting longitudinal seams. The experts also agreed that replacement of the weld at its underwater location could reduce the pipeline's integrity, particularly in view of the apparently high quality of the existing weld. The latter opinion is premised by the many difficulties associated with properly replacing an existing girth weld under adverse working conditions.

Finally, OPSO asked the Department's welding/radiographic experts in Alaska to examine the radiograph of weld No. 49344T to determine the condition of the weld. The experts reported that the weld is of very high quality and exceeds the standards of acceptability under Sec. 6 of API Standard 1104 as incorporated by reference in 49 CFR 195.228.

The Materials Transportation Bureau (MTB) has reviewed the additional information and arguments submitted by Alyeska in connection with its petition for reconsideration. Based on that review and other relevant considerations, MTB finds that the requested waiver is not inconsistent with pipeline safety and is in the public interest. The reasons for this decision are:

1. The girth weld exceeds the standards of acceptability in Sec. 6 of API Standard 1104 and does not contain any weld defect which might grow to an unacceptable level under cyclic loadings.

2. The ductility of the pipe and girth weld metals would provide for localized yielding where high residual stresses may exist and thereby prevent fracture initiation and failure of the weld. (Section 195.218 was adopted when pipe and weld materials in general use were less ductile than the materials at weld No. 49344T.)

3. The similarity of mechanical properties between the girth weld and pipe metals minimizes the likelihood of any concentration of residual stresses existing at the intersection of welds and surrounding heat-affected zone.

4. The fact that the longitudinal seams are ground flush with the inside pipe circumference at the joint mitigates the likelihood of any concentration of residual stresses caused by excess metal at the intersection of welds. (The longitudinal seams were ground flush with the inside circumference at pipe ends when the pipe was manufactured to accommodate an internal line-up clamp during welding.)

5. Replacing weld No. 49344T to comply with Section 195.218 could reduce the pipeline's integrity because of the difficulties in cutting out a segment of the concrete coated crossing and rotating and realigning it, especially in view of the adversities of working in a 30-foot excavation in a river crossing.

Accordingly, effective immediately, Alyeska is hereby granted a waiver from compliance with 49 CFR 195.218 with respect to weld No. 49344T at the Jim River Crossing No. 2 on the Trans-Alaska crude oil pipeline.

(Sec. 6, Pub. L. 89-670, 80 Stat. 937 (49 USC 1655); (18 USC 831-835); 40 FR 43901, 49 CFR 1.53.)

Issued in Washington, D.C. on September 1, 1976.

JAMES T. CURTIS, Jr.,
Director,
Materials Transportation Bureau.

[FR Doc.76-26209 Filed 9-8-76;8:45 am]

National Highway Traffic Safety Administration

[Docket No. EX75-4; Notice 3]

C. H. WATERMAN INDUSTRIES

Petition for Temporary Exemption From Federal Motor Vehicle Safety Standard

C. H. Waterman Industries of Athol, Massachusetts, has petitioned for a 2-year exemption from S7.1.1 of Motor Vehicle Safety Standard No. 208, for an electric powered passenger car on grounds that it would facilitate the development and field evaluation of a low-emission motor vehicle.

Waterman has previously been granted an exemption expiring May 1, 1977, from all or a portion of 15 Federal motor vehicle safety standards, for a European passenger car that it converts to electric propulsion (40 FR 24549). Thus far the company has imported seven such vehicles for tests, and none have been sold for public use. Waterman's current petition states that it has experienced difficulty in locating passenger restraint systems that incorporate "automatic and/or emergency locking and adjusting features" which, it says, must be designed "in conjunction with the design of the vehicle structure in order to integrate the two in a practicable manner." Waterman has not found it possible to date to install in its automobile a restraint system of the sort required by Standard No. 208 since January 1972.

Petitioner argues that the exemption will not unreasonably degrade the safety of the vehicle as it will be equipped with non-retractable Type 2 belt systems in the front seats, and Type 1 lap belts in the rear offering protection equivalent to conforming systems. Waterman argues that it is in the public interest to develop its alternative to the internal combustion engine "despite the small inconveniences of a manually adjusted restraint system."

This notice of receipt of a petition for temporary exemption is published in accordance with the NHTSA regulations on this subject (49 CFR 555.7), and does not represent any agency decision or other exercise of judgment concerning the merits of the petition.

Interested persons are invited to submit comments on the petition of C. H. Waterman Industries, described above. Comments should refer to the docket number and be submitted to: Docket Section, National Highway Traffic Safety Administration, Room 5108, 400 Seventh Street, SW., Washington, D.C. 20590. It is requested but not required that 10 copies be submitted.

All comments received before the close of business on the comment closing date indicated below will be considered. The application and supporting materials and all comments received after the closing date will also be filed and will be considered to the extent possible. If the petition is granted, notice will be published in the FEDERAL REGISTER pursuant to the authority indicated below.

Comment closing date: October 12, 1976.

Proposed effective date: Date of issuance of exemption.

(Sec. 3, Pub. L. 92-548, 86 Stat. 1159 (15 U.S.C. 1410); delegations of authority at 49 CFR 1.50 and 49 CFR 501.8.)

Issued on September 3, 1976.

ROBERT L. CARTER,
Associate Administrator,
Motor Vehicle Programs.

[FR Doc.76-26404 Filed 9-8-76;8:45 am]

CIVIL AERONAUTICS BOARD

AIR NEW ENGLAND, INC.

Meeting

Notice is hereby given that a presentation will be made by Air New England,

Inc., on Thursday, September 23, 1976, at 10:00 a.m. (local time), in Room 1027, Universal Building, 1825 Connecticut Avenue, N.W., Washington, D.C., regarding the status of the carrier as a result of the recent change in its management.

Dated at Washington, D.C., September 3, 1976.

PHYLLIS T. KAYLOR,
Secretary.

[FR Doc.76-26334 Filed 9-8-76;8:45 am]

THE FLYING TIGER LINE INC.

Meeting

Notice is hereby given that a presentation will be made by The Flying Tiger Line Inc., on Wednesday, September 22, 1976, at 10:00 a.m. (local time), in Room 1027, Universal Building, 1825 Connecticut Avenue, NW., Washington, D.C., regarding the marketing study made by the carrier.

Dated at Washington, D.C., September 3, 1976.

PHYLLIS T. KAYLOR,
Secretary.

[FR Doc.76-26345 Filed 9-8-76;8:45 am]

[Docket 27813; Agreement C.A.B. 26064 R-1 through R-15; Order 76-8-147]

INTERNATIONAL AIR TRANSPORT ASSOCIATION

North/Central Pacific Passenger Fares

Issued under delegated authority August 27, 1976.[1]

An agreement has been filed with the Board pursuant to section 412(a) of the Federal Aviation Act of 1958 (the Act) and Part 261 of the Board's Economic Regulations between various air carriers, foreign air carriers, and other carriers embodied in the resolutions of the Traffic Conferences of the International Air Transport Association (IATA). The agreement, establishing North/Central Pacific fares from October 1, 1976 through March 31, 1977, was adopted at a conference held in New York on June 3-4, 1976.

As set forth in the attached appendices, Tokyo-Honolulu/west coast fares would take increases ranging from 3 to 19 percent. Normal economy fares would increase 3 percent and first-class and most promotional fares would increase 5 percent. However, the affinity group fare for 100 or more persons, available only for U.S. originations, would increase by 10 percent and the basic season group inclusive tour (GIT) fare would increase by 14 to 19 percent. Fares to other Far Eastern destinations would, in general, remain at present levels except that first-class fares would increase 4 percent and the basic season GIT fare would increase up to 7 percent.

Most fares from Anchorage would also remain at present levels except first-class, basic season GIT, and affinity group 100 fares to Japan which would increase 4, 7 and 10 percent, respectively.

[1] Appendices filed as part of the original document.

Two new 30/120-day excursion fare plans are proposed: one for round-trip travel eastbound from various Asian points (other than Japan) to the Western Hemisphere, and a second for round-trip travel westbound from Canada to similar Asian destinations but at lower levels than those proposed for eastbound travel.

Lastly, the agreement would remove stopover restrictions on use of GIT fares and would permit passengers using this fare to return individually from their last point of embarkation in Asia to their point of origin in the Western Hemisphere.[2]

The purpose of this order is to establish procedural dates for the submission of carrier justification in support of the agreement and comments from interested persons. The carriers' justifications should be set out in the tabular format suggested in Order 75-7-88, July 17, 1975, with historical data as reported to the Board in Form 41 reports by functional account for total transpacific services for the 12 month period ended June 30, 1976, adjusted to exclude market areas not covered by the agreement, e.g. South Pacific, and all scheduled cargo and charter operations pertaining to the North/Central Pacific market so as to establish the present economic status of scheduled passenger services in the North/Central Pacific market area covered by the agreement. The carriers will also be expected to include a forecast for the year ending September 30, 1977, both including and excluding the increased fares for which approval is sought. The carriers are expected to allocate costs between the passenger and cargo compartments of scheduled passenger aircraft by the "space method" stipulated by the Board in its April 2, 1970 decision in Docket 18381, Nonpriority Mail Rates, Orders 70-4-9 and 70-4-10.[3] In addition the carriers are required to submit detailed traffic data showing revenue passenger miles and revenue by specific fare category as well as capacity and load factor information both for the historical period and for the forecast period and including and excluding the increased fares for which approval is sought.

Northwest Airlines, Inc., a non-IATA carrier, will be required to file data similar to that required of the IATA carriers so that a full economic picture of U.S. carrier operations in the area under consideration may be obtained in order that the Board may be in a position to make a meaningful evaluation in its disposition of the agreement.

Accordingly, IT IS ORDERED THAT:

1. All United States air carrier members of the International Air Transport Association providing North/Central Pacific combination service shall file, within 15 calendar days after the date of service of this order, full documentation and economic justification for the fares and related conditions embodied in the subject agreement;

2. Northwest Airlines, Inc. shall file within 15 calendar days after the date of service of this order, data similar to that required of the IATA carriers;

3. Comments and objections from interested persons and parties shall be submitted within 15 calendar days after the date of service of this order;

4. Replies to submissions received in response to ordering paragraphs 1 and 2 above and replies to comments received pursuant to ordering paragraph 3 above shall be submitted within 25 calendar days after the date of service of this order; and

5. Insofar as air transportation as defined by the Act is concerned, tariffs implementing the subject agreement shall not be filed in advance of Board action on the subject agreement.

This order will be published in the FEDERAL REGISTER.

By James L. Deegan, Chief, Passenger and Cargo Rates Division, Bureau of Economics.

PHYLLIS T. KAYLOR,
Secretary.

[FR Doc.76-26347 Filed 9-8-76;8:45 am]

[Docket 21162]

OHIO/INDIANA POINTS NONSTOP SERVICE INVESTIGATION

Notice of Postponement and Rescheduling of Hearing

Notice is hereby given, pursuant to the provisions of the Federal Aviation Act of 1958, as amended, that the hearing in the above-entitled proceeding presently scheduled to be held on September 30, 1976 (41 F.R. 36537, August 30, 1976) in Columbus, Ohio and then to reconvene on October 5, 1976 in Washington, D.C., is hereby postponed to October 13, 1976 at 10:00 a.m. (local time) in Room 1003, Hearing Room A, Universal Building North, 1875 Connecticut Avenue NW., Washington, D.C.

The entire hearing will be held at the above time and place in Washington, D.C., and the Columbus, Ohio portion of the hearing is hereby cancelled.

Dated at Washington, D.C., September 2, 1976.

WILLIAM H. DAPPER,
Administrative Law Judge.

[FR Doc.76-26346 Filed 9-8-76;8:45 am]

COMMITTEE FOR THE IMPLEMENTATION OF TEXTILE AGREEMENTS

ESTABLISHMENT OF EXPORT VISA REQUIREMENT AND CERTIFICATION FOR EXEMPT TEXTILE PRODUCTS FROM THE REPUBLIC OF THE PHILIPPINES

AUGUST 31, 1976.

Under the terms of the Bilateral Cotton, Wool and Man-Made Fiber Textile

[2] The agreement also incorporates revisions to existing special fares available only for traffic originating in Japan reflecting an agreement reached by Japan Air Lines Company, Ltd., Northwest Airlines, Inc. and Pan American World Airways, Inc. in discussions held during March 1976 as authorized by the Board in Order 76-3-95, March 15, 1976.

[3] In furnishing the data requested, each carrier should provide complete explanatory notes and supporting detail including statistical data to describe the methods used in making the allocations.

Agreement of October 15, 1975, between the Governments of the United States and the Republic of the Philippines, the Government of the Republic of the Philippines has undertaken to limit its exports of cotton, wool and man-made fiber textile products to the United States to certain designated levels. Pursuant to this agreement, the Government of the United States and the Republic of the Philippines have established an administrative mechanism to preclude circumvention of the licensing system for exports to the United States of cotton, wool and man-made fiber textile products, produced or manufactured in the Republic of the Philippines. The two governments have also agreed to establish an administrative mechanism to exempt from the levels of restraint of the bilateral agreement: (1) shipments of cotton, wool and/or man-made fiber textile products valued under $250; (2) handmade cottage industry products of handloomed fabrics; and (3) traditional Philippine folklore handicraft textile products.

Effective on October 10, 1976, entry into the United States for consumption and withdrawal from warehouse for consumption of any cotton, wool or man-made fiber textile products, produced or manufactured in the Republic of the Philippines and exported on and after that date for which the Government of the Republic of the Philippines has not issued an appropriate export visa or certification for exemption, will be prohibited.

Application of these requirements to cotton, wool and man-made fiber textile products exported prior to October 10, 1976, is to become effective on December 9, 1976.

The export visa will be a circular stamp in blue ink on the front of the invoice (Special Customs Invoice Form 5515, successor document, or commercial invoice when such form is used) and will include the signature and title of an official authorized by the Government of the Philippines to issue visas.

Cotton, wool and/or man-made fiber textile products that are to be exempted from the levels of restraint of the bilateral agreement shall be accompanied by a certification issued by the Government of the Republic of the Philippines. The certification will be a rectangular stamp in blue ink on the front of the invoice (Special Customs Invoice Form 5515, successor document, or commercial invoice, when such form is used) and will include the signature and title of the official authorized to issue the certification; identify the items exempted; indicate the date the certification was signed and certified; and carry the certificate number. In the space marked "Description" on the certification stamp, the Government of the Republic of the Philippines will indicate that the shipment is either valued at less than $250; is a handmade cottage industry product of handloomed fabric; or will name the particular Philippine traditional folklore product listed in the attachment of this notice. An export visa will not be required to accompany shipments of exempt items.

Copies of the export visa and certification stamps are published as enclosures to the letter set forth below. The following officials have been authorized by the Government of the Republic of the Philippines to issue visas and certifications:

Alfredo Pio de Roda, Jr.
Woodrow S. Burgos
Eduardo G. Sanchez
Alicia L. de la Cruz

Interested parties are advised to take all necessary steps to insure that cotton, wool and man-made fiber textile products, produced or manufactured in the Republic of the Philippines, which are to be entered into the United States for consumption or withdrawn from warehouse for consumption will meet the stated visa and certification requirements.

There is published below a letter of August 31, 1976 from the Chairman of the Committee for the Implementation of Textile Agreements to the Commissioner of Customs establishing the administrative mechanism.

ARTHUR GAREL,
Acting Chairman, Committee for the Implementation of Textile Agreements, and Director, Office of Textiles, U.S. Department of Commerce.

PHILIPPINE TRADITIONAL FOLKLORE HANDICRAFT TEXTILE PRODUCTS

"Philippine Items" are traditional Philippine products which have been cut, sewn, or otherwise fabricated by hand in cottage units of the cottage industry. The following is the agreed upon list of such items:

1. Batik and Hablon fabrics—Handwoven fabrics of the cottage industry.
2. Banaue cloth—Multicolored cotton handloomed fabric.
3. Other handwoven and handloomed fabrics of the cottage industry.
4. Articles and garments made by hand from handwoven and handloomed fabrics.
5. Hand crocheted garments, shawls, hats and accessories, including the "catsa group" type garments (heavily hand crochet work in combination with coarse or greige or dyed cotton fabric or batik fabric).

COMMITTEE FOR THE IMPLEMENTATION OF TEXTILE AGREEMENTS

COMMISSIONER OF CUSTOMS,
Department of the Treasury,
Washington, D.C. 20229.

AUGUST 31, 1976.

DEAR MR. COMMISSIONER: Under the terms of the Arrangement Regarding International Trade in Textiles done at Geneva on December 20, 1973, pursuant to the Bilateral Cotton, Wool and Man-Made Fiber Textile Agreement of October 15, 1975, between the Governments of the United States and the Republic of the Philippines, and in accordance with the provisions of Executive Order 11651 of March 3, 1972, you are directed to prohibit, effective on October 10, 1976, and until further notice, entry into the United States for consumption and withdrawal from warehouse for consumption of cotton textiles and cotton textile products in Categories 1–64, wool textile products in Categories 101–132, and man-made fiber textile products in Categories 200–243, produced or manufactured in the Republic of the Philippines, for which the Government of the Republic of the Philippines has not issued an appropriate visa.

The export visa will be a circular stamp in blue ink on the front side of the invoice (Special Customs Invoice Form 5515, successor document, or commercial invoice, when such form is used) and will include the signature and title of an official authorized by the Government of the Republic of the Philippines to issue visas. A facsimile of the visa is enclosed.

You are further directed, effective on October 10, 1976, to exempt from the levels of restraint established under the bilateral agreement shipments of cotton, wool, and/or man-made fiber textile products valued under $250; handmade cottage industry products of handloomed fabrics; and traditional Philippine folklore handicraft textile products which have been certified for exemption by the Government of the Republic of the Philippines in accordance with the procedure described below.

The certification will be a rectangular stamp in blue ink on the front side of the invoice (Special Customs Invoice Form 5515, successor document, or commercial invoice, when such form is used) and will include the signature and title of the official authorized to issue the certification; identify the items exempted; indicate the date the certification was signed and certified; and carry the certificate number. In the space marked "Description" on the certification stamp, the Government of the Republic of the Philippines will indicate that the shipment is either valued at less than $250; is a handmade cottage industry product of handloomed fabric; or will include the name of the particular Philippine traditional folklore product. A copy of the certification stamp is also enclosed.

An export visa will not be required to accompany shipments of exempt cotton, wool and man-made fiber textile products.

Cotton, wool and man-made fiber textile products, exported from the Republic of the Philippines prior to the effective date of this directive shall not be denied entry until December 9, 1976.

Merchandise covered by an invoice which has an exempt certification but includes both exempt and non-exempt textile products, will be denied entry.

You are directed to permit entry into the United States for consumption and withdrawal from warehouse for consumption of designated shipments of cotton, wool, and/or man-made fiber textile products, produced or manufactured in the Republic of the Philippines, notwithstanding the designated shipment or shipments do not fulfill the aforementioned visa and certification requirements, whenever requested to do so in writing by the Committee for the Implementation of Textile Agreements.

Textile products of the cottage industry of the Philippines which have been certified exempt from the levels of restraint of the Bilateral Cotton, Wool and Man-Made Fiber Textile Agreement of October 15, 1975, between the Governments of the United States and the Republic of the Philippines should be reported in accordance with the instructions transmitted in the letter of March

7, 1975 from the Chairman of the Committee for the Implementation of Textile Agreements.

A detailed description of the categories in terms of T.S.U.S.A. numbers was published in the FEDERAL REGISTER on February 3, 1975 (40 FR 5010), as amended on December 31, 1975 (40 FR 60220).

In carrying out the above directions, entry into the United States for consumption shall be construed to include entry for consumption into the Commonwealth of Puerto Rico.

The actions taken with respect to the Government of the Republic of the Philippines and with respect to imports of cotton, wool and man-made fiber textile products from the Philippines have been determined by the Committee for the Implementation of Textile Agreements to involve foreign affairs functions of the United States. Therefore, the directions to the Commissioner of Customs, being necessary to the implementation of such actions, fall within the foreign affairs exception to the rule-making provisions of 5 U.S.C. 553. This letter will be published in the FEDERAL REGISTER.

Enclosure.

Sincerely,

ARTHUR GAREL,
Acting Chairman, Committee for the Implementation of Textile Agreements, and Director, Office of Textiles, U.S. Department of Commerce.

REPUBLIC OF THE PHILIPPINES

NO. _____

TEXTILE EXPORT VISA

_____

SIGNATURE

_____

TITLE

_____

DATE

REPUBLIC OF THE PHILIPPINES

_____

CERTIFICATE NO.

EXEMPTED ITEMS

_____

DESCRIPTION

_____

CERTIFIED ON

_____

AUTHORIZED SIGNATURE

_____

TITLE

[FR Doc.76-25987 Filed 9-8-76;8:45 am]

CONSUMER PRODUCT SAFETY COMMISSION

TECHNICAL ADVISORY COMMITTEE ON POISON PREVENTION PACKAGING

Notice of Meeting

Notice is given that the Technical Advisory Committee on Poison Prevention Packaging will meet on September 28, 1976 (8:30 a.m. to 5:00 p.m.) and September 29, 1976 (9:00 a.m. to 4:00 p.m.) at the Consumer Product Safety Commission, 1750 K Street, N.W., 6th Floor Conference Room.

The purpose of the Technical Advisory Committee is to provide advice and recommendations on the types and kinds of packaging that will protect children from injury or illness resulting from handling or ingestion of household substances.

The agenda for the Tuesday, September 28, meeting will include orientation for new members during the morning session and a discussion of concepts of child-resistant packaging by the full Committee during the afternoon session.

On Wednesday, September 29, the morning session will be devoted to (1) a report on the Ammonia Proposal, (2) draft proposal to regulate household cleaning and maintenance products containing petroleum distillates, and (3) requests for exemption outstanding. A discussion on compliance activities under the Poison Prevention Packaging Act will take place in the afternoon.

Persons wishing to make oral or written presentations to the Committee should notify the Secretary of the Consumer Product Safety Commission at least five days in advance of the meeting. The meeting is open to the public, however, space is limited. Further information concerning this meeting may be obtained from the Office of the Secretary, Consumer Product Safety Commission, Washington, D.C. 20207, phone (202) 634-7700.

Dated: September 2, 1976.

SADYE E. DUNN,
Secretary, Consumer Product Safety Commission.

[FR Doc.76-26316 Filed 9-8-76;8:45 am]

ENVIRONMENTAL PROTECTION AGENCY

[OPP-00032; FRL 613-6]

CHLORDANE AND HEPTACHLOR

Notice of Availability of Draft Environmental Impact Statement

On May 7, 1974, the Environmental Protection Agency (EPA) published in the FEDERAL REGISTER (39 FR 16186) a statement of policy announcing its intention to prepare Environmental Impact Statements in accordance with section 102(2)(C) of the National Environmental Policy Act of 1969, in connection with its most significant regulatory actions, although not required to do so by law.

Pursuant to that policy announcement, the EPA has prepared a Draft Environmental Impact Statement (EIS) on the proposed cancellation of chlordane and heptachlor. On November 18, 1974, the Administrator of the EPA determined that the continued registration and use of pesticides containing chlordane or heptachlor posed a substantial question of safety, and accordingly a Notice of intent to cancel was issued; this Notice was published in the FEDERAL REGISTER on November 26, 1974 (39 FR 41298). However, subsequent to the issuance of the Notice, new evidence came to the attention of the Administrator which confirmed and heightened the human cancer hazard posed by these pesticides. As a result, on July 29, 1975, the Administrator announced his intention to suspend the registration of pesticide products containing chlordane and heptachlor for all uses for which cancellation had been proposed in the Federal Register Notice mentioned, pending a final cancellation decision. This Notice of intent to suspend was issued in accordance with the "imminent hazard" provisions under sections 6(c) and 2(l) of the amended Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C. 136), and was published in the FEDERAL REGISTER on August 15, 1975 (40 FR 34456). On December 24, 1975, following 43 days of public hearings, the Administrator issued a decision and order suspending some, but not all uses of these two pesticide chemicals; a Federal Register document containing the decision and order and other administrative actions on this subject was published on February 19, 1976 (41 FR 7552).

The EIS, a document totalling 51 pages including appendices, summarizes scientific information on chlordane and heptachlor with regard to toxicity to humans and animals, hazards to the environment, and costs and benefits of cancellation and other alternative regulatory actions.

Significant facts about chlordane and heptachlor are:

1. They have been used for over 20 years in considerable quantities for a variety of crop and noncrop pest control purposes.

2. They are chemically similar; chlordane contains about 10% heptachlor.

3. They and their toxic breakdown products are very persistent in the environment, resisting chemical or biological breakdown into harmless substances.

4. They or their toxic breakdown products are found as residues throughout the environment, i.e., in soil, water, air, wildlife, and food.

5. Their toxic breakdown products are found to have accumulated in human adipose tissue and in human milk.

6. They and some of their breakdown products are acutely toxic to many forms of life, in addition to target species.

7. Heptachlor epoxide has been found to have accumulated in the organs of stillborn infants.

8. Heptachlor, heptachlor epoxide and chlordane induce tumors in laboratory animals, and thus pose a cancer threat to man.

9. If cancellation occurs, economic impact on agricultural commodities and consumer prices would be minor, com-

pared with normal year-to-year variations due to weather and other market factors.

EPA will file a copy of this draft statement with the Council on Environmental Quality on September 13, 1976. All comments on the EIS must be received by EPA within 45 days after the Council on Environmental Quality also lists its availability in the FEDERAL REGISTER. To be sure of receiving full consideration on the preparation of the final EIS, all comments should reach EPA within this time frame and should bear the identifying notation OPP-00032. Comments should be filed in triplicate and addressed to EPA, Office of the Federal Register Section, Attn: Sandy Radinsky, Technical Services Division (WH-569), Office of Pesticide Programs, Room 401, East Tower, 401 M Street, SW., Washington, D.C. 20460.

Two background reports on chlordane and heptachlor are available along with a copy of this draft statement. One report, "Pesticidal Aspects of Chlordane and Heptachlor in Relation to Man and Environment; A Further Review, 1972–1975" (85 pages) considers the toxicity of the compounds. Another 1975 report, "EPA Actions to Cancel and Suspend Uses of Chlordane and Heptachlor as Pesticides" (355 pages), presents the economic and social implications of regulatory actions and EPA economic testimony at the chlordane/heptachlor suspension Hearings.

Copies of the EIS and accompanying background materials have been forwarded to Federal agencies, state pesticide groups, EPA regional offices, national environmental and conservation organizations and agricultural, trade and chemical groups.

This EIS and background materials are available for inspection in the EPA Office of the Federal Register Section (see address above); single copies of these materials will be provided free of charge.

Dated: September 3, 1976.

ANDREW W. BREIDENBACH,
Assistant Administrator for Water and Hazardous Materials.

[FR Doc.76-26403 Filed 9-8-76;8:45 am]

[FRL 613-7]

ENERGY RELATED AUTHORITY

Report on Progress and Impact

Section 119(k)(2) of the Clean Air Act, as amended by the Energy Supply and Environmental Coordination Act of 1974, directs the Administrator to publish in the FEDERAL REGISTER at no less than 180 day intervals beginning January 1975, certain reports and findings on the implementation of EPA's energy related authority under section 119 of the Act. Specifically, the Administrator is directed to publish a concise summary of progress reports required to be filed by any person or source owner or operator to which the compliance data extension provisions of subsection 119(c) apply. Such reports are to include information on the status of compliance with requirements imposed by the Administrator under subsection 119(c). In addition, the Administrator is directed to publish up-to-date findings on the impact of Section 119 upon applicable State Implementation Plans and upon ambient air quality. On January 27, 1975, August 8, 1975, and February 23, 1976, notices meeting the requirements of Section 119(k)(2) were published in the FEDERAL REGISTER at 40 FR 4034, 40 FR 33489 and 41 FR 7989 respectively.

As of July 15, 1976, some applications for compliance date extensions under subsection 119(c) have been received by the Administrator; however, no such extensions have been granted as yet. Therefore, no progress reports were required of or filed by any person or source owner or operator under subsection 119(c). In addition, no postponements under subsection 119(i) were sought or granted before July 15, 1976. No actions taken during the period covered by this report resulted in any impact on air quality or state implementation plans.

Whenever the Federal Energy Administrator issues an order to a fuel-burning source under section 2(a) of the Energy Supply and Environmental Coordination Act of 1974 which will apply after June 30, 1975, the Administrator of EPA is required to notify FEA if the source can burn coal and comply immediately with all applicable air pollution requirements without a compliance date extension. If such notification is not given, then the EPA Administrator must certify to FEA: (1) when the source can comply with primary standard conditions and/or regional limitations in the case of a source which is receiving a compliance date extension; or (2) when the source can comply with all air pollution requirements in the case of a source which is not receiving a compliance date extension.

As of July 15, 1976, the Administrator of EPA has notified FEA that seven plants can burn coal and comply immediately with all air pollution requirements without a compliance date extension. Those plants are: (1) Ames Station, Unit 7, Ames Electric Utility, Ames, Iowa; (2) Maynard Station, Unit 14, Iowa Public Service Company, Waterloo, Iowa; (3) Des Moines Station, Units 10 and 11, Iowa Power and Light Company, Des Moines, Iowa; (4) Weston Station, Unit 2, Wisconsin Public Service Corporation, Rothchild, Wisconsin; (5) McWilliams Station, Unit 3, Alabama Electric Cooperative Inc., Gantt, Alabama; (6) Sheldon Station, Unit 2, Nebraska Public Power District, Columbus, Nebraska; and (7) Quindaro 3 Station, Units 1 and 2, Kansas City Board of Public Utilities, Kansas City, Kansas.

Also, the Administrator of EPA has certified to FEA that the following six stations cannot comply with all applicable air pollution requirements until beyond the statutory deadline for compliance, and therefore cannot receive compliance date extensions: (1) St. Clair Station, Unit 5, Detroit Edison Company, East China Township, Michigan; (2) Edge Moor Station, Units 1, 2, 3, and 4, Delmarva Power and Light Company, Wilmington, Delaware; (3) Crane Station, Units 1 and 2, Baltimore Gas and Electric Company, Baltimore, Maryland; (4) Wagner Station, Units 1 and 2, Baltimore Gas and Electric Company, Baltimore, Maryland; (5) Riverside Station, Units 4 and 5, Baltimore Gas and Electric Company, Baltimore, Maryland; and (6) Winnetka Station, Units 5, 6, 7, and 8, Village of Winnetka, Winnetka, Illinois. FEA's orders for these plants, therefore, cannot become effective until after January 1, 1979.

Two units at one plant (Hawthorne Station, Units 4 and 5, Kansas City Power and Light Company, Kansas City, Missouri) were ineligible for compliance date extensions because the units had generated more than half of their electricity through the use of coal during the period between Sept. 15, 1973 and March 15, 1974. The Administrator therefore certified January 1, 1977 and December 15, 1978 as the earliest dates on which the Federal Energy Administration's prohibition orders to units 4 and 5, respectively, may take effect. The Administrator also certified to FEA that the following two power plants will be able to burn coal in compliance with all applicable air pollution requirements within 6 months of the issuance of FEA's Notice of Effectiveness to the plants: (1) Chesterfield Station, Units 3, 4, 5, and 6, Virginia Electric Power Company, Chester, Virginia; and (2) Morgantown Station, Units 1 and 2, Potomac Electric Power Company, Newburg, Maryland.

Dated: August 31, 1976.

STANLEY W. LEGRO,
Assistant Administrator for Enforcement.

[FR Doc.76-26402 Filed 9-8-76;8:45 am]

[OPP-180083; FRL 613-5]

MASSACHUSETTS DEPARTMENT OF ENVIRONMENTAL QUALITY ENGINEERING

Issuance of a Specific Exemption To Use Guthion To Control the Carrot Weevil

Pursuant to the provisions of section 18 of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended (86 Stat. 973; 7 U.S.C. 136), notice is hereby given that the Environmental Protection Agency (EPA) has granted a specific exemption to the Massachusetts Department of Environmental Quality Engineering (hereafter referred to as the "Applicant"). Azinphos methyl (Guthion) will be used on thirty acres of carrot seedlings for the control of the carrot weevil in Middlesex County and certain other areas in Massachusetts. This exemption was granted in accordance with, and is subject to, the provisions of 40 CFR Part 166, issued December 3, 1973 (38 FR 33303), which prescribes requirements for exemption of Federal and State agencies for use of pesticides under emergency conditions.

This notice contains a summary of certain information required by regulation to be included in the notice. For more detailed information, interested

parties are referred to the application on file with the Registration Division (WH–567), Office of Pesticide Programs, EPA, 401 M Street, S.W., Room E–315, Washington, D.C. 20460.

According to the Applicant, the appearance of the Carrot Weevil (*Listronotus oregonensis*) as a problem is cyclical. The problem occurs every 4–5 years and lasts for a period of two years. Massachusetts is now in the second year of the present outbreak. If not controlled, the pest can inflict severe damage. Carrot weevil larvae tunnel in the tap root of carrots, leaving rust-colored feeding trails. Larval feeding early in the season results in mortality of seedling carrots, reducing the row-density. Later injury reduces the quality of market carrots, rendering many unmarketable. Further losses occur when carrots are placed in cold storage due to increased incidence of storage rot disease organisms (fungi and bacteria) which enter the carrots through weevil larvae feeding tunnels.

There appear to be neither alternative registered pesticides nor non-chemical methods of control available to suppress this insect. The Applicant proposed to apply azinphos methyl (Guthion) to carrot seedlings being grown both for processing and for consumption as a fresh vegetable. The pesticide will be applied at the rate of one-half (½) pound of actual insecticide per acre. No more than 3 applications will be made on any given field during the growing season. A thirty-five (35) day waiting period between treatment and harvest will be observed for carrots treated with Guthion. The pesticide will be applied with ground rigs only to carrot fields where the weevil has been detected visually or by means of traps. Application will be to 20–30 acres mainly in central Middlesex County; some applications will be made in scattered locations in western Massachusetts. These operations will be carried out under the supervision of the Extension Entomologist at the University of Massachusetts. Approximately 45 pounds of actual Guthion will be used.

The Applicant says the carrot crop has a value of $1,800 per acre to the growers; thus a thirty-acre crop would be worth $54,000 and an estimated fifty (50) percent loss due to carrot weevil damage would be an economic loss of $27,000.

Guthion is registered for a number of agricultural uses, many of which occur in Massachusetts in the process of growing fruits and vegetables. It is anticipated that no adverse effects on man and the environment will occur with this limited use of Guthion.

After reviewing the application and other available information, EPA has determined that (a) a pest outbreak of carrot weevils has occurred; (b) there is no pesticide presently registered and available for use to control the carrot weevil in Massachusetts; (c) there are no alternative means of control, taking into account the efficacy and hazard; (d) significant economic problems may result if the carrot weevils are not controlled; and (e) the time available for action to mitigate the problems posed is insufficient for a pesticide to be registered for this use. Accordingly, the Applicant has been granted a specific exemption to use the pesticide noted above until September 15, 1976, to the extent and in the manner set forth in the application. The specific exemption is also subject to the following restrictions:

1. The carrot acreage to be treated with azinphos methyl (Guthion) is limited to thirty (30) acres;

2. The azinphos methyl (Guthion) will be applied with ground equipment;

3. The dosage rate may not exceed one-half (½) pound of actual azinphos methyl per acre per application;

4. The number of applications may not exceed three (3);

5. A thirty-five day preharvest interval must be observed;

6. Carrot tops treated with azinphos methyl may not be used for food, feed, or forage;

7. A residue level not to exceed 0.5 ppm on carrot roots has been determined to be adequate to protect the public health. The Food and Drug Administration of the U.S. Department of Health, Education, and Welfare, has been advised of this action; and

8. The Applicant is responsible for ensuring that the restrictions pursuant to this specific exemption are met.

Dated: September 2, 1976.

EDWIN L. JOHNSON,
Deputy Assistant Administrator for Pesticide Programs.

[FR Doc.76–26285 Filed 9–8–76;8:45 am]

[OPP–180089; FRL 613–4]

NEVADA DIVISION OF HEALTH

Crisis Exemption Using DDT To Control Flea Vectors of Plague

Pursuant to the provisions of section 18 of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended (86 Stat. 973; 7 U.S.C. 136), the Environmental Protection Agency (EPA) gives notice that the Nevada Division of Health (hereafter referred to as the "Applicant") has availed itself of a crisis exemption. The Applicant used DDT to control plague-infected fleas in rodent burrows at Nevada Beach, Lake Tahoe, Nevada. This exemption was subject to the provisions of sections 166.2, 166.8, and 166.9 of 40 CFR Part 166. These regulations concerning the exemption of Federal and State agencies for the use of pesticides under emergency conditions were published in the Federal Register on December 3, 1973 (38 FR 33303). As required, the Applicant has submitted in writing the following certified information.

According to the Applicant, there was a bubonic plague outbreak in rodents at Nevada Beach at Lake Tahoe. At Nevada Beach, rodents were trapped to determine the percentage of flea infestation on rodents; this data was used to calculate a flea index on the number of rodents obtained by trapping. The rodents involved were the California Ground Squirrel, the Mantled Ground Squirrel, the Deer Mouse, the Douglas Chickaree, and the Northwest Chipmunk. On July 8, 1976, one hundred pounds of DDT in five-pound cans was obtained from the Sierra Army Depot in Herlong, California. On July 9, rodent burrows were dusted with 25 pounds (5 cans). Rodents were again trapped and flea infestation determined. The percentage dropped, but not significantly, according to the Applicant; re-dusting of the burrows was required.

On July 22, the burrows were again dusted, using 25 pounds (5 cans) of DDT. Flea infestation showed a drop, but was still high. The Applicant decided to use DDT bait dust stations to assure better dusting of the rodents. On July 27, approximately 250 DDT bait dust stations were set, requiring 10 pounds of DDT. Flea infestation was checked on July 29, 1976; infestation had dropped to a permissable level, and the Beach was permitted to reopen. The total amount of DDT used was 60 pounds (12 five-pound cans). Applications were made by trained personnel.

The official file concerning this exemption is available for inspection in the Registration Division (WH–567), Office of Pesticide Programs, EPA, Room E–315, 401 M St., S.W., Washington, D.C. 20460.

Dated: September 2, 1976.

JOHN B. RITCH, Jr.,
Director, Registration Division.

[FR Doc.76–26284 Filed 9–8–76;8:45 am]

[FRL 606–7; OPP–50249]

S. B. PENICK AND CO. ET AL.

Issuance of Experimental Use Permits

Correction

In FR Doc. 76–25087 appearing at page 36247 in the issue for Friday, August 27, 1976, on page 36248, in the first column, in the first paragraph, the first line should read as follows:

"No. 148–EUP–23 Thompson-Hayward"

ENERGY RESEARCH AND DEVELOPMENT ADMINISTRATION

HIGH ENERGY PHYSICS ADVISORY PANEL

Meeting

Pursuant to the provisions of the Federal Advisory Committee Act, the High Energy Physics Advisory Panel (HEPAP) will meet September 27 and 28, 1976. The meeting will be held at the Energy Research and Development Administration offices at 400 First Street, NW., Washington, D.C. in Conference Room 200. The portion of the meeting which will be open to the public will convene from 10 a.m. to approximately 6 p.m. on September 27, and will resume at 9 a.m. to end at approximately 11:30 a.m. on September 28.

The Panel will examine the current status of budget requests for the High Energy Physics Program; consider plans for future facility recommendations; discuss criteria for foreign travel and con-

ference delegations; consider computer policies at national laboratories; discuss the influence of the international Very Big Accelerator on regional plans; consider the research program and current facility development at the ZGS; and discuss the role of the High Energy Physics Program within the Energy Research and Development Administration.

Two (2) executive sessions of the Panel are scheduled. The first executive session will occur at approximately 9 a.m. prior to the open session on September 27; the second will begin at approximately 1 p.m. on September 28 and continue throughout the end of the meeting at approximately 4:30 p.m. Topics to be discussed at these executive sessions are the future allocation of resources for operations, priorities among proposed future construction projects and other similar matters.

I have determined, in accordance with subsection 10(d) of Pub. L. 92-463 that these executive sessions will consist of an exchange of opinions and formulation of recommendations, the discussion of which, if written would fall within exemption (5) of 5 U.S.C. 552(b).

It is essential to close these portions of the meeting to protect the free interchange of internal views to avoid undue interference with Agency or Committee operation.

The Chairman is empowered to conduct the meeting in a manner that in his judgment will facilitate the orderly conduct of business.

With respect to public participation in the meeting, the following requirements shall apply:

(a) Persons wishing to submit written statements on the topics fo discussion may do so by mailing 25 copies thereof, postmarked, if possible no later than September 17, 1976, to the Executive Secretary, High Energy Physics Advisory Panel, Dr. Ernest Coleman, Division of Physical Research, U.S. Energy Research and Development Administration, Washington, D.C. 20545. Minutes of the meeting will be kept open for 30 days for receipt of written statements for the record.

(b) Those persons submitting a written statement in accordance with paragraph (a) above may request an opportunity to make oral statements concerning the written statement, and shall set forth reasons justifying the need for such oral statements and their usefulness to the Panel. To the extent that the time available for the meeting permits, the Panel will receive oral statements during a period of not more than 30 minutes at an appropriate time, chosen by the Chairman.

(c) Requests for the opportunity to make oral statements shall be ruled on by the Chairman of the Panel, who is empowered to apportion the time available among those selected by him to make oral statements.

(d) Information as to the Chairman's ruling on requests for the opportunity to present oral statements, and the time allotted, can be obtained by a prepaid telephone call on September 22, 1976, to the office of the Executive Secretary of the Panel on (301) 353-3624 between 8:30 a.m. and 5 p.m. Eastern Time.

(e) Questions at the meeting may be asked only by members of the Advisory Panel.

(f) Seating for the public will be made available on a first-come first-served basis.

(g) The use of still, motion picture, and television cameras, the physical installation and presence of which will not interfere with the course of the meeting, will be permitted both before and after the open portions of the meeting and during any recess. The use of such equipment will not, however, be allowed while the meeting is in session.

(h) Copies of minutes of public sessions will be made available for copying, following their certification by the Chairman, in accordance with the Federal Advisory Committee Act, at the U.S. Energy Research and Development Administration's Public Document Room, 20 Massachusetts Avenue, NW., Washington, D.C., upon payment of all charges required by law.

K. DEAN HELMS,
Acting Deputy Advisory Committee Management Officer.

[FR Doc.76-26327 Filed 9-8-76;8:45 am]

HIGH LEVEL WASTE STORAGE AND HANDLING FACILITIES HANFORD RESERVATION, RICHLAND, WASHINGTON

Negative Declaration

Pursuant to Part 1500.6(e) of the Council on Environmental Quality Guidelines of August 1, 1973, (38 FR 20550) and 10 CFR 711.7(d) [formerly 10 CFR 11.7(d)], the U.S. Energy Research and Development Administration (ERDA) hereby gives notice that an environmental statement is not being prepared for the construction project, High Level Waste Storage and Handling Facilities, at the Hanford Reservation, Richland, Washington which has been included in the President's FY 1977 Budget as submitted to the Congress.

The proposed project is to construct six additional double-shelled waste storage tanks at the ERDA Hanford Plant at Richland, Washington for the interim storage of high-level radioactive waste. Similar waste tank projects in previous budgets have had environmental statements prepared in view of the controversial nature of radioactive waste management. However, it has been determined that no separate statement need be prepared for this Project since its environmental impact had been evaluated previously in the Final Environmental Statement, Waste Management Operations, Hanford Reservation, ERDA-1538 (December 1975).

Copies of this negative declaration and its supporting documentation have been placed for public inspection in the following ERDA public document rooms:

ERDA Headquarters, 20 Massachusetts Avenue, NW, Washington, DC 20545.
Albuquerque Operations Office, Kirtland Air Force Base East, Albuquerque, NM 87115.
Chicago Operations Office, 9500 South Cass Avenue, Argonne, IL 60439.
Idaho Operations Office, 550 Second Street, Idaho Falls, ID 83401.
Oak Ridge Operations Office, Federal Building, Oak Ridge, TN 37830.
Nevada Operations Office, 2753 South Highland Drive, Las Vegas, NV 89114.
Richland Operations Office, Federal Building, Richland, WA 99352.
San Francisco Operations Office, 1333 Broadway, Oakland, CA 94612.
Savannah River Operations Office, Savannah River Plant, Aiken, SC 29810.
Bartlesville Energy Research Center, P.O. Box 1398, Bartlesville, OK 74003.
Grand Forks Energy Research Center, P.O. Box 8213, University Station, Grand Forks, ND 58202.
Laramie Energy Research Center, P.O. Box 3395, University Station, Laramie, WY 82070.
Morgantown Energy Research Center, P.O. Box 880, Morgantown, WV 26505.
Pittsburgh Energy Research Center, 4800 Forbes Avenue, Pittsburgh, PA 15213.

Dated at Germantown, Maryland, this 2d day of September 1976.

For the Energy Research and Development Administration.

JAMES L. LIVERMAN,
Assistant Administrator for Environment and Safety.

[FR Doc.76-26288 Filed 9-8-76;8:45 am]

[ERDA-1546]

POSITRON-ELECTRON STORAGE RING PROJECT STANFORD LINEAR ACCELERATOR CENTER STANFORD, CALIFORNIA

Notice of Availability of Final Environmental Statement

Notice is hereby given that the Final Environmental Statement, ERDA-1546, Positron-Electron Storage Ring Project, Stanford Linear Accelerator Center, Stanford, California, was issued pursuant to the Energy Research and Development Administration's (ERDA) implementation of the National Environmental Policy Act of 1969. The statement was prepared in support of the project which was included in the ERDA Fiscal Year 1976 Appropriations Act.

Copies of the final statement are available for public inspection in the ERDA public document rooms at:

ERDA Headquarters, 20 Massachusetts Avenue, NW., Washington, D.C.
Albuquerque Operations Office, Kirtland Air Force Base East, Albuquerque, New Mexico.
Chicago Operations Office, 9800 South Cass Avenue, Argonne, Illinois.
Idaho Operations Office, 550 Second Street, Idaho Falls, Idaho.
Nevada Operations Office, 2753 South Highland Drive, Las Vegas, Nevada.
Oak Ridge Operations Office, Federal Building, Oak Ridge, Tennessee.
Richland Operations Office, Federal Building, Richland, Washington.
San Francisco Operations Office, 1333 Broadway, Oakland, California.
Savannah River Operations Office, Savannah River Plant, Aiken, South Carolina.

Copies have been furnished to those who commented on the draft statement that was issued by the Energy Research and Development Administration as

ERDA–1546, January 28, 1976. Copies are also available for public inspection at designated Federal Depository Libraries.

A limited number of single copies are available for distribution by the Technical Information Center, P.O. Box 62, Oak Ridge, Tennessee 27830 (615) 483–8611, Extension 34672. The statement is also available from the National Technical Information Service, Springfield, Virginia 22161.

Dated at Germantown, Maryland, this 3rd day of September 1976.

For the Energy Research and Development Administration.

JAMES L. LIVERMAN,
Assistant Administrator for Environment and Safety.

[FR Doc.76–26326 Filed 9–8–76;8:45 am]

FEDERAL COMMUNICATIONS COMMISSION

[Docket No. 20817]

AN INQUIRY RELATING TO THE COMMISSION'S RADIO OPERATOR LICENSING PROGRAM

Order Extending Time To File Comments and Reply Comments

Adopted: August 25, 1976.

Released: August 27, 1976.

1. The Electronic Industries Association's (EIA) Land Mobile Communications Section and the National Association of Broadcasters (NAB) have submitted requests for an extension of time within which Comments and Reply Comments in the above-captioned matter (41 FR 22981, June 8, 1976) might be filed.

2. Because of the importance and complexity of this proceeding, and because of the Commission's desire to obtain the widest possible response, an extension of time to November 1, 1976 for the filing of Comments and November 15, 1976 for the filing of Reply Comments is ordered, pursuant to section 0.311 of the Commission's rules.

C. PHYLL HORNE,
Chief, Filed Operations Bureau.

[FR Doc.76–26353 Filed 9–8–76;8:45 am]

[Docket No. 20820, File No. BPCT–4674; Docket No. 20821, File No. BPCT–4826; FCC 76R–239]

MIDWEST ST. LOUIS, INC. ST. LOUIS, MISSOURI; NEW LIFE EVANGELISTIC CENTER, INC. ST. LOUIS, MISSOURI

Applications for Construction Permit for a New Television Broadcast Station

MEMORANDUM OPINION AND ORDER

Adopted September 1, 1976;

Released: September 7, 1976

By the Review Board: Board Member Kessler concurring in result. 1. This proceeding involves the mutually exclusive applications of Midwest St. Louis, Inc. (Midwest) and New Life Evangelistic Center, Inc. (New Life) for construction permits for a new television broadcast station to operate on Channel 24, St. Louis, Missouri. Now before the Review Board for consideration is a petition to enlarge issues, filed by New Life on June 29, 1976, which seeks to add "viability," Rule 1.65,[1] lack of candor, and ascertainment issues against Midwest.[2]

2. As relevant background to understanding New Life's request for "viability" issues, the Board notes the following. At the time of designation,[3] the Commission also had before it an application by Midwest for authorization to conduct subscription television (STV) operations over the facilities of its proposed station on Channel 24 and a mutually exclusive application for STV authority filed by Evans Broadcasting Corporation (Evans), licensee of Station KDNL–TV, St. Louis. The Commission decided that examination of the STV application of Midwest was not necessary to the basic comparison between Midwest and New Life, and that action on the Midwest STV application should be deferred pending the outcome of this hearing. It also stated that should Midwest prevail herein, it would then undertake a comparative evaluation of the Midwest and Evans STV applications. However, it held that the STV programming proposal of Midwest could be compared with the programming proposal of New Life under the standard comparative issue.

3. New Life submits that Midwest's application for a construction permit is an integral part of its overall proposal to operate an STV service in St. Louis, and that since Midwest has not applied simply for a construction permit and the Commission has not made the STV application part of this proceeding, a question arises as to the viability of Midwest's proposal. Indeed, New Life asserts, should Midwest prevail in this hearing, it may actually obtain an authorization for a facility it does not wish—a conventional television broadcast station. In support, New Life cites the transmittal letter submitted by Midwest to the Commission with its application which recites that Midwest's conventional and STV applications are "mutually contingent";[4] furthermore, New Life contends that Midwest's financial proposal contemplates an STV authorization and that the loan commitment upon which it relies is predicated on the construction of a television station and operation of an STV facility.[5] Thus, New Life argues that Midwest has not made a financial or, for that matter, an ascertainment showing with respect to the operation of a conventional station and that it is not clear whether Midwest will operate at all unless it receives an STV authorization. New Life submits that issues are required to determine whether Midwest's conventional television application is a viable proposal, whether Midwest intends to construct and operate a conventional facility irrespective of and pending its success in obtaining an STV authorization, and whether Midwest is financially qualified to operate the proposed facility pending and irrespective of receipt of an authorization for STV service. Finally, New Life states that the Board may wish to certify to the Commission the question of whether the Evans application for STV authority should be consolidated in this proceeding.

4. The Broadcast Bureau supports enlargement of the issues but states that the request for certification should be made in a separate pleading. Evans also opposes certification, essentially on the ground that the Commission first must determine which of the two applicants for Channel 24 (New Life and Midwest) should receive a construction permit. Midwest, in opposition, initially agrees with New Life that certain "anomalies" could result from the bifurcated hearing process adopted by the Commission—such as Midwest being left with a construction permit it does not want should it prevail against New Life herein but lose subsequently to Evans in the STV comparative hearing. Midwest refers the Board to its Petition for Inquiry and Rulemaking filed with the Commission July 23, 1976, wherein it seeks reexamination of Commission policy and establishment of uniform standards to govern designation in this area. Midwest also supports certification of the question regarding consolidation of the Evans application. Because it believes rulemaking rather than ad hoc evidentiary hearing is the appropriate forum for these questions, Midwest opposes New Life's requested viability issue. Furthermore, Midwest states, in view of its representations in its pleadings to the Board and the Commission, there is no factual question requiring hearing as to whether it will construct and operate a conventional facility irrespective of its success

[1] Rule 1.65 requires applicants to advise the Commission of changes which may be of decisional significance within thirty days of their occurrence.

[2] Related pleadings before the Board are: (a) opposition, filed July 13, 1976, by Evans Broadcasting Corporation; (b) reply, filed July 23, 1976, by Midwest; (c) comments, filed August 4, 1976, by the Broadcast Bureau; (d) opposition, filed August 4, 1976, by Midwest; (e) reply, filed August 20, 1976, by New Life Evangelistic Center.

[3] 41 FR 24015, published June 14, 1976.

[4] The letter states: There is submitted herewith on behalf of our client, Midwest St. Louis, Inc., an application in triplicate for a construction permit for a UHF station in St. Louis on Channel 24, There is also enclosed an application for STV authority for the St. Louis market. The attention of the Commission is respectfully invited to the fact that the two applications are mutually contingent.

[5] Midwest relies on a letter of credit from its parent corporation to meet its total cash requirements. The letter states in pertinent part: This letter will advise your corporation (hereinafter "St. Louis") that Midwest Radio-Television, Inc. (hereinafter "WCCO") is prepared to advance to St. Louis as loans, through the purchase of your securities, or by guaranteeing loans from financial institutions, such sums as may be required for the processing of the St. Louis applications for a construction permit for a UHF station in St. Louis and for STV authority for that market; for the construction and for the operation of the UHF station, should the construction permit be issued by the Federal Communications Commission; and for the costs of operating a subscription television system in the St. Louis market.

in obtaining STV authorization. Finally, Midwest states, in view of the aforenoted mutual contingency of its conventional and STV applications, the question of whether Midwest would finance a conventional station even if it fails to receive STV authorization is hypothetical and its resolution irrelevant.

5. We see no need for issues concerning the viability of Midwest's application for a conventional television operation, or concerning Midwest's intentions to construct a conventional television facility in the event it is unsuccessful in obtaining an authorization for subscription television operations. Although the applications for a basic construction permit and for authority to conduct STV operations have been filed separately, it is now perfectly clear that Midwest does not want any authorization which does not include authority for STV operations. This position is improper. The Commission's rules, see Section 73.642(a), 47 CFR 73.642(a), provide for the grant of an authorization for STV service to "[a]n applicant for a construction permit for a new commercial television broadcast station * * *," as well as to the licensee or permittee of a commercial television broadcast station. The only proviso is that an authorization for STV operations will not be issued prior to issuance of the construction permit for the new station. Thus, while it is clear that an authorization for STV operation will not be issued unless the applicant is also basically qualified for a construction permit, there is no reason why the two applications cannot be considered together, and it is quite unrealistic, at least in the context of this case, to separate the two applications and judge Midwest upon the basis of something it is not in fact seeking and which the rules do not require it to seek—authority for a purely conventional operation. Since Midwest has now made its position unmistakably clear, there is no good reason to add issues concerning its intentions or the viability of its application for construction permit without regard to its application for STV authority. Nor, for the same reason, is there any warrant for adding the additional issue sought by New Life as to whether Midwest is financially qualified to construct and operate a conventional television facility "pending and irrespective of" receipt of authority to operate a subscription television service.

6. We also believe, since Midwest's intentions have now been made clear, that we should certify to the Commission for its further consideration the question of whether the STV application of Midwest should be included in this hearing and the further question of whether the application of Evans for STV operation should also be considered in the same proceeding. In this connection, we note that while a grant to New Life in the present posture of the matter would create no procedural difficulties, a finding that Midwest is to be preferred to New Life (assuming both parties are found basically qualified) could result in the unnecessary denial of the application of New Life and a grant to Midwest of something it does not seek (an authorization for a purely conventional operation) if Evans were later found superior to Midwest. Furthermore, considerable extra time might be required to compare New Life and Midwest in one proceeding and then to institute a new proceeding to compare Midwest and Evans. Since the efficiency of the presently designated hearing process must be determined upon the basis of both possible outcomes, i.e., a grant to either Midwest or New Life, it would seem that the present hearing structure might not be the most efficient. The remedy would appear to be a simultaneous consideration of all of the pending applications, so that the Commission could determine in one hearing proceeding the grant or grants required by the public interest. Since it is beyond the power of the Board to achieve this result, and since we think the parties have presented problems which warrant further consideration, we will rsepectfully refer these questions to the Commission for its judgment.

7. In support of its requests for Rule 1.65 and lack of candor issues, New Life recites that on May 3, 1973, Midwest consummated an agreement with The St. Louis Educational Television Commission (St. Louis), the licensee of station KETC–TV, for use of the latter's transmitter tower as Midwest's proposed antenna location for purposes of this application. However, New Life asserts, by letter dated December 20, 1975, Robert C. Glazier, Executive Director of St. Louis, advised Midwest that the agreement, which was due to expire May 3, 1976, could not be extended beyond that date "under any conditions."[6] New Life contends that Midwest has failed to notify the Commission of this development and concludes that the significance of the change in availability of Midwest's proposed transmitter site and the applicant's dereliction in notifying the Commission necessitate addition of Rule 1.65 and lack of candor issues.[7] In opposition, Midwest submits that it did comply with Rule 1.65 by reporting to the Commission the unavailability of its proposed site on July 29, 1976, which, it claims, was within thirty days of receiving a June 26, 1976 letter from St. Louis informing it that its option could not be renegotiated. Until that time, Midwest asserts, it believed it could convince St. Louis to reconsider its disinclination to renew the agreement.

8. The Board will add a Rule 1.65 issue. We agree with New Life that the unavailability of an applicant's proposed transmitter site is a decisionally significant matter which must be reported within thirty days. *Dale A. Owens*, 56 FCC 2d 482, 35 RR 2d 508 (Rev. Bd. 1975). Here, it is clear from the plain language of the correspondence from St. Louis to Midwest in December 1975 that Midwest did not have reasonable assurance of its proposed site after May 3, 1976, and it is also clear from Robert Glazier's affidavit that, in fact, Midwest's option did expire on the latter date. Nevertheless, Midwest did not inform the Commission of these developments until July 29, 1976, subsequent to the filing of New Life's petition herein. Although Midwest claims it acted promptly after receiving notification from St. Louis that the agreement would not be renegotiated, we have difficulty accepting this explanation, absent evidentiary inquiry, in view of the language of Glazier's letters in December, 1975. Accordingly, we will specify a Rule 1.65 issue encompassing inquiry into the applicant's basic and/or comparative qualifications; in view of the scope of this issue, a separate lack of candor issue is unnecessary.

9. New Life's final request is for issues relating to the adequacy of Midwest's efforts to ascertain community needs and to ascertain STV programming needs. We shall dismiss New Life's allegations with respect to STV ascertainment since Midwest's STV application is not part of this proceeding. With respect to Midwest's ascertainment of community problems, New Life initially alleges that Midwest contacted only 34 community leaders, and that this number is insufficient to represent the proposed service area. As a related matter, New Life points out that contacts with leaders of only two outlying communities were included in the survey. In addition, New Life asserts that Midwest has not consulted with leaders of all significant groups and that, in fact, representatives of the military,[8] consumer services, the elderly, and agriculture were not contacted.[9] Moreover, petitioner asserts that no representatives of transportation (other than aviation), medicine and health services (other than mental health), or professional and scholastic sports were interviewed, although these groups are identified by Midwest as being significant. New Life also challenges the adequacy of Midwest's general public survey, noting that the 202 telephone interviews listed were conducted by Edward G. Doody Co., and contending that Midwest's application does not specify whether this firm is a professional research or survey service. Furthermore, petitioner points out that Midwest characterizes the Doody survey as being "directed toward STV programming preferences, rather than toward traditional community needs, problems, and interests," and contends that this does not comply with the suvey requirements contained in the *Primer on Ascertainment of Community Needs by Broadcast Appli-*

[6] New Life submits a copy of the letter in question, as well as a letter to the same effect dated December 27, 1975, and a subsequent affidavit from Glazier, dated June 25, 1976, which states that Midwest's option for space on the KETC–TV tower has expired and "will not be renewed."

[7] An issue as to the availability of Midwest's proposed site has already been specified in the designation Order.

[8] Specifically, petitioner refers to the U.S. Army Records Center located in St. Louis.

[9] Petitioner derives these categories from the Commission's recent *Primer on Ascertainment of Community Problems by Broadcast Renewal Applicants*, 57 FCC 2d 418, 35 RR 2d 1555 (1976).

cants, 27 FCC 2d 650, 21 RR 2d 1507 (1971).[10]

10. The Board will add a general ascertainment issue. Before discussing the alleged inadequacies pointed out by New Life, we note that a prime deficiency in Midwest's showing is its failure, except for some rudimentary information as to population, racial composition, and general community characteristics, to provide the demographic composition of its proposed community of license called for by the *Primer*. Without a more specific breakdown of the governmental and economic activities, the public service organizations, and the other elements of the community that make it distinctive, we cannot be assured that the applicant's contracts are representative of the important groups in its community. See *Primer*, Q. and A. 4, 9, and 10; *Robert Cowan Wagner*, 38 FCC 2d 403, 25 RR 2d 1095 (Rev. Bd. 1972). Furthermore, as correctly noted by petitioner, significant groups which Midwest does indicate exist in St. Louis do not appear to be adequately reflected in the community leader survey. Thus, although Midwest characterizes transportation as an important part of the St. Louis economy and states that St. Louis is a medical center, the one purported representative from each of these groups listed is not clearly a leader in the field.[11] Similarly, although the manufacturing industry is stated to be an important activity by Midwest, no interviews with leaders representing this group were conducted. See *Voice of Dixie, Inc.*, 45 FCC 2d 1027, 29 RR 2d 1127 (1974). Nor is it clear from the descriptions of some of the individuals listed by Midwest—*e.g.*, staff representative, UAW; office manager, League of Women Voters; store manager, Arrow Shirts—that these persons are community leaders.[12] Moreover, although Midwest argues in its opposition pleading that many of its 34 interviewees are active in more than one organization so that actually 58 significant groups are represented in its survey, the applicant has only set forth the "primary" organizational affiliation of each of these individuals and therefore it is impossible to conclude that a leader of each organization has been contracted. Outside of St. Louis, Midwest appears to have contacted purported leaders of only two communities, East St. Louis and Clayton; however, it has not explained why representatives of such nearby and apparently major communities as University City (1970 population 46,309), Webster Groves (1970 population 26,995), Ferguson (1970 population 28,915), and Kirkwood (1970 population 31,890) were not contacted. This would appear to violate Q. & A. 6 of the *Primer*. Finally, although Midwest lists a number of community problems ascertained from its survey, few of these appear to be reflected in its programming proposal, and the proposal itself is general and does not appear to comport with Q. & A. 28 of the *Primer* which requires specific information as to program description, time segment, frequency of broadcast, and problem or problems treated. In sum, Midwest's ascertainment showing appears to be deficient in many important respects and, consequently, we believe a general ascertainment issue is called for.[13]

11. Accordingly, it is ordered, That the petition to enlarge issues, filed by New Life Evangelistic Center, Inc. on June 29, 1976 is granted to the extent indicated herein, and is denied in all other respects; and

12. It is further ordered, That the issues in this proceeding are enlarged to include the following:

(2) (e) To determine whether Midwest St. Louis, Inc. has violated Rule 1.65 by failing to notify the Commission of the unavailability of its transmitter site and, if so, the effect on the applicant's basic and/or comparative qualifications.

(2) (f) To determine the efforts made by Midwest St. Louis, Inc. to ascertain the community problems of the area to be served and the means by which it proposes to meet those problems.

13. It is further ordered, That the burden of proceeding with respect to issue (2) (e) added herein shall be on New Life Evangelistic Center, Inc., and the burden of proceeding with respect to issue (2) (f) and the burden of proof under both of the issues added herein shall be on Midwest St. Louis, Inc.

14. It is further ordered, That there are certified to the Commission the questions whether the STV applications of Midwest St. Louis, Inc., and Evans Broadcasting Corporation, and associated revised issues, should be added to this proceeding.

FEDERAL COMMUNICATIONS COMMISSION,
VINCENT J. MULLINS,
Secretary.

[FR Doc.76-26349 Filed 9-8-76;8:45 am]

[10] Midwest apparently used the same survey for purposes of its STV and non-STV ascertainment.

[11] Thus, with respect to the medical area, Miss Ida Boon is listed by Midwest as associated with the St. Louis Mental Health Association; however, her position in that organization or as a leader in her field is not indicated. Moreover, in a December 22, 1975 amendment in which Midwest seeks to clarify the organizational affiliations of its contactees, Ida Boon is identified as "Director, Local NAACP." With regard to transportation, although Midwest states that St. Louis is the nation's second largest railway center, its second largest trucking center, and the busiest port on the Mississippi River, the sole interviewee in the transportation field is the manager of the local airport.

[12] Also, Midwest claims it has contacted representatives of the elderly by speaking with a leader of the United Fund and the St. Louis Mental Health Association. However, Midwest has not demonstrated that these are organizations of or for the elderly. Similarly Midwest has made no contacts with representatives of youth organizations.

[13] We note, however, that Midwest has adequately responded to the questions raised as to its general public survey by indicating first, that the Doody firm is a professional research and survey organization, and, second, that the survey form distributed by the Doody company did contain questions designed to elicit community needs as well as STV programming preferences.

TV TRANSLATOR

Applications Ready and Available for Processing

Adopted: August 30, 1976.

Released: September 3, 1976.

By the Chief, Broadcast Bureau Notice is hereby given pursuant to §§ 1.572(c) and 1.573(d) of the Commission's rules, that on October 22, 1976, the TV translator applications listed in the attached Appendix will be considered as ready and available for processing. Pursuant to § 1.227(d) and § 1.591(b) of the Commission's rules, an application, in order to be considered with any application appearing on the attached list or with any other application on file by the close of business on October 21, 1976, which involves a conflict necessitating a hearing with any application on this list, must be substantially complete and submitted for filing at the offices of the Commission in Washington, D.C., by the close of business on October 21, 1976.

The attention of any party in interest desiring to file pleadings concerning any pending TV translator application, pursuant to section 309(d)(1) of the Communications Act of 1934, as amended, is directed to § 1.580(i) of the Commission's rules for provisions governing the time for filing and other requirements relating to such pleadings.

FEDERAL COMMUNICATIONS COMMISSION,
VINCENT J. MULLINS,
Secretary.

Attachment.

UHF TV TRANSLATOR APPLICATIONS

BPTT-3042	New, Kirtland, Ohio Educational Television Association of Metropolitan Cleveland Req: Channel 59, 10 watts Primary: WVIZ(TV), Cleveland, Ohio
BPTT-3043	New, Willoughby Hills Area, Ohio Educational Television Association of Metropolitan Cleveland Req: Channel 63, 10 watts Primary: WVIZ(TV), Cleveland, Ohio
BPTT-3044	New, Chagrin Falls, Ohio Educational Television Association of Metropolitan Cleveland Req: Channel 65, 10 watts Primary: WVIZ(TV), Cleveland, Ohio
BPTT-3045	New, Gates, Ohio Educational Television Association of Metropolitan Cleveland Req: Channel 67, 10 watts Primary: WVIZ(TV), Cleveland, Ohio
BPTT-3046	New, Alton & Rural Kane County, Utah University of Utah Req: Channel 57, 20 watts Primary: KUED(TV), Salt Lake City, Utah
BPTT-3047	New, Wellsville, New York Board of Cooperative Educational Services of Allegany County Req: Channel 56, 100 watts Primary: WNED(TV), Buffalo, New York

BPTT-3048 New, Rushford, New York
Board of Cooperative Educational Services of Allegany County
Req: Channel 56, 1 watt
Primary: WNED(TV), Buffalo, New York

BPTT-3049 New, Allentown, New York
Board of Cooperative Educational Services of Allegany County
Req: Channel 59, 10 watts
Primary: WNED(TV), Buffalo, New York

BPTT-3050 New, Andover, New York
Board of Cooperative Educational Services of Allegany County
Req: Channel 62, 10 watts
Primary: WNED(TV), Buffalo, New York

BPTT-3051 New, Fillmore, New York
Board of Cooperative Educational Services of Allegany County
Req: Channel 62, 10 watts
Primary: WNED(TV), Buffalo, New York

BPTT-3052 New, Friendship, New York
Board of Cooperative Educational Services of Allegany County
Req: Channel 62, 1 watt
Primary: WNED(TV), Buffalo, New York

BPTT-3053 New, Whitesville, New York
Board of Cooperative Educational Services of Allegany County
Req: Channel 64, 1 watt
Primary: WNED(TV), Buffalo, New York

BPTT-3054 New, Angelica, New York
Board of Cooperative Educational Services of Allegany County
Req: Channel 65, 1 watt
Primary: WNED(TV), Buffalo, New York

BPTT-3055 New, Bolivar, New York
Board of Cooperative Educational Services of Allegany County
Req: Channel 65, 10 watts
Primary: WNED(TV), New York

BPTT-3056 New, Centerville, (Belfast), New York
Board of Cooperative Educational Services of Allegany County
Req: Channel 67, 100 watts
Primary: WNED(TV), Buffalo, New York

BPTT-3057 New, Rapid City, South Dakota
Wyneco Communications, Inc.
Req: Channel 15, 100 watts
Primary: KYCU(TV), Cheyenne, Wyoming

BPTTV-5635A New, California Polytechnic State University, California
California Polytechnic State University
Req: Channel 7, 1 watt
Primary: KCOY(TV), Santa Maria, California

BPTTV-5637 New, Shell, Wyoming
Shell TV Association
Req: Channel 5, 1 watt
Primary: KURL(TV), Billings, Montana

BPTTV-5638 New, Shell, Wyoming
Shell TV Association
Req: Channel 12, 1 watt
Primary: KTVQ(TV), Billings, Montana

BPTTV-5639 New, Lonerock, Oregon
Lonerock, Television
Req: Channel 13, 1 watt
Primary: KGW(TV), Portland, Oregon

BPTTV-5645 New, Fort Benton, Montana
Fort Benton TV Club
Req: Channel 9, 1 watt
Primary: KTCM(TV), Helena, Montana

Application deleted from Public Notice released March 25, 1976, (Mimeo No. 62550, 41 F.R. 12922)

BPTTV-5490 New, California Polytechnic State University, California
California Polytechnic State University
Req: Channel 9, 1 watt
Primary: KCOY(TV), Santa Maria, California

(Assigned new file number BPTTV-5635A)

[FR Doc.76-26348 Filed 9-8-76;8:45 am]

[Docket No. 20899; FCC 76-808]

WADE H. PATRICK, D/B/A WASHINGTON COUNTY UTILITY DISTRICT CATV DIVISION, WASHINGTON COUNTY, TENNESSEE

Cease and Desist Order

Adopted: August 24, 1976.
Released: September 2, 1976.

By the Commission: Commissioner Wasburn absent. 1. Actions initiating this proceeding commenced with the visit of an engineer from the Commission's Atlanta, Georgia, Field Operations Bureau office to the Washington County Utility District cable television system in order to obtain data concerning the system's technical performance measurements. The Commission engineer spoke with the system's manager and engineer. During the inspection the Commission's engineer determined that not only was the system technically deficient, but also that it had failed to conduct its technical performance tests as required by the Commission's Rules.[1] Moreover, the system's manager indicated that the system had been in operation since July 1969 without having made the required notifications or filings with the Commission.[2]

2. Upon receipt of this information, the Cable Television Bureau reviewed its files and determined that none of the required filings had been made. Therefore, the Bureau directed an inquiry (via certified mail, return receipt requested) to the cable television system to ascertain the nature and scope of its cable television operations. No response was received even though the certified receipt was returned evidencing delivery of the correspondence. The Bureau then initiated a follow-up letter, again via certified mail and the receipt was returned evidencing delivery. However, to date, no response has been received.

3. Information supplied to the Bureau by the Field Operations Bureau indicates that the facility serves approximately 1800 subscribers in Washington County, Tennessee, and carries the signals of the following television broadcast stations:[3]

WATE–TV (NBC, Channel 6), Knoxville, Tennessee.

WBIR–TV (CBS, Channel 10), Knoxville, Tennessee.

WKPT–TV (ABC, Channel 19), Kingsport, Tennessee.

WJHL–TV (CBS, Channel 11), Johnson City, Tennessee.

WSJK–TV (Educ., Channel 2), Sneedville, Tennessee.

WBTV (CBS, Channel 3), Charlotte, North Carolina.

WLOS–TV (ABC, Channel 13), Asheville, North Carolina.

WFBC–TV (NBC, Channel 4), Greenville, South Carolina.

WCYB–TV (NBC, Channel 5), Bristol, Virginia.

4. Commission correspondence to the cable system provided sufficient information concerning the Rules and afforded an opportunity for Washington County Utility District to bring its operation into compliance voluntarily. The letters also cautioned against operation in violation of the Commission's Rules. Moreover, Commission staff provided ample opportunity for the cable operator to request special temporary authority. Additionally, the correspondence cautioned the system that it could be subject to administrative sanctions.

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[1] Section 76.601 (a) and (c) state in pertinent part:

"(a) The operator of each cable television system shall be responsible for insuring that each such system is designed, installed, and operated in a manner that fully complies with the provisions of this subpart. Each system operator shall be prepared to show, on request by an authorized representative of the Commission, that the system does, in fact, comply with the rules.

(c) The operator of each cable television system shall conduct complete performance tests of that system at least once each calendar year (at intervals not to exceed 14 months) and shall maintain the resulting test data on file at the system's local office for at least five (5) years. It shall be made available for inspection by the Commission on request * * *"

[2] Former Section 74.1105 of the Commission's Rules generally required cable television systems which began operations prior to March 31, 1972, to notify station licensees or permittees of proposed signal carriage and to file such notifications with the Commission. Additionally, every cable television system is required to file annual reports on FCC Forms 325, 326, and 395 (if applicable).

[3] We note that with the exception of the signals of WKPT–TV, WJHL–TV, WSJK–TV and WCYB–TV the remaining signals carried by the cable system are not authorized by Section 76.59 of the Rules and since it appears the 74.1105 notice was never given, the carriage of these signals may not be properly grandfathered. However, the system may be permitted to continue to carry these signals because there are other systems in Washington County which are lawfully carrying them. This issue is appropriate for examination at the hearing we are ordering.

5. It appears that the continued operation of the subject cable television system without a certificate of compliance is in violation of our Rules since it was not lawfully carrying television broadcast signals prior to March 31, 1972, and has not obtained a certificate of compliance. At a minimum, former Section 74.1105 of the Rules—which was deleted with the adoption of the 1972 Cable Television Report and Order—required the operator of a proposed cable television system to notify the licensees of local television broadcast stations that cable service would be undertaken. No such notification has been shown by Washington County Utility District to have ever been served nor do Commission records reflect that notification. Additionally, five of the signals currently carried are inconsistent with Section 76.59 of the Rules. The system has neither conducted technical performance tests as required by Section 76.601 of the Rules, nor filed its annual reports as required by Section 76.401 et seq. Finally, Washington County Utility District, although it has had ample opportunity, has failed to respond to official Commission correspondence. Finally, in this instance, enforcement of the Commission's Rules is stymied by Washington County Utility District's silence and forces us to rely upon unrebutted information in the action we take today. Given the cable system's failure to reply, coupled with its apparent violations of our Rules we believe the issuance of this Order to Show Cause is appropriate.

Accordingly, it is ordered, That pursuant to Section 312 (b) and (c) of the Communications Act of 1934, as amended, 47 U.S.C. 312 (b) and (c), Washington County Utility District, CATV Division, is directed to show cause why it should not be ordered to cease and desist from further violations of Part 76 of the Commission's Rules and Regulations by its cable television system in Washington County, Tennessee.

It is further ordered, That Washington County Utility District, CATV Division, is directed to appear and give evidence with respect to the matters described above at a hearing to be held at a time and place to be specified by subsequent order before an Administrative Law Judge, unless the hearing is waived in which event a written statement may be submitted.

It is further ordered, That the Secretary of the Federal Communications Commission shall send copies of this order by certified mail to Washington County Utility District, CATV Division, Johnson City, Tennessee.

FEDERAL COMMUNICATIONS COMMISSION,
VINCENT J. MULLINS,
Secretary.

[FR Doc.76-26350 Filed 9-8-76;8:45 am]

FEDERAL ENERGY ADMINISTRATION

VOLUNTARY AGREEMENT AND PLAN OF ACTION TO IMPLEMENT THE INTERNATIONAL ENERGY PROGRAM

Meeting

In accordance with section 252(c)(1)(A)(i) of the Energy Policy and Conservation Act (Pub. L. 94-163), notice is hereby provided of a meeting of Subcommittee C of the Industry Advisory Board (IAB) to the International Energy Agency (IEA) to be held on September 20, 1976, at the offices of Mobil Oil Corporation, 150 East 42nd Street, New York, New York, beginning at 10 a.m.

1. Opening remarks by Chairman.
2. Settlement of Disputes.

A. Draft on procedures/structure of a disputes settlement body.

3. Extraordinary Costs.

A. Draft on illustrative examples of situations which could lead to extraordinary costs claims.

B. Suggested redraft of IEA paper on extraordinary costs.

4. Pricing in an Emergency.

A. Draft paper on how complaints to the IEA would be handled.

B. Draft on disputes settlement when pricing issues are involved.

C. Draft papers on data availability.

1. Description of pricing data available to the IEA and member countries from published sources.

2. Data available to IEA countries from national sources.

D. Draft describing data available to the IEA from the SOM system.

E. Discuss how to incorporate items 4 (A) through (D) above, in the Secretariat summary paper.

5. Future Work Program of Subcommittee C.

As provided in section 252(c)(1)(A)(ii) of the Energy Policy and Conservation Act, this meeting will not be open to the public.

Issued in Washington, D.C., September 2, 1976.

MICHAEL F. BUTLER,
General Counsel,
Federal Energy Administration.

[FR Doc.76-26295 Filed 9-3-76;10:12 am]

FEDERAL POWER COMMISSION

[Docket Nos. E-7738, E-7784, and E-8885]

BOSTON EDISON CO.

Notice of Conference

AUGUST 30, 1976.

Take notice that on September 17, 1976, Staff is convening a conference of all interested persons for the purpose of discussing the issues in the above-captioned dockets with a view toward settling these proceedings in Room 3200 (North Building) at the offices of the Federal Power Commission, 941 North Capitol Street, N.E., Washington, D.C. 20426 at 10:00 a.m.

All parties will be expected to come fully prepared to discuss the merits of all issues concerning the lawfulness of the proposed rate increases or to make commitments with respect to such issues and any offers of settlement or stipulations discussed at the conference.

KENNETH F. PLUMB,
Secretary.

[FR Doc.76-26272 Filed 9-8-76;8:45 am]

[Docket No. ER76-819]

CENTRAL ILLINOIS LIGHT CO.

Order Accepting for Filing and Suspending Proposed Tariff Sheets, Granting Intervention and Establishing Procedure

AUGUST 27, 1976.

Before Commissioners: Richard L. Dunham, Chairman; Don S. Smith, John H. Holloman III, and James G. Watt.

On July 29, 1976, Central Illinois Light Company (CILCO) submitted for filing increases in the wholesale rate schedules applicable to two municipals and one cooperative customer.[1]

Under the wholesale rate schedule MW-2, demand charge would be raised to $6.00/kVa for the first 1,000 kVa or less and $5.50/kVa for additional demand from the old rates of $2.50/kVa and $2.35/kVa, respectively. Energy charge would be raised to 1.50¢/kWh for the first 300 kWh per kVa of demand and .90¢/kWh thereafter from .94¢/kWh and .80¢/kWh, respectively. A monthly charge of $90.00 has been instituted.

[1] See the following table:

Designation	Instrument	Customer
(1) Supp. No. 2 to rate schedule FPC No. 17 (supersedes supp. No. 1).	Rate MW-2	Village of Riverton, Ill.
(2) Supp. No. 3 to rate schedule FPC No. 17	Fuel clause	Do.
(3) Supp. No. 2 to rate schedule FPC No. 18 (supersedes supp. No. 1).	Rate MW-2	Village of Chatham, Ill.
(4) Supp. No. 3 to rate schedule FPC No. 18	Fuel clause	Do.
(5) Supp. No. 3 to rate schedule FPC No. 19 (supersedes supp. No. 2).	Rate REA-2	Corn Belt Electric Cooperative, Inc.
(6) Supp. No. 4 to rate schedule FPC No. 19	Fuel clause	Do.

Under the wholesale rate schedule REA-2, demand charge for the first 1,000 kVa or less will be raised to $4.50/kVa and for additional kVa would be raised to $4.00/kVa from the old rates of $2.40/kVa and $2.00/kVa, respectively. Energy charge would be raised to the same level as in MW-2. A monthly charge of $125.00 has been instituted. Billing demand under both schedules is subject to a 60%, eleven-month ratchet clause. The maximum monthly demand in any month shall not be less than 1,000 kVa, up from 500 kVa previously.

Public notice of CILCO's increase was issued on August 5, 1976, with comments, protests or petitions to intervene due on or before August 17, 1976. On August 16, 1976, Petitions to Intervene were filed by the Village of Chatham (Chatham) and Corn Belt Electric Cooperative, Inc. (Cooperative).

Chatham and Cooperative state that they will be directly and adversely affected by CILCO's proposed changes, that their respective interests cannot be adequately represented by other parties and, therefore, they request to intervene in this proceeding.

Chatham maintains that CILCO's proposed revised charges will result in an increase in rates to Chatham of 68%, that such increase is excessive and may be unjust and unreasonable.

Cooperative contends 1) that the proposed increase of 48% applicable to its rates is unreasonably high; 2) that the proposed increase is based on the Period II future test year ending June 30, 1977, which is not required for applications involving rate increases less than $1 million, 3) that the proposed increase should be based upon an existing test year, 4) that the wholesale rate cost of service allocation should be based on a ratio of summer peaks rather than a ratio of the twelve month average peaks, and 5) that CILCO's proposed rate results in an unreasonable rate of return on common equity.

The Commission's review of CILCO's proposed rate charges indicates that CILCO's proposed rate increases have not been shown to be just and reasonable and, therefore may be unjust, unreasonable, unduly discriminatory or preferential or otherwise unlawful. Accordingly, the proposed rate increases should be accepted for filing and suspended for five months.

CILCO proposes an effective date, after five month suspension, of February 1, 1977 for its filed increases. Such effective date is not within the ninety days prescribed by Section 35.3 of the Commission's Rules and Regulations. Good cause exists to waive the ninety day requirement as provided in Section 35.3(b), but in light of Cooperative's request for five month suspension and our decision to grant it, such waiver is unnecessary.

The Commission finds: (1) CILCO's proposed rate increases should be accepted for filing and suspended for five months.

(2) Good cause exists to allow Chatham and Cooperative to intervene in this proceeding.

The Commission orders: (A) Supplements No. 2 and No. 3 to Rate Schedule FPC No. 17, Supplements No. 2 and No. 3 to Rate Schedule FPC No. 18 and Supplements No. 3 and No. 4 to Rate Schedule FPC No. 19 are hereby accepted for filing and use thereof suspended for five months, or until February 1, 1977, at which time they may become effective, subject to refund, pending the outcome of the litigation thereon.

(B) Pursuant to the authority of the Federal Power Act, particularly Sections 205 and 206 thereof, the Commission's Rules of Practice and Procedure, and the Regulations under the Federal Power Act (18 CFR Chapter I), a public hearing shall be held concerning the justness and reasonableness of the rates, charges, terms, and conditions of service included in CILCO's FPC Electric Tariff MRS as proposed to be revised by the subject filings.

(C) The Staff shall prepare and serve top sheets on all parties for settlement purposes on or before February 1, 1977. (See Administrative Order No. 157).

(D) A Presiding Administrative Law Judge to be designated by the Chief Administrative Law Judge for that purpose, (See Delegation of Authority, 18 CFR 3.5 (d)), shall convene a settlement conference in this proceeding on a date certain within 10 days after the service of top sheets by the Staff, in a hearing or conference room of the Federal Power Commission, 825 North Capitol Street, N.E., Washington, D.C. 20426. Said Presiding Administrative Law Judge is hereby authorized to establish all procedural dates and to rule upon all motions (with the exceptions of petitions to intervene, motions to consolidate and sever, and motions to dismiss), as provided for in the Rules of Practice and Procedure.

(E) CILCO shall file monthly with the Commission the report on billing determinants and revenues collected under the presently effective rates and the proposed increased rates filed herein, as required by Section 35.19a of the Commission Regulations, 18 CFR Section 35.19a.

(F) Chatham and Cooperative are hereby permitted to intervene in this proceeding, *Provided, however,* that participation by them shall be limited to matters affecting asserted rights and interests as specifically set forth in their petitions to intervene; and *Provided, further,* that the admission of these parties shall not be construed as recognition by the Commission that they might be aggrieved because of any order or orders of the Commission entered in this proceeding.

(G) The Secretary shall cause prompt publication of this order to be made in the FEDERAL REGISTER and shall serve a copy thereof on the wholesale customers of CILCO.

By the Commission.

KENNETH F. PLUMB,
Secretary.

[FR Doc.76-26271 Filed 9-8-76;8:45 am]

[Docket No. RP73-109]

EL PASO NATURAL GAS CO. (NORTHWEST DIVISION)

Order Approving Settlement Agreement With Condition; Pipelines Rates: Settlement

AUGUST 31, 1976.

Before Commissioners: Richard L. Dunham, Chairman; Don S. Smith, John H. Holloman III, and James G. Watt.

On December 17, 1975, Presiding Administrative Law Judge Howe certified to the Commission a Stipulation and Agreement intended to settle a part of the captioned docket. Commission review of the proposed settlement agreement indicates that, as hereinafter ordered and conditioned, it represents a resolution in the public interest of the issues raised and should be approved and adopted.

This proceeding involves a rate increase filing for El Paso Natural Gas Company's then Northwest Division System filed on May 25, 1973. The increased rates went into effect, subject to refund, on November 25, 1973, and were intended to recover claimed increased costs of $3,427,112 annually. El Paso's Northwest Division System was divested on February 1, 1974, at which time Northwest Pipeline Corporation succeeded to the operation of the properties at the rates filed in Docket No. RP73-109. El Paso's refund liability as to the proposed rates terminated at the divestiture. Thus, it collected the proposed increase from November 25, 1973, through January 31, 1974.

El Paso proposes that it will reduce its rates for the refund period (November 25, 1973 through January 31, 1974) to the level of rates in effect prior to the rate increase filing,[1] exclusive of purchased gas cost adjustment increases, and refund the increase collected under the higher rates[2] with interest at 7% per annum.

The Commission believes that, except as to the interest rate to be used in computing refunds, the settlement agreement represents an appropriate resolution of the rate increase proposed herein for El Paso's former Northwest Division System. By Order No. 513-A,[3] issued July 14, 1976, the Commission amended its Regulations under the Natural Gas Act to comply with the court's mandate in *American Public Gas Association, et al.* v. *F.P.C.*, No. 75-1104 (D.C. Cir., May 19, 1976), to require that interest accrue at 9% per annum after October 10, 1974, on excess revenues collected prior to October 10, 1974. We shall accept and approve the settlement agreement on condition that El Paso repay the excess amounts collected, with interest accruing at the rate of 7% per annum from the date of collection through October 9, 1974, and at 9% per annum from Octo-

[1] The reduction amounts to 0.074¢ per therm under Rate Schedule PL-1 and 0.071¢ per therm under all other rate schedules.

[2] The principal amount of the increase during the refund period is computed as $672,875.01.

[3] Rate of Interest on Amounts Subject to Refund, Docket No. RM74-18.

ber 10, 1974, to the date refunds are made.

The Commission finds: The settlement agreement filed herein is in the public interest and should be approved, subject to the condition hereinafter ordered.

The Commission orders: (A) The settlement agreement filed by El Paso, incorporated herein by reference, is hereby approved and adopted, subject to the condition hereinafter ordered.

(B) El Paso shall refund all revenues collected in excess of the settlement rates proposed, with interest at 7% per annum from the date of collection through October 9, 1974, and with interest at 9% per annum from October 10, 1974, until the date of payment of the refunds.

(C) This order is without prejudice to any findings or orders which have been made or which may hereafter be made by the Commission, and is without prejudice to any claims or contentions which may be made by Commission, its Staff, or El Paso in any proceeding now pending or hereinafter instituted by or against El Paso or any other person or party.

(D) The Secretary shall cause prompt publication of this order to be made in the Federal Register.

By the Commission.

KENNETH F. PLUMB,
Secretary.

[FR Doc.76-26276 Filed 9-8-76;8:45 am]

[Docket No. RP76-97]

GULF ENERGY AND DEVELOPMENT CORP.

Notice of Extension of Procedural Date

AUGUST 31, 1976.

On August 24, 1976, Staff Counsel filed a motion to extend the date, fixed by order issued May 27, 1976, for service of Staff Top Sheets in the above-designated proceeding.

Upon consideration, notice is hereby given that an extension of time is granted to and including November 30, 1976, within which Staff shall serve Top Sheets on all parties in the above-designated proceeding.

KENNETH F. PLUMB,
Secretary.

[FR Doc.76-26277 Filed 9-8-76;8:45 am]

[Docket No. CI76-228]

KENT GLASGOW

Notice of Extension of Time

AUGUST 31, 1976.

On August 17, 1976, Champlin Petroleum Company filed a motion to extend the time within which to file certain contract amendments and related rate supplements to reflect rates approved by Commission order issued July 20, 1976.

Upon consideration, notice is hereby given that an extension of time is granted to and including September 17, 1976, within which Mr. Glasgow and Champlin Vetroleum Company shall file the data required by Commission order.

KENNETH F. PLUMB,
Secretary.

[FR Doc.76-26278 Filed 9-8-76;8:45 am]

[Docket No. ER76-678]

MAINE ELECTRIC POWER CO.

Notice of Filing Revising Prior Filing

AUGUST 31, 1976.

Take notice that on August 16, 1976, Maine Electric Power Company (MEP CO) revised its May 4, 1976, filing of a supplement to its Rate Schedule FPC No. 1. The instant filing is in response to a deficiency letter from the Commission dated July 28, 1976, and to a Protest and Petition to Intervene filed by New England Power Company (NEP) on July 19, 1976.

MEPCO formally filed a Power Purchase and Transmission Agreement between MEPCO and certain New England electric utilities whereby MEPCO will transmit and sell power it purchases from the New Brunswick Electric Power Commission (New Brunswick) under a "Unit Participation Agreement" (submitted in the May 4, 1976, filing) to these utilities in accordance with rates specified thereunder.

MEPCO requests that the rate supplement become effective retroactively as of May 24, 1976, and that the normal notice requirements of 18 C.F.R. 35.11 be waived. MEPCO further requests a waiver of the requirements of 18 C.F.R. 35.13 since the additional information is either unavailable or has already been submitted through other filings with the Commission.

A major objection of the NEP Protest and Petition to Intervene was directed toward a "refund charge" imposed on MEPCO by New Brunswick and passed on by MEPCO to NEP, among others. MEPCO informs the Commission that, since the NEP Protest and Petition to Intervene was filed, New Brunswick has agreed that the subject refund charge is not a proper item of cost.

MEPCO states that copies of the filing were sent to all participants in the Power Purchase Transmission Agreement.

Any person desiring to be heard or to protest said filing should file a petition to intervene or protest with the Federal Power Commission, 825 North Capitol Street, N.E., Washington, D.C. 20426, in accordance with Sections 1.8 and 1.10 of the Commission's Rules of Practice and Procedure (18 CFR 1.8 or 1.10). All such petitions or protests should be filed on or before September 14, 1976. Protests will be considered by the Commission in determining the appropriate action to be taken, but will not serve to make the protestants parties to the proceeding. Any person wishing to become a party must file a petition to intervene. Copies of this filing are on file with the Commission and are available for public inspection.

KENNETH F. PLUMB,
Secretary.

[FR Doc.76-26279 Filed 9-8-76;8:45 am]

[Docket No. RP73-43 (PGA 76-3a)]

MID LOUISIANA GAS CO.

Notice of Proposed Change in Rates

AUGUST 30, 1976.

Take notice that Mid Louisiana Gas Company (Mid Louisiana), on August 12, 1976, tendered for filing as a part of First Revised Volume No. 1 of its FPC Gas Tariff, Twenty-first Revised Sheet No. 3a and Twenty-second Revised Sheet No. 3a.

Mid Louisiana states that the purpose of the filing is to reflect a Purchased Gas Cost Current Adjustment to Mid Louisiana's Rate Schedules G-1, SG-1, I-1 and E-1 to be effective August 1, 1976 and August 2, 1976, pursuant to Commission Order dated July 30, 1976. Mid-Louisiana further states that copies of the filing were served on interested customers and state commissions.

Any person desiring to be heard or to protest said application should file a petition to intervene or protest with the Federal Power Commission, 825 North Capitol Street, N.E., Washington, D.C. 20426, in accordance with Sections 1.8 and 1.10 of the Commission's Rules of Practice and Procedure (18 CFR 1.8, 1.10). All such petitions or protests should be filed on or before September 10, 1976. Protests will be considered by the Commission in determining the appropriate action to be taken, but will not serve to make protestants parties to the proceeding. Any person wishing to become a party must file a petition to intervene. Copies of this application are on file with the Commission and are available for public inspection.

KENNETH F. PLUMB,
Secretary.

[FR Doc.76-26273 Filed 9-8-76;8:45 am]

[Docket No. ER76-830]

MISSISSIPPI POWER & LIGHT CO.

Order Accepting for Filing and Suspending Proposed Rate Changes, Granting Interventions and Establishing Procedures; Electric Rates

AUGUST 27, 1976.

Before Commissioners: Richard L. Dunham, Chairman; Don S. Smith, John H. Holloman III, and James G. Watt.

On July 30, 1976, Mississippi Power and Light Company (MP&L) tendered for filing proposed changes [1] in its wholesale electric rate schedules applicable to seven electric power associations at 60 delivery points and five municipals, which proposed changes would result in an increase in annual revenues of

[1] See Attachment A for designations.

$3,321,383 (12.3%) based on the 12 month period ending August 31, 1977. Said increase is based on the inclusion of construction work in progress (CWIP) in rate base as requested by MP&L in its filing. The proposed effective date of the rate increase is September 1, 1976. For the reasons hereinafter stated the Commission shall accept the proposed rate schedules for filing, suspend the proposed rates for three months, or until December 1, 1976, to be collected thereafter subject to refund, require MP&L to file within sixty (60) days revised charges reflecting the elimination of CWIP from rate base, and establish hearing procedures.

MP&L asserts that the principal reason for the increase in rates is that jurisdictional revenues at present rates are inadequate to meet cost of service and provide fair rate of return. MP&L further asserts that the required increase reflects a rate of return of 10.17% which is the minimum return required to carry on its operations, discharge its obligations to its investors and attract necessary additional capital to serve the future electric requirements of its customers.

MP&L asserts that the inclusion of CWIP in rate base is justified in that over 50% of the CWIP included in its rate base for period II represents projects relating to the conversion of existing generating units from gas to oil, and as such do not produce future revenue, and in that it anticipates a favorable ruling in the rulemaking proceeding in Docket No. RM75-13 which would allow all CWIP in rate base by the time the subject increased rates would be allowed to go into effect.

Public notice of MP&L's proposed increase was issued on August 17, 1976 with comments, protests or petitions to intervene due on or before August 25, 1976. On August 20, 1976, a protest, petition to intervene, and request for hearing and five month suspension was filed by the seven electric power associations and five municipals (hereinafter referred to as petitioners) being served under the rate schedules that MP&L proposes to change as described above. Said petitioners state that they will be directly and adversely affected by MP&L's proposed changes and that their interests cannot be represented adequately by other parties, and therefore, they request to intervene in the proceeding. Petitioners allege that: (1) the proposed increased rates tendered by MP&L for filing on July 30, 1976, are unjust and unreasonable because they are excessive; (2) several errors in the MP&L filing indisputably establish that the cost of service study substantially overstates the actual cost to MP&L of furnishing service to petitioners; and (3) the proposed increased rates to them are discriminatory and anti-competitive, representing a "price squeeze" which violates the antitrust laws as recognized in *FPC* v. *Conway Corp.*, 44 USLW 4777. Based on the forgoing petitioners request a full five month suspension.

Commission review of MP&L's proposed rate filing indicates the improper inclusion of CWIP in rate base in cost of service calculations.

The Commission's review indicates that that proposed increased rates filed July 30, 1976 have not been shown to be just and reasonable and may be unjust, unreasonable, unduly discriminatory, preferential or otherwise unlawful. Many of the issues raised in the protest and petition to intervene by MP&L's wholesale customers are properly the subject for further development and consideration at hearing rather than at this state of the proceeding. The decision to suspend is discretionary and the Commission does not believe a full five month suspension is warranted in this case.

Recent Commission decisions have made it clear that the Commission will not currently allow utilities to base rates upon the inclusion of CWIP in rate base.[1] As we stated in the Order Denying Application For Rehearing,[2] Georgia Power Company, Docket No. E-9091, issued September 19, 1975:

> The majority rule of public utility regulation holds that the value of plant under construction cannot be included in the rate base until the plant is "used and useful" in providing service to jurisdictional customers. We have consistently applied the "used and useful" rule throughout our formally reported final decisions. Our Uniform System of Accounts for public utilities and licensees clearly reflects that principle, although it has not been formally codified in a separate regulation, as in the case for gas pipeline companies, Sec. 154.63(f), 18 CFR.

We note that while it has not been the policy of this Commission to permit utilities to earn a return on CWIP, that practice is currently being reviewed in Docket No. RM75-13.[4] For all of the above reasons, it would therefore be inappropriate for MP&L to reflect in its rates the inclusion of CWIP in rate base for facilities which will not be placed into service prior to the end of the test period (Period II). Accordingly, we shall accept the proposed rate schedules for filing, require MP&L to file within 60 days revised charges reflecting the elimination of CWIP from rate base, suspend the proposed revised rates for three months until December 1, 1976, subject to refund, and establish hearing procedures.

The Commission finds: (1) Good cause exists to accept for filing MP&L's proposed rates filed July 30, 1976, and to suspend those rates for three months, or until December 1, 1976, when they may be permitted to become effective, subject to refund, pending the outcome of a hearing and decision thereon.

(2) Good cause exists to require MP&L to file within sixty days of the issuance of this order revised charges reflecting the elimination of CWIP from rate base.

(3) Good cause exists to allow the above-named petitioners to intervene in this proceeding.

The Commission orders: (A) Pending a hearing and decision thereon, MP&L's proposed rate schedules are hereby accepted for filing and suspended from operation for three months, to become effective December 1, 1976, subject to refund.

(B) Pursuant to the authority of the Federal Power Act, particularly Sections 205 and 206 thereof, and the Commission's Rules and Regulations, a hearing shall be held concerning the justness and reasonableness of the subject rate increase.

(C) The Commission Staff shall prepare and serve top sheets on all parties for purposes of settlement on or before March 1, 1977. (Administrative Order No. 157.)

(D) MP&L shall file within sixty days of the issuance of this order revised charges reflecting the elimination of CWIP from rate base.

(E) A Presiding Administrative Law Judge to be designated by the Chief Administrative Law Judge for that purpose (See Delegation of Authority, 18 CFR 3.5(d)), shall convene a settlement conference in this proceeding on a date certain within 10 days after the service of top sheets by the Staff, in a hearing or conference room of the Federal Power Commission, 825 North Capitol Street NE., Washington, D.C. 20426. Said Presiding Administrative Law Judge is hereby authorized to establish all procedural dates and to rule upon all motions (with the exceptions of petitions to intervene, motions to consolidate and sever, and motions to dismiss), as provided for in the Rules of Practice and Procedure.

(F) MP&L shall file monthly with the Commission the report on billing determinants and revenues collected under the presently effective rates and the proposed increased rates filed herein, as required by Section 35.19a of the Commission's Regulations, 18 CFR Section 35.19a.

(G) The above-named petitioners are hereby permitted to intervene in these proceedings subject to the rules and regulations of the Commission; *Provided, however,* That participation of such intervenors shall be limited to matters affecting asserted rights and interests as specifically set forth in the petition to intervene; and *Provided further,* That the admission of such intervenors shall not be construed as recognition by the Commission that it might be aggrieved because of any order or orders of the Commission entered in this proceeding.

(H) The Secretary shall cause prompt publication of this order to be made in the FEDERAL REGISTER.

By the Commission.

KENNETH F. PLUMB,
Secretary.

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[1] See e.g., Central Vermont Public Service Corporation, Docket No. E-9040, issued August 5, 1975; Green Mountain Power Corporation, Docket No. E-9446, issued June 13, 1975; New England Power Company, Docket Nos. E-9316 and E-9140, issued August 5, 1975; and Georgia Power Company, Docket No. E-9091, issued August 5, 1975.

[2] Pending review in *Georgia Power Company* v. *FPC*, No. 75-1940, D.C. Circuit, Denial of Application for Stay, issued October 3, 1975.

[4] Notice of Proposed Rulemaking issued November 14, 1974.

ATTACHMENT A—MISSISSIPPI POWER & LIGHT COMPANY

RATE SCHEDULE MW–14

Rate schedule designations:	Other party (municipals)
(1) Supplement No. 6 to rate schedule FPC No. 88 (supersedes supplement No. 5).	Canton, Miss.
(2) Supplement No. 6 to rate schedule FPC No. 87 (supersedes supplement No. 5).	Kosciusko, Miss.
(3) Supplement No. 6 to rate schedule FPC No. 93 (supersedes supplement No. 5).	Leland, Miss.
(4) Supplement No. 2 to rate schedule FPC No. 236 (supersedes supplement No. 1).	Durant, Miss.
(5) Supplement No. 2 to rate schedule FPC No. 238 (supersedes supplement No. 1).	Itta Bena, Miss.

Rate schedule REA–14

Designations	Other party	Delivery point
(1) Supp. No. 4 to rate schedule FPC No. 165 (supersedes supp. No. 3).	Coahoma EPA	Clarksdale.
(2) Supp. No. 4 to rate schedule FPC No. 166 (supersedes supp. No. 3).	do	Darling.
(3) Supp. No. 4 to rate schedule FPC No. 168 (supersedes supp. No. 3).	do	Lula.
(4) Supp. No. 4 to rate schedule FPC No. 169 (supersedes supp. No. 3).	do	Sunflower.
(5) Supp. No. 4 to rate schedule FPC No. 170 (supersedes supp. No. 3).	do	Shelby.
(6) Supp. No. 4 to rate schedule FPC No. 171 (supersedes supp. No. 3).	do	Tunica.
(7) Supp. No. 4 to rate schedule FPC No. 172 (supersedes supp. No. 3).	do	Walls.
(8) Supp. No. 4 to rate schedule FPC No. 173 (supersedes supp. No. 3).	Delta EPA	Cleveland.
(9) Supp. No. 4 to rate schedule FPC No. 174 (supersedes supp. No. 3).	do	Greenville.
(10) Supp. No. 4 to rate schedule FPC No. 175 (supersedes supp. No. 3).	do	Greenwood.
(11) Supp. No. 4 to rate schedule FPC No. 176 (supersedes supp. No. 3).	do	Indianola.
(12) Supp. No. 4 to rate schedule FPC No. 177 (supersedes supp. No. 3).	do	Inverness.
(13) Supp. No. 4 to rate schedule FPC No. 178 (supersedes supp. No. 3).	do	Pace.
(14) Supp. No. 4 to rate schedule FPC No. 179 (supersedes supp. No. 3).	do	Schlater.
(15) Supp. No. 4 to rate schedule FPC No. 181 (supersedes supp. No. 3).	do	Winona.
(16) Supp. No. 4 to rate schedule FPC No. 182 (supersedes supp. No. 3).	Magnolia EPA	Brookhaven.
(17) Supp. No. 4 to rate schedule FPC No. 184 (supersedes supp. No. 3).	do	Fernwood.
(18) Supp. No. 4 to rate schedule FPC No. 185 (supersedes supp. No. 3).	do	Liberty.
(19) Supp. No. 4 to rate schedule FPC No. 186 (supersedes supp. No. 3).	do	Norfield.
(20) Supp. No. 4 to rate schedule FPC No. 188 (supersedes supp. No. 3).	do	Tylertown.
(21) Supp. No. 4 to rate schedule FPC No. 189 (supersedes supp. No. 3).	Southwest Mississippi EPA	Brookhaven.
(22) Supp. No. 4 to rate schedule FPC No. 190 (supersedes supp. No. 3).	do	Crosby.
(23) Supp. No. 4 to rate schedule FPC No. 191 (supersedes supp. No. 3).	do	Lorman.
(24) Supp. No. 4 to rate schedule FPC No. 192 (supersedes supp. No. 3).	do	Port Gibson.
(25) Supp. No. 4 to rate schedule FPC No. 194 (supersedes supp. No. 3).	do	Washington.
(26) Supp. No. 4 to rate schedule FPC No. 196 (supersedes supp. No. 3).	Twin County, EPA	Belzoni.
(27) Supp. No. 4 to rate schedule FPC No. 197 (supersedes supp. No. 3).	do	Greenville.
(28) Supp. No. 4 to rate schedule FPC No. 198 (supersedes supp. No. 3).	do	Hollandale.
(29) Supp. No. 4 to rate schedule FPC No. 199 (supersedes supp. No. 3).	do	Leland.
(30) Supp. No. 4 to rate schedule FPC No. 200 (supersedes supp. No. 3).	do	Onward.
(31) Supp. No. 4 to rate schedule FPC No. 201 (supersedes supp. No. 3).	do	Rolling Fork.
(32) Supp. No. 4 to rate schedule FPC No. 202 (supersedes supp. No. 3).	Yazoo Valley, EPA	Anchorage.
(33) Supp. No. 4 to rate schedule FPC No. 203 (supersedes supp. No. 3).	do	Lexington.
(34) Supp. No. 4 to rate schedule FPC No. 204 (supersedes supp. No. 3).	do	Pickens.
(35) Supp. No. 4 to rate schedule FPC No. 205 (supersedes supp. No. 3).	do	Redwood.
(36) Supp. No. 4 to rate schedule FPC No. 206 (supersedes supp. No. 3).	do	Yazoo City.
(37) Supp. No. 4 to rate schedule FPC No. 207 (supersedes supp. No. 3).	Southwest Mississippi EPA	Roxie.
(38) Supp. No. 4 to rate schedule FPC No. 208 (supersedes supp. No. 3).	Delta EPA	Minter City.
(39) Supp. No. 4 to rate schedule FPC No. 209 (supersedes supp. No. 3).	do	Shaw.
(40) Supp. No. 4 to rate schedule FPC No. 210 (supersedes supp. No. 3).	Coahoma	Marks.
(41) Supp. No. 4 to rate schedule FPC No. 211 (supersedes supp. No. 3).	Yazoo Valley EPA	Little Yazoo.
(42) Supp. No. 5 to rate schedule FPC No. 212 (supersedes supp. No. 4).	Southwest Mississippi EPA	Natchez.
(43) Supp. No. 5 to rate schedule FPC No. 213 (supersedes supp. No. 4).	Magnolia EPA	Jayess.

Designations	Other party	Delivery point
(44) Supp. No. 4 to rate schedule FPC No. 214 (supersedes supp. No. 3).	Delta EPA	Moorhead.
(45) Supp. No. 4 to rate schedule FPC No. 216 (supersedes supp. No. 3).	Southwest Mississippi EPA	Utica.
(46) Supp. No. 4 to rate schedule FPC No. 218 (supersedes supp. No. 3).	Magnolia EPA	Progress.
(47) Supp. No. 4 to rate schedule FPC No. 219 (supersedes supp. No. 3).	Delta EPA	Itta Bena.
(48) Supp. No. 4 to rate schedule FPC No. 220 (supersedes supp. No. 3).	do	Carrollton.
(49) Supp. No. 4 to rate schedule FPC No. 222 (supersedes supp. No. 3).	Southwest Mississippi EPA	Woodville.
(50) Supp. No. 4 to rate schedule FPC No. 223 (supersedes supp. No. 3).	Delta EPA	South Cleveland.
(51) Supp. No. 4 to rate schedule FPC No. 224 (supersedes supp. No. 3).	Magnolia EPA	Smithdale.
(52) Supp. No. 4 to rate schedule FPC No. 225 (supersedes supp. No. 3).	Delta EPA	Stringtown.
(53) Supp. No. 5 to rate schedule FPC No. 226 (supersedes supp. No. 7).	Southern Pine EPA	Silver Creek, Haslehurst, Florence, Monticello.
(54) Supp. No. 4 to rate schedule FPC No. 227 (supersedes supp. No. 3).	Magnolia EPA	Gillsburg.
(55) Supp. No. 4 to rate schedule FPC No. 231 (supersedes supp. No. 3).	Delta EPA	Capline.
(56) Supp. No. 4 to rate schedule FPC No. 232 (supersedes supp. No. 3).	Southwest Mississippi EPA	Pineridge.
(57) Supp. No. 4 to rate schedule FPC No. 233 (supersedes supp. No. 3).	Delta EPA	Acona.
(58) Supp. No. 2 to rate schedule FPC No. 237 (supersedes supp. No. 1).	Yazoo Valley EPA	Midway.

[FR Doc.76-26282 Filed 9-8-76;8:45 am]

[Docket Nos. CP76-52, CP76-166]

NORTHERN NATURAL GAS CO. OPERATING AS PEOPLES NATURAL GAS DIVISION

Order Providing for Formal Hearing, Consolidating Proceedings, Granting Petitions To Intervene, and Prescribing Procedures

AUGUST 31, 1976.

Before Commissioners: Richard L. Dunham, Chairman; Don S. Smith, John H. Holloman III, and James G. Watt.

On August 11, 1975, Northern Natural Gas Company (Northern) filed an application in Docket No. CP76-52 pursuant to Section 7(c) of the Natural Gas Act for a certificate of public convenience and necessity authorizing the transportation of vaporized liquefied natural gas (LNG) for its Peoples Natural Gas Division (Peoples) and the construction and operation of certain interconnection facilities. On November 20, 1975, an application, as supplemented March 22, 1976, was filed by Northern on behalf of Peoples requesting a declaratory order disclaiming jurisdiction or, in the alternative an order issuing a certificate of public convenience and necessity pursuant to Section 7(c) of the Act authorizing Peoples to construct and operate facilities for the liquefaction, storage and vaporization of natural gas in Hancock County, Iowa.

The applications indicate that Peoples is planning to construct an LNC plant with a net storage capacity of 1.5 million Mcf equivalent of varporous natural gas and a sendout design rate of 50,000 Mcf per day. The plant is proposed to be located approximately 4 miles south of Northern's Ventura Compressor Station in Hancock County. Northern states that the plant would be used for peak shaving during the heating season.

Northern states in its application in Docket No. CP76-166 that the proposed LNG facility is designed and would be used to aid and assist Peoples in the local distribution of natural gas in Iowa, Nebraska and Minnesota. The estimated cost of the proposed LNG plant is $28,406,350. Northern alleges that volumes of gas to be made available to the LNG facility in the summer for liquefaction would be volumes within Peoples' authorized contract demand from Northern of 436,507 Mcf per day. The application states that the volumes which would be made available from the facility during the winter would, by displacement, be utilized in the various distribution systems operated by Peoples for sale and delivery to residential and small volume consumers.

Northern alleges that the proposed LNG plant is nonjurisdictional under Section 1(b) of the Natural Gas Act as a facility used for local distribution of natural gas. Northern maintains that even though the facility is designed and would be used to assist Peoples in the distribution of gas in Iowa, Nebraska and Minnesota, such facility would be used for (local) distribution within these states and would not be used for the transportation of natural gas in interstate commerce. Northern requests a disclaimer of jurisdiction over said facilities or in the alternative certificate authorization therefor.

In Docket No. CP76-52, Northern requests a certificate of public convenience and necessity authorizing the transportation of LNG for Peoples and the construction and operation of certain interconnection facilities. Interconnection facilities are estimated to cost $210,000 which would be reimbursed by Peoples.

Thirteen customers of Northern have petitioned to intervene in these proceedings. Several petitioners voice concern that approval of the proposed LNG plant and interconnective facilities may increase the risk of curtailment to existing customers by allowing Peoples to provide service to new, higher priority customers during periods of gas supply shortages. In addition, on January 9, 1976, The Brick People, et al., filed a document entitled protest, petition to intervene out of time and request for formal hearing in Docket No. CP76-52, as well as a motion to consolidate for hearing the applications in Docket Nos. CP76-52 and CP76-166. The Brick People, et al.,[1] state in their petition in Docket No. CP76-52 that Northern's application therein for authorization to construct certain interconnection facilities and to transport LNG is contingent upon Peoples building an LNG plant in Hancock County. The Brick People, et al., allege that they had not recognized the potential far-reaching ramifications of the proceeding in Docket No. CP76-52 until reading the notice of application issued in Docket No. CP76-166 wherein it was indicated that the proposed LNG facilities would be used to serve new high priority customers. The Brick People, et al., assert that the question of growth is one of the most serious issues confronting Northern and its customers. In their motion to consolidate, The Brick People, et al., dispute Northern's contention that the proposed LNG plant is exempt under Section 1(b) of the Act, contending that there is nothing "local" about said proposed plant or its operations. The motion asserts that both proceedings involve common questions of law and fact and should be consolidated for formal hearing.

Section 1(b) of the Natural Gas Act states that the provisions of the Act shall apply to the transportation of natural gas in interstate commerce but exempts from Commission jurisdiction the local distribution of natural gas. The application in Docket No. CP76-166 indicates that the proposed LNG plant is designed and will be used to assist Peoples in the distribution of natural gas to consumers in three states. Northern argues that the Commission should declare the LNG facility exempt from jurisdiction since it would be involved in "local" distribution of gas and because Peoples' rates allegedly will be subject to state and city council jurisdiction.

Under the Natural Gas Act either transportation of natural gas in interstate commerce, or the sale in interstate commerce for resale is sufficient to confer jurisdiction upon the Commission. Moreover, Section 5(b) of the Act recognizes that a company may be a "natural-gas company" in cases where its rates may not be subject to the Commission's jurisdiction. In light of the foregoing statutory provisions of the Natural Gas Act and the legal and factual challenges that have been raised to Northern's request for a disclaimer, we decline to issue a declaratory order. Northern and/or Peoples will be afforded an opportunity in the formal hearing hereinafter scheduled to present evidence and argument in support of their contention that the proposed facilities do not fall within this Commission's jurisdiction.

[1] The Brick People, et al., consist of The Brick People, Region Six of Brick Institute of America, Griffin Pipe Products Company, Sewer Pipe Division of Can-Tex Industries, and Dickey Clay Manufacturing Company.

The proposal in Docket No. CP76–52 to construct interconnective facilities to the proposed LNG facility and request for transportation authorization are intrinsically related with the proposal in the application in Docket No. CP76–166. Common questions of law and fact appear to exist sufficient to warrant consolidation of these two applications. A formal hearing will be provided to develop, inter alia, a record regarding:

1. How does construction of the proposed LNG plant and interconnective facilities attaching said plant to Northern's transmission facilities advance the public interest and necessity?

2. What customers and which markets will be served should the the LNG plant and interconnection facilities be constructed?

3. What effect would such proposed construction and operation have on existing customers?

4. Who would pay the cost of the proposed facilities and service?

5. Explain the operational relationship between Northern and its Peoples' Division, identify which entity would construct and operate the LNG plant and describe how said entity would obtain gas to operate the LNG facility?

6. Identify Peoples' 467–B priority 1 peak day requirements and priority 1 daily contract demand supplied by Northern? Identify the maximum volume of gas which could be served by Peoples during a period of peak demand, with and without the proposed LNG facility?

7. Will any existing customers of Peoples receive less gas on an annual basis as a result of the LNG plant?

8. If new customers are proposed to be served what gas usages are proposed and are alternative fuels available to meet these uses? How does continued addition of new customers advance the public interest?

The application in Docket No. CP76–52 was noticed on August 26, 1975, with interventions due by September 18, 1975. The application in Docket No. CP76–166 was noticed on December 18, 1975, with interventions due by January 9, 1976. The following petitions to intervene have been filed:

Party	Dockets Nos.	
	CP76–52	CP76–166
City of Duluth, Minn.	Sept. 22, 1975	
Farmland Industries, Inc.		Jan. 9, 1976
Inter-City Gas Ltd.	Sept. 18, 1975	
Interstate Power Co.	Sept. 8, 1975	
Iowa Electric Light & Power Co.	Sept. 12, 1975	Jan. 12, 1976
Iowa Power & Light Co.	Sept. 18, 1975	
Iowa Southern Utilities Co.	Aug. 25, 1975	
North Central Public Service Co.	Sept. 18, 1975	
Northern States Power Co.	Sept. 15, 1975	
Minnesota Gas Co.	Sept. 26, 1975	Jan. 7, 1976
Terra Chemicals International, Inc.		Jan. 9, 1976
The Brick People, et al.	Jan. 9, 1976	Jan. 9, 1976
Wisconsin Gas Co.	Sept. 17, 1975	

On October 14, 1975, and January 9, 1976, The Iowa State Commerce Commission filed notices of intervention in Docket Nos. CP76–52 and CP76–166, respectively.

Petitioners to intervene and the Iowa State Commerce Commission indicate that they have interests in this proceeding that may not adequately be represented by existing parties.

Late petitions to intervene have been filed in Docket No. CP76–52 by Minnesota Gas Company and the Brick People, *et al.*; however, both petitioners have filed timely petitions to intervene in Docket No. CP76–166. A timely petition to intervene was filed in Docket No. CP76–52 by Iowa Electric Light and Power Company which company filed a late petition to intervene in Docket No. CP76–166. A late notice of intervention was filed by Iowa State Commerce Commission in Docket No. CP76–52; however, a timely notice of intervention was filed by it in Docket No. CP76–166. A late petition to intervene was filed in Docket No. CP76–52 by City of Duluth, Minnesota, alleging that said petitioner did not determine until September 16, 1975, that Northern's application might affect its ability to serve City of Duluth's requirements. The petition states that the City of Duluth purchases all its gas from Northern. Petitioner states it does not have sufficient information to determine whether Northern's proposal will affect service to the City of Duluth but should a hearing be held the city desires to be a party to represent the interests of its customers.

The Commission finds: (1) It is necessary and appropriate in carrying out the provisions of the Natural Gas Act that a public hearing be held on the matters involved and the issues presented in these proceedings as hereinbefore described.

(2) Due to the related nature of the applications and since there may be common questions of law or fact involved, it is appropriate to consolidate the proceedings in Docket Nos. CP76–52 and CP76–166.

(3) Participation by Iowa Southern Utilities Company, Interstate Power Company, Iowa Electric Light and Power Company, Northern States Power Company, Wisconsin Gas Company, North Central Public Service Company, Inter-City Gas Limited, Iowa Power and Light Company, City of Duluth, Minnesota Gas Company, Terra Chemicals International, Inc., Farmland Industries, Inc., The Brick People, *et al.*, and the Iowa State Commerce Commission may be in the public interest. Permitting the filing of late petitions to intervene and Iowa State Commission's late notice of intervention will not delay the proceedings and may be in the public interest.

The Commission orders: (A) The above-mentioned intervenors are permitted to intervene in the instant consolidated proceeding subject to the rules and regulations of the Commission; *Provided*, however, that participation of such interveners shall be limited to matters affecting asserted rights and interests as specifically set forth in the petitions to intervene; and *Provided, further*, that the admission of such interveners shall not be construed as recognition by the Commission that they might be aggrieved because of any order of the Commission entered in the proceeding.

(B) Pursuant to the authority of the Natural Gas Act, particularly Sections 4, 5 and 15 thereof, the Commission's Rules of Practice and Procedure (18 CFR Chapter 1), and the Regulations under the Natural Gas Act, a prehearing conference shall be held on September 21, 1976, commencing at 10:00 a.m. in a hearing room of the Federal Power Commission, 825 North Capitol Street, N.E., Washington, D.C. 20426, to discuss procedural issues and for the clarification of issues.

(C) An Administrative Law Judge, to be designated by the Chief Administrative Law Judge for that purpose, (See Delegation of Authority, 18 CFR 3.5(d)), shall preside at the prehearing conference in this proceeding, with authority to establish and change all procedural dates, and to rule on all motions, (with the sole exception of petitions to intervene, motions to consolidate and sever, and motions to dismiss), as provided for in the Rules of Practice and Procedure.

(D) The direct cases of Northern and Peoples, including testimony on the issues raised by this order, shall be filed and served on all parties, the Presiding Administrative Law Judge, and the Commission Staff on or before September 15, 1976. All supporting interveners, shall file testimony and exhibits comprising their cases in chief on or before September 15, 1976.

By the Commission.

KENNETH F. PLUMB,
Secretary.

[FR Doc.76–26280 Filed 9–8–76;8:45 am]

[Docket Nos. RP72–156, (PGA76–3) and RP72–64 (DCA76–2)]

TEXAS GAS TRANSMISSION CORP.

Notice of Filing

AUGUST 30, 1976.

Take notice that on August 13, 1976, the Texas Gas Transmission Corporation (Texas Gas) tendered for filing a revised tariff sheet reflecting the exclusion of costs associated with small producers in excess of the "130 percent formula" prescribed in Opinion No. 742 and costs associated with emergency purchases at rates in excess of those prescribed in Opinion No. 699–H, which costs were reflected in Texas Gas' filing of June 14, 1976. Texas Gas also filed a list of small producers from whom the company is purchasing gas at rates in excess of the "130 percent formula" in compliance with the Commission's order of July 30,

1976, whereby the Commission accepted the filing of June 14, 1976, and assigned it an effective date of August 2, 1976. Texas Gas requests that its revised tariff sheet becomes effective on August 1, 1976.

Texas Gas states that copies of the filing have been sent to all of its customers as well as interested State Commissions.

Any person desiring to be heard or to protest said filing should file a petition to intervene or protest with the Federal Power Commission, 825 North Capitol Street, NE., Washington, D.C. 20426, in accordance with §§ 1.8 and 1.10 of the Commission's rules of practice and procedure (18 CFR 1.8, 1.10). All such petitions or protests should be filed on or before Sept. 10, 1976. Protests will be considered by the Commission in determining the appropriate action to be taken, but will not serve to make protestants parties to the proceeding. Any person wishing to become a party must file a petition to intervene. Copies of this application are on file with the Commission and are available for public inspection.

KENNETH F. PLUMB,
Secretary.

[FR Doc.76-26274 Filed 9-8-76;8:45 am]

[Docket No. RP75-75 (AP76-10)]

TRANSCONTINENTAL GAS PIPE LINE CORP.

Order Accepting Filing Subject to Refund and Setting Procedures; Pipeline Rates: Advance Payments

AUGUST 31, 1976.

On July 16, 1976, Transcontinental Gas Pipe Line Corporation (Transco) tendered for filing certain revised tariff sheets [1] containing an increase in rates reflecting increases in the level of advance payments [2] made by Transco to producers of natural gas. The proposed effective date is September 1, 1976. The filing is made pursuant to the terms of the settlement agreement approved by the Commission in Docket No. RP75-75. Because the advances may not be reasonable, appropriate procedures will be established to undertake their review. In accordance with the terms of the settlement agreement the increase will be accepted for filing and the rates made effective without suspension but subject to refund.

Transco's proposed increase reflects an increase of $14,317,676 in the advance payments amount over the level imbedded in Transco's rates which became effective July 1, 1976, subject to refund. The additional advance payments consist of (1) $327,021 attributable to two new advance payment agreements [3] and (2) $13,990,655 of additional advances less repayments received under agreements reflected in presently effective rates.

Public notice of Transco's filing was issued July 26, 1976, with Protests and Petitions to Intervene due on or before August 16, 1976.

The Commission's review indicates that the increased rates reflecting additional advances made pursuant to agreements subject to pending proceedings [4] should be allowed, subject to refund, pending the outcome of such proceedings. Commission review of the new advances listed in footnote 3 herein indicates that they have not been shown to be reasonably related to the producers' expenditures for exploration, development and production as required by Order No. 499, 50 FPC 2111 (1973) reh. den. 51 FPC 818 (1974). The Commission shall therefore convene a hearing to determine the lawfulness of those two advances.

The Commission finds: (1) Transco's rate increase, filed July 16, 1976, has not been shown to be just and reasonable in that the advance payments upon which it is based have not been shown to be reasonable and appropriate.

(2) The lawfulness of Transco's instant rate increase as it relates to the advances made pursuant to agreements that are the subject of litigation in other dockets is made subject to the outcome of those cases.

(3) The Commission should convene a hearing concerning the the lawfulness of the advances contained in the instant filing made pursuant to agreements which have not been the subject of prior Commission litigation.

The Commission orders: (A) Transco's filing is accepted for filing to become effective September 1, 1976, subject to refund.

(B) A Presiding Administrative Law Judge, to be designated by the Chief Administrative Law Judge for that purpose (See Delegation of Authority, 18 CFR 3.5 (d)), shall convene a prehearing conference in this proceeding on September 2, 1976, at 9:30 A.M., in a hearing room of the Federal Power Commission, 825 North Capitol Street, Washington, D.C. 20426. The issues in the proceeding shall be limited to the lawfulness of Transco's instant filing as it relates to advances made pursuant to agreements identified in footnote 3, *supra*. Said Presiding Administrative Law Judge is hereby authorized to establish all procedural dates and to rule upon all motions (with the exceptions of petitions to intervene, motions to consolidate and sever, and motions to dismiss), as provided for in the Rules of Practice and Procedure.

(C) The lawfulness of Transco's rate increase as it relates to advances made pursuant to agreements which are the subject of prior Commission litigation at Docket Nos. RP75-48, and 75-3 and Docket No. RP75-75 (Advance Payments), *et al.*, is made subject to the outcome of such litigation.

(D) Nothing contained herein shall be construed as limiting the rights of the parties to this proceeding regarding the convening of conferences or offers of settlement pursuant to Section 1.18 of the Commission's Rules of Practice and Procedure.

(E) The Secretary shall cause prompt publication of this order in the FEDERAL REGISTER.

By the Commission.

KENNETH F. PLUMB,
Secretary.

[FR Doc.76-26281 Filed 9-8-76;8:45 am]

[Docket No. E-9147 (Phase II)]

VIRGINIA ELECTRIC AND POWER CO.

Notice of Further Extension of Procedural Dates

AUGUST 30, 1976.

On August 16, 1976, ElectriCities of North Carolina filed a motion to extend the procedural dates, fixed by order issued January 22, 1975, as most recently modified by Notice issued May 25, 1976, in the above-designated proceeding. The motion states that parties to the proceeding have no objection.

Upon consideration, notice is hereby given that the procedural dates in the above proceeding are modified as follows:

Service of Intervenor Testimony, December 7, 1976.
Service of Staff Testimony, January 5, 1977.
Service of Company Rebuttal, January 19, 1977.
Service of Intervenor Rebuttal, February 9, 1977.
Hearing, February 16, 1977.

By direction of the Commission.

KENNETH F. PLUMB,
Secretary.

[FR Doc.76-26275 Filed 9-8-76;8:45 am]

GENERAL ACCOUNTING OFFICE

REGULATORY REPORTS REVIEW

Notice of Receipt of Report Proposals

The following requests for clearance of reports intended for use in collecting information from the public were received by the Regulatory Reports Review Staff, GAO, on August 31, 1976. See 44 U.S.C. 3512 (c) and (d). The purpose of publishing this notice in the Federal Register is to inform the public of such receipt.

The notice includes the title of each request received; the name of the agency sponsoring the proposed collection of information; the agency form number, if

[1] Twenty-ninth Revised Sheet No. 5 and Twenty-fourth Revised Sheet No. 6 to First Revised Volume No. 1 and Twenty-third Revised Sheet No. 52, Eleventh Revised Sheet No. 121, Nineteenth Revised Sheet No. 321, Fifteenth Revised Sheet No. 416 and Fourteenth Revised Sheet No. 495 to Original Volume No. 2.

[2] 18 C.F.R., Chapter 1, Part 201, Acc't 166.

[3] See the following table:

Producer	Agreement	Balance (June 30, 1976)
McMoRan Exploration Co.	Nov. 28, 1975	$323,095
Transco Exploration Co.	Aug. 15, 1975	3,928

[4] Docket Nos. RP74-48, and 75-3 and Docket No. RP75-75 (Advance Payments), *et al.*

applicable; and the frequency with which the information is proposed to be collected.

Written comments on the proposed FTC and FEA requests are invited from all interested persons, organizations, public interest groups, and affected businesses. Because of the limited amount of time GAO has to review the proposed requests comments (in triplicate) must be received on or before September 27, 1976, and should be addressed to Mr. John M. Lovelady, Acting Assistant Director, Regulatory Reports Review, Room 5216, 425 I Street, NW, Washington, D.C. 20548.

Further information may be obtained from Patsy J. Stuart of the Regulatory Reports Review Staff, 202–376–5425.

FEDERAL TRADE COMMISSION

FTC requests clearance of a new single time questionnaire to be set to 23 insurance companies, 2 investment brokers, 8 mutual funds, 21 savings and loan associations and 21 banks requesting information about advertising and marketing practices in connection with the establishment of Individual Retirement Accounts/Annuities (IRAs) created under the Pension Reform Act of 1974. FTC estimates respondent burden to average 12 hours for each of the 75 respondents who represent a sample of the respondent universe in each category.

FEDERAL ENERGY ADMINISTRATION

FEA requests clearance of two new schedules, Schedule B—Supplier and Inventory Data, and Schedule C—Class of Purchaser Price Data, to be appended to schedules A–0, A–1, and A–2 of the FEA Form P112–M–1: No. 2 Heating Oil Supply/Price Monitoring Report which was accorded emergency clearance by GAO on August 5, 1976. These new schedules have been designed in response to a commitment made to Congress by the FEA to monitor price movements of No. 2 heating oil after decontrol and hold public hearings if prices appear to increase more than two cents per gallon to determine if any corrective measures are required. The Emergency Petroleum Allocation Act of 1973 (P.L. 93–159) as amended by the Energy Policy and Conservation Act (P.L. 94–163) provides that following the exemption of any product from regulation, FEA shall have the authority at any time to reimpose controls. Schedules B and C will be mailed out to a scientifically selected sample of 600 respondents from a universe of refiners, resellers, retailers and reseller-retailers of No. 2 heating oil. These schedules are to be held in a standby status and are not to be filed unless controls are reinstated and the companies are directed to do so by the FEA. By having these schedules in the hands of the potential respondents, FEA states that the respondents will be familiar with the contents and have less difficulty filing them in the event controls are reinstated. If required, the reports must be filed by the twentieth of the month following the reporting month. FEA estimates the reporting burden for schedules B and C average 8½ hours per month per response.

NORMAN F. HEYL,
Regulatory Reports Review Officer.

[FR Doc.76–26340 Filed 9–8–76;8:45 am]

LEGAL SERVICES CORPORATION

BOARD OF DIRECTORS

Meeting

The next meeting of the Board of Directors of the Legal Services Corporation will be held on September 17–18, 1976 in the Auditorium of the D.C. Chapter of the American National Red Cross, 20th and E Streets, NW., Washington, D.C.

The meeting will begin at 9:00 a.m. on both days and will be for the purpose of considering and acting on reports from the Board's Committees and the President of the Corporation.

The meeting is open to the public.

SEPTEMBER 7, 1976.

THOMAS EHRLICH,
President.

TENTATIVE AGENDA, BOARD OF DIRECTORS MEETING, SEPTEMBER 17–18, 1976

Auditorium, D.C. Chapter, American National Red Cross, 20th and E Streets, NW., Washington, D.C.

1. Adoption of agenda.
2. Approval of minutes of July 23–24, 1976 meeting.
3. Reports by committees:

a. Regulations; (i) part 1617—class actions, (ii) part 1618—enforcement procedures, (iii) part 1619—public disclosure of recipient policies.

b. Appropriations and audit; (i) investment policies, (ii) 1977 budget allocation, (iii) 1978 budget request.

c. Provision of legal services.

4. Report by the president: a. support centers.
5. Other business.

The meeting will begin at 9:00 a.m. on September 17, 1976, and will continue until about 5:00 p.m., with an adjournment for lunch. The meeting will continue on September 18, 1976, if necessary. The Board will hold a brief executive session to discuss personnel matters and pending litigation at lunch on September 17. The film on legal services sponsored by the Corporation, the ABA Standing Committee on Legal Aid and Indigent Defendants, and the National Legal Aid and Defender Association will be shown immediately after lunch at 2:00 p.m. on September 17.

[FR Doc.76–26577 Filed 9–8–76;8:45 am]

LEGAL SERVICES OF NORTH FLORIDA

Notice of Grant and Contracts; Correction

SEPTEMBER 2, 1976.

Pursuant to Section 1007(f) of the Legal Services Corporation Act of 1974 (Public Law 93–355, 88 Stat. 378, 42 U.S.C. 2996–2996*l*) the Legal Services Corporation announced its intention to fund Florida Legal Services, Tallahassee.

Notice is hereby given that the intended grantee should have been Legal Services of North Florida, Tallahassee, Florida.

Additional information may be obtained by writing the Legal Services Corporation, 733 Fifteenth Street, NW., Suite 700, Washington, D.C. 20005.

THOMAS EHRLICH,
President.

[FR Doc.76–26305 Filed 9–8–76;8:45 am]

NATIONAL FOUNDATION ON THE ARTS AND THE HUMANITIES

National Endowment for the Humanities

ADVISORY COMMITTEE ON SCIENCE, TECHNOLOGY AND HUMAN VALUES

Meeting

In accordance with the Federal Advisory Committee Act, P.L. 92–463, the National Endowment for the Humanities announces the following meeting:

Name: Advisory Committee on Science, Technology and Human Values Meeting in Collaborative Session with the Advisory Committee on Ethical and Human Value Implications of Science and Technology, of the National Science Foundation.

Date: October 1, 1976.

Time: 9:30 a.m.

Place: Room 540, National Science Foundation, 1800 G Street N.W., Washington, D.C.

Type of Meeting: Open.

Contact person: Dr. Richard Hedrich, Coordinator, Program of Science Technology and Human Values, Office of Planning and Analysis, National Endowment for the Humanities, Washington, D.C. 20506. (Telephone 202–382–5996.) Individuals planning to attend are requested to notify Dr. Hedrich by September 28.

Purpose of Advisory Committee: To provide advice and recommendations concerning support of scholarly activities in the field of ethical and human value relationships to developments in science and technology, in conjunction with cooperative programs of the National Endowment for the Humanities and the National Science Foundation.

AGENDA

Reports on recent program activities.
Discussion of current patterns in college courses in science, technology and values.
Discussion of international perspectives on science, technology and values field.
Review of program plans and priorities.

JOHN W. JORDAN,
Advisory Committee Management Officer.

[FR Doc.76–26297 Filed 9–8–76;8:45 am]

NUCLEAR REGULATORY COMMISSION

ADVISORY COMMITTEE ON REACTOR SAFEGUARDS SUBCOMMITTEE ON THE CLINCH RIVER BREEDER REACTOR

Meeting

In accordance with the purposes of Sections 29 and 182b. of the Atomic Energy Act (42 U.S.C. 2039, 2232 b.), the ACRS Subcommittee on the Clinch River Breeder Reactor will meet on September 28–29, 1976 in the Auditorium of the

American Museum of Atomic Energy, South Tulane Street, Oak Ridge, TN 37830.

The purpose of this meeting is to develop information for consideration by the ACRS in its review of the combined application of the U.S. Energy Research and Development Administration, the Tennessee Valley Authority, and the Project Management Corporation (hereafter referred to as the CRBR Project Office) for a permit to construct this nuclear power plant. The facility will be located in Oak Ridge, TN. The plant is to use a liquid metal fast breeder reactor and is to have a gross capacity of 380 MW(e).

The agenda for subject meeting shall be as follows:

TUESDAY, SEPTEMBER 28, 1976

8:00 a.m.

The Subcommittee will meet in closed Executive Session, with any of its consultants who may be present, to exchange opinions and discuss preliminary views and recommendations, relating to the above review.

8:30 a.m. until the conclusion of business on September 28

The Subcommittee will hear presentations by representatives of the NRC Staff and the CRBR Project Office and will hold discussions with these groups pertinent to the review of the application for a permit to construct the Clinch River Breeder Reactor Plant. In particular, this review will concern aspects of structural design of the plant.

WEDNESDAY, SEPTEMBER 29, 1976

8:00 a.m.

The Subcommittee will meet in closed Executive Session, with any of its consultants who may be present, to exchange opinions and discuss preliminary views and recommendations relating to the above review.

8:30 a.m. until the close of business on September 29

The Subcommittee will hear additional presentations by representatives of the NRC Staff and the CRBR Project Office and will discuss aspects of a core disruptive accident.

At the conclusion of the open session on each day, the Subcommittee may caucus in a brief, closed session to determine whether the matters identified in the initial closed session have been adequately covered and whether the project is ready for review by the full Committee. During these sessions, Subcommittee members and consultants will discuss their final opinions and recommendations on these matters. Upon conclusion of the caucus, the Subcommittee may meet again in brief open session to announce its determination.

In addition to these closed deliberative sessions, it may be necessary for the Subcommittee to hold one or more closed sessions with the NRC Staff and applicant for the purpose of discussing confidential proprietary information.

I have determined, in accordance with Subsection 10(d) of Pub. L. 92–463, that it is necessary to conduct the above closed sessions to protect the free interchange of internal views in the final stages of the Subcommittee's deliberative process (5 U.S.C. 552(b)(5)) and to protect proprietary information (5 U.S.C. 552(b)(4)). Separation of factual material from individuals' advice, opinions, and recommendations while closed Executive Sessions are in progress is considered impractical.

Practical considerations may dictate alterations in the above agenda or schedule. The Chairman of the Subcommittee is empowered to conduct the meeting in a manner that, in his judgment, will facilitate the orderly conduct of business, including provisions to carry over an incompleted open session from one day to the next.

With respect to public participation in the open portion of the meeting, the following requirements shall apply:

(a) Persons wishing to submit written statements regarding the agenda may do so by providing 15 readily reproducible copies to the Subcommittee at the beginning of the meeting. Comments should be limited to safety related areas within the Committee's purview.

Persons desiring to mail written comments may do so by sending a readily reproducible copy thereof in time for consideration at this meeting. Comments postmarked no later than September 21, 1976 to Mr. T. G. McCreless, ACRS, NRC, Washington, DC 20555 will normally be received in time to be considered at this meeting.

Background information concerning the Clinch River Breeder Reactor can be found in documents on file and available for public inspection at the NRC Public Document Room, 1717 H St., N.W., Washington, DC 20555, at the Oak Ridge Public Library, Civic Center, Oak Ridge, TN 37830, and at the Lawson McGhee Public Library, 500 W. Church Street, Knoxville, TN 37902.

(b) Those persons wishing to make an oral statement at the meeting should make a written request to do so, identifying the topics and desired presentation time so that appropriate arrangements can be made. The Committee will receive oral statements on topics relevant to the Committee's purview at an appropriate time chosen by the Chairman of the Subcommittee.

(c) Further information regarding topics to be discussed, whether the meeting has been cancelled or rescheduled, the Chairman's ruling on requests for the opportunity to present oral statements and the time allotted therefor can be obtained by a prepaid telephone call on September 27, 1976 to the Office of the Executive Director of the Committee (telephone 202/634–1374, Attn: Mr. T. G. McCreless) between 8:15 a.m. and 5:00 p.m., EDT.

(d) Questions may be propounded only by members of the Subcommittee and its consultants.

(e) The use of still, motion picture, and television cameras, the physical installation and presence of which will not interfere with the conduct of the meeting, will be permitted both before and after the meeting and during any recess. The use of such equipment will not, however, be allowed while the meeting is in session.

(f) Persons with agreements or orders permitting access to proprietary information, may attend portions of ACRS meetings where this material is being discussed upon confirmation that such agreements are effective and relate to the material being discussed.

The Executive Director of the ACRS should be informed of such an agreement at least three working days prior to the meeting so that the agreement can be confirmed and a determination can be made regarding the applicability of the agreement to the material that will be discussed during the meeting. Minimum information provided should include information regarding the date of the agreement, the scope of material included in the agreement, the project or projects involved, and the names and titles of the persons signing the agreement. Additional information may be requested to identify the specific agreement involved. A copy of the executed agreement should be provided to Mr. T. G. McCreless of the ACRS Office, prior to the beginning of the meeting.

(g) A copy of the transcript of the open portion of the meeting will be available for inspection on or after October 6, 1976 at the NRC Public Document Room, 1717 H St., NW., Washington, DC 20555, at the Oak Ridge Public Library, Civic Center, Oak Ridge, TN 37830, and at the Lawson McGhee Public Library, 500 W. Church Street, Knoxville, TN 37902.

Copies of the minutes of the meeting will be made available for inspection at the NRC Public Document Room, 1717 H St., NW., Washington, DC 20555 after December 29, 1976. Copies may be obtained upon payment of appropriate charges.

Dated: September 7, 1976.

JOHN C. HOYLE,
Advisory Committee Management Officer.

[FR Doc.76–26504 Filed 9–8–76;8:45 am]

ADVISORY COMMITTEE ON REACTOR SAFEGUARDS, SUBCOMMITTEE ON THE THREE MILE ISLAND NUCLEAR STATION, UNIT 2

Meeting

In accordance with the purposes of sections 29 and 182b. of the Atomic Energy Act (42 U.S.C. 2039, 2232b.), the ACRS Subcommittee on the Three Mile Island Nuclear Station, Unit 2, will meet on September 23 and 24, 1976 at the Quality Inn, 5680 Allentown Boulevard, Harrisburg, PA 17112. The purpose of this meeting is to review the application of the Metropolitan Edison Company for a license to operate Unit 2.

The agenda for subject meeting shall be as follows:

Thursday, September 23, 1976, 1:00 p.m. The Subcommittee will meet in closed Executive Session, with any of its consultants who may be present, to exchange opinions and discuss preliminary views and recommendations relating to the above review.

2:00 p.m. until the conclusion of business on September 23, and 8:30 a.m. until the conclusion of business on September 24. The Subcommittee will meet in open session to hear presentations by representatives of the NRC Staff, the Metropolitan Edison Company, and their consultants, and will hold discussions with these groups pertinent to its review.

At the conclusion of the open session, the Subcommittee may caucus in a brief, closed session to determine whether the matters identified in the initial closed session have been adequately covered and whether the project is ready for review by the full Committee. During the session Subcommittee members and consultants will discuss their opinions and recommendations on these matters. Upon conclusion of this caucus, the Subcommittee may meet again in brief open session to announce its determination.

In addition to these closed deliberative sessions, it may be necessary for the Subcommittee to hold one or more closed sessions with the NRC Staff and Applicant for the purpose of discussing confidential proprietary information.

I have determined, in accordance with subsection 10(d) of Pub. L. 92-463, that it is necessary to conduct the above closed sessions to protect the free interchange of internal views in the final stages of the Subcommittee's deliberative process (5 U.S.C. 552(b)(5)) and to protect proprietary information (5 U.S.C. 552(b)(4)). Separation of factual material from individuals' advice, opinions, and recommendations while closed Executive Sessions are in progress is considered impractical.

Practical considerations may dictate alterations in the above agenda or schedule. The Chairman of the Subcommittee is empowered to conduct the meeting in a manner that, in his judgment, will facilitate the orderly conduct of business, including provisions to carry over an incompleted open session from one day to the next.

With respect to public participation in the open portion of the meeting, the following requirements shall apply:

(a) Persons wishing to submit written statements regarding the agenda may do so by providing 15 readily reproducible copies to the Subcommittee at the beginning of the meeting. Comments should be limited to safety related areas within the Committee's purview.

Persons desiring to mail written comments may do so by sending a readily reproducible copy thereof in time for consideration at this meeting. Comments postmarked no later than September 17, 1976 to Mr. R. Muller, ACRS, NRC, Washington, DC 20555 will normally be received in time to be considered at this meeting.

Background information concerning items to be considered at this meeting can be found in documents on file and available for public inspection at the NRC Public Document Room, 1717 H St., N.W., Washington, DC 20555 and at the Government Publications Section, State Library of Pennsylvania, Box 1601 (Education Building), Harrisburg, PA 17126.

(b) Those persons wishing to make an oral statement at the meeting should make a written request to do so, identifying the topics and desired presentation time so that appropriate arrangements can be made. The Committee will receive oral statements on topics relevant to the Committee's purview at an appropriate time chosen by the Chairman of the Subcommittee.

(c) Further information regarding topics to be discussed, whether the meeting has been cancelled or rescheduled, the Chairman's ruling on requests for the opportunity to present oral statements and the time allotted therefor can be obtained by a prepaid telephone call on September 22, 1976 to the Office of the Executive Director of the Committee (telephone 202/634-1413, Attn: Mr. R. Muller) between 8:15 a.m. and 5:00 p.m., EDT.

(d) Questions may be propounded only by members of the Subcommittee and its consultants.

(e) The use of still, motion picture, and television cameras, the physical installation and presence of which will not interfere with the conduct of the meeting, will be permitted both before and after the meeting and during any recess. The use of such equipment will not, however, be allowed while the meeting is in session.

(f) Persons with agreements or orders permitting access to proprietary information may attend portions of ACRS meetings where this material is being discussed upon confirmation that such agreements are effective and relate to the material being discussed.

The Executive Director of the ACRS should be informed of such an agreement at least three working days prior to the meeting so that the agreement can be confirmed and a determination can be made regarding the applicability of the agreement to the material that will be discussed during the meeting. Minimum information provided should include information regarding the date of the agreement, the scope of material included in the agreement, the project or projects involved, and the names and titles of the persons signing the agreement. Additional information may be requested to identify the specific agreement involved. A copy of the executed agreement should be provided to Mr. R. Muller of the ACRS Office, prior to the beginning of the meeting.

(g) A copy of the transcript of the open portion of the meeting will be available for inspection on or after October 1, 1976 at the NRC Public Document Room, 1717 H St., N.W., Washington, DC 20555 and at the Government Publications Section, State Library of Pennsylvania, Box 1601 (Education Building), Harrisburg, PA 17126.

Copies of the minutes of the meeting will be made available for inspection at the NRC Public Document Room, 1717 H St., N.W., Washington, D.C. 20555 after December 24, 1976. Copies may be obtained upon payment of appropriate charges.

Dated: August 31, 1976.

JOHN C. HOYLE,
Advisory Committee,
Management Officer.

[FR Doc.76-25843 Filed 9-3-76;8:45 am]

[Docket No. 50-261]

CAROLINA POWER AND LIGHT CO. (H. B. ROBINSON STEAM ELECTRIC PLANT UNIT NO. 2)

Order for Modification of License

I. Carolina Power and Light Company (the Licensee), is the holder of Facility Operating License No. DPR-23 which authorizes the operation of a nuclear power reactor known as H. B. Robinson Steam Electric Plant Unit No. 2 (the facility) at steady state reactor power levels not in excess of 2200 thermal megawatts (rated power). The facility is a pressurized water reactor (PWR) located at the Licensee's site near Hartsville, South Carolina.

II. In conformance with evaluations of the performance of the Emergency Core Cooling System (ECCS) of the facility submitted by the Licensee on October 14, 1975, as supplemented by correspondence dated August 3 and 22, October 17, November 13, 18, and 24, 1975, the Technical Specifications issued December 3, 1975, for the facility limit the reactor total nuclear peaking factor (F_Q) to 2.30. The ECCS performance evaluation submitted by the Licensee was based upon a previously approved ECCS evaluation model developed by the Westinghouse Electric Corporation (Westinghouse), the designer of the facility and supplier of part of the nuclear fuel, to conform with the requirements of the Commission's ECCS Acceptance Criteria, 10 CFR Part 50, 50.46 and Appendix K. The evaluation indicated that with a total nuclear peaking factor limited as set forth above, and with the other limits set forth in the facility's Technical Specifications, the ECCS cooling performance for the facility would conform with the criteria contained in 10 CFR 50.46(b) which govern calculated peak clad temperature, maximum cladding oxidation, maximum hydrogen generation, coolable geometry and long term cooling. The total nuclear peaking factor limits established above for the Westinghouse fuel are also conservative for the nuclear fuel supplied by the Exxon Nuclear Corporation.

Due to the configuration of the Westinghouse reactor vessel design, a small portion of reactor inlet water which is cooler than outlet water is directed through several nozzles located on the periphery of the vessel to cool the upper portion of the vessel head. Accordingly, upper head temperatures used in evaluating ECCS performance were assumed to

be equal to the reactor inlet water temperature. However, recent operating data gathered at the Connecticut Yankee facility has indicated that, contrary to this expectation, the temperature of the water in the upper head is higher than the reactor inlet water temperature, by about 60% of the difference between reactor inlet and reactor outlet temperature. This higher upper head water temperature would have the effect of increasing the calculated peak clad temperature in the event of a loss of coolant accident.

In a meeting with the staff on August 9, 1976, Westinghouse presented generic evaluations of the effect on calculated peak clad temperature for the worst break identified in previous calculations for each type of Westinghouse reactor and fuel design using an upper head water temperature exceeding reactor inlet water temperature by an amount equal to 75% of the reactor inlet-reactor outlet differential. On August 12, 1976, the staff instructed the licensee to submit an analysis similar to the Westinghouse evaluation with the clearly conservative assumption of upper head water temperature equal to reactor outlet temperature (100% of the reactor outlet-reactor inlet differential) and to operate the facility in accordance with the results of this analysis. The results of the evaluation submitted for the H. B. Robinson, Unit No. 2 reactor indicated that with this modification of the upper head water temperature the calculated peak clad temperature for the worst case break would exceed the Commission's ECCS performance criteria by about 200° F.

Extensive sensitivity studies, submitted with previous calculations in connection with assessment of Westinghouse evaluation models, have established a relationship between the reactor total nuclear peaking factor (F_Q) and calculated peak clad temperature such that if F_Q is reduced by .20 the calculated peak clad temperature for the H. B. Robinson, Unit No. 2 reactor would not exceed 2200° F. As directed by the NRC staff, the licensee agreed to operate the facility with the total nuclear peaking factor reduced by 0.20 to 2.10. However, subsequent to the licensee's submittal, further review of data presented by Westinghouse has led the staff to conclude that an additional reduction in F_Q over that presented by the licensee is warranted. This is based on the fact that the Westinghouse generic evaluation for plants with three reactor coolant loops, used the results from two different, but approved, ECCS models (the March 1975 and the October 1975 models). When consistent ECCS models are used the calculated peak clad temperature could increase by an additional 50° F.

After discussions with the NRC staff, on August 25, 1976, the Licensee amended his previous submission to account for this additional increase in peak clad temperature, by reducing F_Q to 2.05. The NRC staff believes that the licensee's actions, under the circumstances, are appropriate and should be confirmed by NRC Order.

The staff expects that, when revised calculations for the facility are submitted using an approved evaluation model with correct input for upper head water temperature, or assuming that the upper head water temperature equals reactor vessel outlet water temperature, such calculations will demonstrate that operation with this total nuclear peaking factor would conform with the criteria of 10 CFR 50.46 (b). Such revised calculations fully conforming to the requirements of 10 CFR 50.46 are to be provided for the facility as soon as possible. The additional limitations set forth in this Order will provide reasonable assurance that the public health and safety will not be endangered.

Copies of the following documents are available for public inspection in the Commission's Public Document Room, 1717 H Street NW., Washington, D.C. 20555 and at the Hartsville Memorial Library, Home and Fifth Avenue, Hartsville, South Carolina 29550, (1) Licensee's letters of August 3 and 22, October 14 and 17, and November 13, 18, and 24, 1975, (2) Amendment No. 15 to Facility License No. DPR–23, (3) Licensee's letters of August 18 and 25, 1976, and (4) This Order for Modification of License, In the Matter of Carolina Power and Light Company, H. B. Robinson Steam Electric Plant Unit No. 2, Docket No. 50–261.

III. Accordingly, pursuant to the Atomic Energy Act of 1954, as amended, and the Commission's Rules and Regulations in 10 CFR Parts 2 and 50: *It is ordered*, that Facility Operating License No. DPR–23 is hereby amended by adding the following new provisions:

1. As soon as possible, the Licensee shall submit a reevaluation of ECCS cooling performance calculated in accordance with an approved Westinghouse Evaluation Model, with appropriate correction for upper head water temperature.

2. Until further authorization by the Commission, the Technical Specification limit for total nuclear peaking factor (F_Q) shall be reduced to 2.05.

Dated in Bethesda, Md., this 27th day of August 1976.

For the Nuclear Regulatory Commission.

BEN C. RUSCHE,
Director, Office of Nuclear Reactor Regulation.

[FR Doc.76-26159 Filed 9-8-76;8:45 am]

[Dockets Nos. 50–295, 50–304]

COMMONWEALTH EDISON CO. ZION STATION UNITS NOS. 1 & 2

Order for Modification of License

I. The Commonwealth Edison Company (the Licensee), is the holder of Facility Operating Licenses Nos. DPR–39 and DPR–48 which authorize the operation of the nuclear power reactors known as Zion Station, Units Nos. 1 and 2 (the facility) at steady state reactor power levels not in excess of 3250 megawatts thermal (rated power). The facility consists of two pressurized water reactors (PWR) located at the Licensee's site near Zion, Illinois.

II. In conformance with evaluations of the performance of the Emergency Core Cooling System (ECCS) of the facility submitted by the Licensee on September 3, 1974 and April 21, 1975, the Technical Specifications issued May 12, 1976 for the facilities limit the reactor total nuclear peaking factor (F_Q) to 2.25 and 2.20 for Units Nos. 1 and 2, respectively. The ECCS performance evaluation submitted by the Licensee was based upon a previously approved ECCS evaluation model developed by Westinghouse Electric Corporation (Westinghouse), the designer of the facility, to conform to the requirements of the Commission's ECCS Acceptance Criteria, 10 CFR Part 50, § 50.46 and Appendix K. The evaluation indicated that with a total nuclear peaking factor limited as set forth above, and with the other limits set forth in the facilities' Technical Specifications, the ECCS cooling performance for the facility would confrom to the criteria contained in 10 CFR 50.46(b) which govern calculated peak clad temperature, maximum cladding oxidation, maximum hydrogen generation, coolable geometry and long term cooling.

Due to the configuration of the Westinghouse reactor vessel design, a small portion of relatively cooler reactor inlet water is directed through several nozzles located on the periphery of the vessel to cool the upper portion of the head. Accordingly, upper head temperatures were assumed in evaluating ECCS performance to be equal to the reactor inlet water temperature. However, recent operating data gathered at the Connecticut Yankee facility has indicated that, contrary to this expectation, the temperature of the water in the upper head is warmer than the reactor inlet water temperature, by about 60 percent of the difference between reactor inlet and reactor outlet temperature. This higher upper head water temperature would have the effect of increasing the calculated peak clad temperature in the event of a loss of coolant accident.

In a meeting with the staff on August 9, 1976, Westinghouse presented generic evaluations of the effect on calculated peak clad temperature for the worst break identified in previous calculations for each type of Westinghouse reactor and fuel design using an upper head water temperature exceeding reactor inlet water temperature by an amount equal to 75 percent of the reactor inlet—reactor outlet differential. On August 12, 1976, the staff directed the licensee to submit an analysis similar to the Westinghouse evaluation with the clearly conservative assumption of upper head water temperature equal to reactor outlet temperature (100 percent of the reactor outlet—reactor inlet differenial) and to operate the facility in accordance with the results of this analysis. The results of the evaluation submitted for the Zion Station reactors indicated that with this modification of the upper head water temperature the calculated peak clad temperature for the worst case break would exceed the Commission's ECCS performance criteria by about 40° F.

Extensive sensitivity studies, provided with previous calculations submitted in connection with assessment of Westinghouse evaluation models, have established a relationship between the reactor

total nuclear peaking factor (FQ) and calculated peak clad temperature such that if F_Q is reduced by 0.04 the calculated peak clad temperature for the Zion Station reactors would not exceed 2200° F.

As directed by the NRC staff, the Licensee agreed to operate the facility with the total nuclear peaking factor reduced by 0.04 to 2.21 and 2.16, for Units Nos. 1 and 2, respectively. The staff believes that the Licensee's action, under the circumstances, is appropriate and that this action should be confirmed by NRC Order.

The staff expects that, when revised calculations for the facility are submitted using an approved evaluation model with correct input for upper head water temperature, or assuming that the upper head water temperature equals reactor vessel outlet water temperature, such calculations will demonstrate that operation with this total nuclear peaking factor would conform to the criteria of 10 CFR 50.46(b). Such revised calculations fully conforming to the requirements of 10 CFR 50.46 are to be provided for the facility as soon as possible. The additional limitations set forth in this order will provide reasonable assurance that the public health and safety will not be endangered.

Copies of the following documents are available for public inspection in the Commission's Public Document Room, 1717 H Street, NW., Washington, D.C. 20555 and in the Waukegan Public Library, 128 North County Street, Waukegan, Illinois, (1) the ECCS evaluations dated September 3, 1974 and April 21, 1975, (2) Amendments 20 and 17 to Facility Licenses Nos. DPR–39 and DPR–48, (3) the Licensee's August 18, 1976 letter, and (4) This Order for Modification of License, In the Matter of Commonwealth Edison Company, Dockets Nos. 50–295 and 50–304.

III. Accordingly, pursuant to the Atomic Energy Act of 1954, as amended, and the Commission's rules and regulations in 10 CFR Parts 2 and 50: *It is ordered,* That Facility Operating Licenses Nos. DPR–39 and DPR–48 are hereby amended by adding the following new provisions:

1. As soon as possible, the Licensee shall submit a re-evaluation of ECCS cooling performance calculated in accordance with an approved Westinghouse Evaluation Model, with appropriate correction for upper head water temperature.

2. Until further authorization by the Commission, the Technical Specification limit for total nuclear peaking factor (F_Q) shall be reduced to 2.21 and 2.16 for Units Nos. 1 and 2, respectively.

Dated in Bethesda, Md., this August 27, 1976.

For the Nuclear Regulatory Commission.

BEN C. RUSCHE,
Director,
Office of Nuclear Reactor Regulation.

[FR Doc.76-26151 Filed 9-8-76;8:45 am]

[Docket Nos. 50-254, 50-265]

COMMONWEALTH EDISON CO. IOWA-ILLINOIS GAS AND ELECTRIC CO.

Issuance of Amendments to Facility Operating Licenses

The U.S. Nuclear Regulatory Commission (the Commission) has issued Amendment Nos. 30 and 29 to Facility Operating License Nos. DPR–29 and DPR–30, issued to Commonwealth Edison Company (acting for itself and on behalf of the Iowa-Illinois Gas and Electric Company), which revised Technical Specifications for operation of the Quad Cities Station Unit Nos. 1 and 2 (the facilities) located in Rock Island County, Illinois. The amendments are effective as of their date of issuance.

The amendments reissued the Technical Specifications contained in Appendices A and B of License Nos. DPR–29 and DPR–30 in their entirety as a separate document for each of the two units. Previously there was a single document applicable to both units. The format and section numbering of the reissued Technical Specifications have been revised to be consistent with current regulatory practice. There were no changes in requirements or limitations.

The application for these amendments complies with the standards and requirements of the Atomic Energy Act of 1954, as amended (the Act), and the Commission's rules and regulations. The Commission has made appropriate findings as required by the Act and the Commission's rules and regulations in 10 CFR Ch. I, which are set forth in the license amendments. Prior public notice of these amendments was not required since the amendments do not involve a significant hazards consideration.

The Commission has determined that the issuance of these amendments will not result in any significant environmental impact and that pursuant to 10 CFR 51.5(d)(4) an environmental impact statement, negative declaration or environmental impact appraisal need not be prepared in connection with issuance of these amendments.

For further details with respect to this action, see (1) the application for the amendments dated February 9, 1976, and supplements thereto dated July 8 and July 20, 1976, (2) Amendment Nos. 30 and 29 to License Nos. DPR–29 and DPR–30, and (3) the Commission's concurrently issued related Safety Evaluation. All of these items are available for public inspection at the Commission's Public Document Room, 1717 H Street, NW., Washington, D.C. and at the Moline Public Library, 504 17th Street, Moline, Illinois 60625.

A copy of items (2) and (3) may be obtained upon request addressed to the U.S. Nuclear Regulatory Commission, Washington, D.C. 20555, Attention: Director, Division of Operating Reactors.

Dated at Bethesda, Md., this 25th day of August 1976.

For the Nuclear Regulatory Commission.

DENNIS L. ZIEMANN,
Chief, Operating Reactors Branch #2, Division of Operating Reactors.

[FR Doc.76-26163 Filed 9-8-76;8:45 am]

[Docket No. 50-247]

CONSOLIDATED EDISON CO. OF NEW YORK, INC. (INDIAN POINT NUCLEAR GENERATING UNIT NO. 2)

Order for Modification of License

I. Consolidated Edison Company of New York, Inc. (the Licensee), is the holder of Facility Operating License No. DPR–26 which authorizes the operation of a nuclear power reactor known as Indian Point Nuclear Generating Unit No. 2 (the facility) at steady state reactor power levels not in excess of 2758 thermal megawatts. The facility is a pressurized water reactor (PWR) located at the Licensee's site in Westchester County, New York.

II. Evaluations of the performance of the Emergency Core Cooling System (ECCS) of the facility were submitted by the Licensee by letter dated September 6, 1974, as supplemented by letters dated October 21, 1974, November 6, 1974, December 2 and 6, 1974, January 29, 1975, April 21 and 29, 1975, May 21, 1975, July 9 and 21, 1975, February 4, 9, and 19, 1976, April 22, 1976, May 27, 1976, June 14, 1976, and July 13 and 15, 1976. The Commission's Order issued December 27, 1974, for the facility limits the reactor nuclear peaking factor (F_Q) to 2.32. The ECCS performance evaluation submitted by the Licensee was based upon a previously approved ECCS evaluation model developed by the Westinghouse Electric Corporation (Westinghouse), the designer of the facility, to conform with the requirements of the Commission's ECCS Acceptance Criteria, 10 CFR Part 50, § 50.46 and Appendix K. The evaluation indicated that with a total nuclear peaking factor limited as set forth above, and with the other limits set forth in the facility's Technical Specifications, the ECCS cooling performance for the facility would conform with the criteria contained in 10 CFR 50.46(b) which govern calculated peak clad temperature, maximum cladding oxidation, maximum hydrogen generation, coolable geometry and long term cooling.

Due to the configuration of the Westinghouse reactor vessel design, a small portion of reactor inlet water which is cooler than outlet water is directed through several nozzles located on the periphery of the vessel to cool the upper portion of the vessel head. Accordingly, upper head temperatures used in evaluating ECCS performance were assumed to be equal to the reactor inlet water temperature. However, recent operating data gathered at the Connecticut Yankee facility has indicated that, contrary to this expectation, the temperature of the water in the upper

head is higher than the reactor inlet water temperature, by about 60 percent of the difference between reactor inlet and reactor outlet temperature. This higher upper head water temperature would have the effect of increasing the calculated peak clad temperature in the event of a loss of coolant accident.

In a meeting with the staff on August 9, 1976, Westinghouse presented generic evaluations of the effect on calculated peak clad temperature for the worst break identified in previous calculations for each type of Westinghouse reactor and fuel design using an upper head water temperature exceeding reactor inlet water temperature by an amount equal to 75 percent of the reactor inlet—reactor outlet differential. On August 12, 1976, the staff instructed the licensee to submit an analysis similar to the Westinghouse evaluation with the clearly conservative assumption of upper head water temperature equal to reactor outlet temperature (100 percent of the reactor outlet—reactor inlet differential) and to operate the facility in accordance with the results of this analysis. The results of the evaluation submitted for the Indian Point Unit No. 2 reactor indicated that with this modification of the upper head water temperature the calculated peak clad temperature for the worst case break would not exceed the Commission's ECCS performance criteria.

The staff expects that, when revised calculations for the facility are submitted using an approved evaluation model with correct input for upper head water temperature, or assuming that the upper head water temperature equals reactor vessel outlet water temperature, such calculations will demonstrate that operation with this total nuclear peaking factor would conform to the criteria of 10 CFR 50.46(b). Such revised calculations fully conforming to the requirements of 10 CFR 50.46 are to be provided for the facility as soon as possible. The limitations presently incorporated in the Technical Specifications for the facility continue to provide reasonable assurance that the public health and safety will not be endangered.

Copies of the following documents are available for public inspection in the Commission's Public Document Room, 1717 H Street, NW., Washington, D.C., 20555 and at the Hendrick Hudson Free Library, 31 Albany Post Road, Montrose, New York, (1) letter from Consolidated Edison dated September 6, 1974, and supplements relative to ECCS, (2) letter from Consolidated Edison dated August 17, 1976, and (3) This Order for Modification of License, In the Matter of Consolidated Edison Company of New York, Inc., Indian Point Nuclear Generating Unit No. 2, Docket No. 50-247.

III. Accordingly, pursuant to the Atomic Energy Act of 1954, as amended, and the Commission's rules and regulations in 10 CFR Parts 2 and 50: *It is ordered*, That Facility Operating License No. DPR-26 is hereby amended by adding the following new provision:

As soon as possible, the Licensee shall submit a reevaluation of ECCS cooling performance calculated in accordance with an approved Westinghouse Evaluation Model, with appropriate correction for upper head water temperature.

Dated in Bethesda, Md., this 27th day of August 1976.

For the Nuclear Regulatory Commission.

BEN C. RUSCHE,
Director, Office of Nuclear Reactor Regulation.

[FR Doc.76-26158 Filed 9-8-76;8:45 am]

[Docket No. 50-286]

CONSOLIDATED EDISON CO. OF NEW YORK, INC. (INDIAN POINT NUCLEAR GENERATING UNIT NO. 3)

Order for Modification of License

I. The Consolidated Edison Company of New York, Inc. (the Licensee), is the holder of Facility Operating License No. DPR-64 which authorizes the operation of a nuclear power reactor known as Indian Point Nuclear Generating Unit No. 3 (the facility) at steady state reactor power levels not in excess of 2760 thermal megawatts. The facility is a pressurized water reactor (PWR) located at the Licensee's site in Westchester County, New York.

II. In conformance with evaluations of the performance of the Emergency Core Cooling System (ECCS) of the facility submitted by the Licensee on October 10, 1975, November 12, 1975, March 11, 1976, and April 1, 1976, the Technical Specifications issued April 5, 1976, for the facility limit the reactor total nuclear peaking factor (F_Q) to 2.32. The ECCS performance evaluation submitted by the Licensee was based upon a previously approved ECCS evaluation model developed by Westinghouse Electric Corporation (Westinghouse), the designer of the facility, to conform with requirements of the Commission's ECCS Acceptance Criteria, 10 CFR Part 50, § 50.46 and Appendix K. The evaluation indicated that with a total nuclear peaking factor limited as set forth above, and with the other limits set forth in the facility's Technical Specifications, the ECCS cooling performance for the facility would conform with the criteria contained in 10 CFR 50.46(b) which govern calculated peak clad temperature, maximum cladding oxidation, maximum hydrogen generation, coolable geometry and long term cooling.

Due to the configuration of the Westinghouse reactor vessel design, a small portion of reactor inlet water which is cooler than outlet water is directed through several nozzles located on the periphery of the vessel to cool the upper portion of the vessel head. Accordingly, upper head temperatures used in evaluating ECCS performance were assumed to be equal to the reactor inlet water temperature. However, recent operating data gathered at the Connecticut Yankee facility has indicated that, contrary to this expectation, the temperature of the water in the upper head is higher than the reactor inlet water temperature, by about 60 percent of the difference between reactor inlet and reactor outlet temperature. This higher upper head water temperature would have the effect of increasing the calculated peak clad temperature in the event of a loss of coolant accident.

In a meeting with the staff on August 9, 1976, Westinghouse presented generic evaluations of the effect on calculated peak clad temperature for the worst break identified in previous calculations for each type of Westinghouse reactor and fuel design using an upper head water temperature exceeding reactor inlet water temperature by an amount equal to 75 percent of the reactor inlet-reactor outlet differential. On August 12, 1976, the staff instructed the licensee to submit an analysis similar to the Westinghouse evaluation with the clearly conservative assumption of upper head water temperature equal to reactor outlet temperature (100 percent of the reactor outlet-reactor inlet differential) and to operate the facility in accordance with the results of this analysis. The results of the evaluation submitted for the Indian Point Unit No. 3 reactor indicated that with this modification of the upper head water temperature the calculated peak clad temperature for the worst case break would exceed the Commission's ECCS performance criteria by about 8° F.

Extensive sensitivity studies, submitted with previous calculations submitted in connection with assessment of Westinghouse evaluation models, have established a relationship between the reactor total nuclear peaking factor (F_Q) and calculated peak clad temperature such that if F_Q is reduced by 0.01 the calculated peak clad temperature for the reactor would not exceed 2200° F.

As directed by the NRC staff, the Licensee agreed to operate the facility with the total nuclear peaking factor reduced by 0.01 to 2.31. The staff believes that the Licensee's action, under the circumstances, is appropriate and that this action should be confirmed by NRC Order.

The staff expects that, when revised calculations for the facility are submitted using an approved evaluation model with correct input for upper head water temperature, or assuming that the upper head water temperature equals reactor vessel outlet water temperature, such calculations will demonstrate that operation with this total nuclear peaking factor would conform to the criteria of 10 CFR 50.46(b). Such revised calculations fully conforming to the requirements of 10 CFR 50.46 are to be provided for the facility as soon as possible. The additional limitations set forth in this Order will provide reasonable assurance that the public health and safety will not be endangered.

Copies of the following documents are available for public inspection in the Commission's Public Document Room, 1717 H Street, NW., Washington, D.C., 20555 and at the Hendrick Hudson Free Library, 31 Albany Post Road, Montrose, New York, (1) letters from Consolidated Edison dated October 10, 1975, Novem-

ber 12, 1975, March 11, 1976, and April 1, 1976, (2) DPR–64 License Amendment dated April 5, 1976, (3) letter from Consolidated Edison dated August 18, 1976, and (4) This Order for Modification of License, In the Matter of Consolidated Edison Company of New York, Inc., Indian Point Nuclear Generating Unit No. 3, Docket No. 50–286.

III. Accordingly, pursuant to the Atomic Energy Act of 1954, as amended, and the Commission's rules and regulations in 10 CFR Parts 2 and 50: *It is ordered*, That Facility Operating License No. DPR–64 is hereby amended by adding the following new provisions:

1. As soon as possible, the Licensee shall submit a reevaluation of ECCS cooling performance calculated in accordance with an approved Westinghouse Evaluation Model, with appropriate correction for upper head water temperature.

2. Until further authorization by the Commission, the Technical Specification limit for total nuclear peaking factor (F_Q) shall be reduced to 2.31.

Dated in Bethesda, Md., this 27th day of August 1976.

For the Nuclear Regulatory Commission.

BEN C. RUSCHE,
Director, Office of Nuclear Reactor Regulation.

[FR Doc.76-26161 Filed 9-8-76;8:45 am]

[Dockets Nos. 50-269, 50-270 and 50-287]

DUKE POWER CO.

Issuance of Amendments to Facility Operating Licenses

The U.S. Nuclear Regulatory Commission (the Commission) has issued Amendments Nos. 31, 31, and 28 to Facility Operating Licenses Nos. DPR–38, DPR–47 and DPR–55, respectively, issued to Duke Power Company which revised Technical Specifications for operation of the Oconee Nuclear Station Units Nos. 1, 2, and 3, located in Oconee County, South Carolina. The amendments are effective as of the date of issuance.

The amendments establish provisions for implementing alternate measures to assure that liquid waste effluent release limits are not exceeded whenever liquid waste monitors cannot be set to properly alarm and control liquid releases.

The application for these amendments complies with the standards and requirements of the Atomic Energy Act of 1954, as amended (the Act), and the Commission's rules and regulations. The Commission has made appropriate findings as required by the Act and the Commission's rules and regulations in 10 CFR Ch. I, which are set forth in the license amendments. Prior public notice of these amendments was not required since the amendments do not involve a significant hazards consideration.

The Commission has determined that the issuance of these amendments will not result in any significant environmental impact and that pursuant to 10 CRF 51.5(d)(4) an environmental impact statement, negative declaration, or environmental impact appraisal not be prepared in connection with issuance of these amendments.

For further details with respect to this action, see (1) the application for amendments dated July 30, 1976, (2) Amendments Nos. 31, 31, and 28 to Licenses Nos. DPR–38, DPR–47 and DPR–55, respectively, and (3) the Commission's related Safety Evaluation. All of these items are available for public inspection at the Commission's Public Document Room, 1717 H Street, NW., Washington, D.C. 20555 and at the Oconee County Library, 201 South Spring Street, Walhalla, South Carolina 29691. A copy of items (2) and (3) may be obtained upon request addressed to the U.S. Nuclear Regulatory Commission, Washington, D.C. 20555, Attention: Director, Division of Operating Reactors.

Dated at Bethesda, Maryland, this 24th day of August 1976.

For the Nuclear Regulatory Commission.

A. SCHWENCER,
Chief, Operating Reactors Branch No. 1, Division of Operating Reactors.

[FR Doc.76-26164 Filed 9-8-76;8:45 am]

[Docket No. 50-334]

DUQUESNE LIGHT CO., ET AL. (BEAVER VALLEY POWER STATION UNIT NO. 1)

Order for Modification of License

I. Duquesne Light Company, Ohio Edison Company, and Pennsylvania Power Company (the licensees), are the holders of Facility Operating License No. DPR-66 which authorizes the operation of a nuclear power reactor known as Beaver Valley Power Station, Unit No. 1 (the facility) at steady state reactor power levels not in excess of 2652 thermal megawatts (rated power). The facility is a pressurized water reactor (PWR) located at the Licensee's site in Beaver County, Pennsylvania.

II. In conformance with evaluations of the performance of the Emergency Core Cooling System (ECCS) of the facility submitted by the Licensee on June 5, 1975, the Technical Specifications issued January 30, 1976, for the facility limit the reactor total nuclear peaking factor (F_Q) to 2.23. Although the present Technical Specifications limit the reactor total nuclear peaking factor to 2.23, the Licensee has submitted revised ECCS analyses which support a change in F_Q from the present limit of 2.23 to 2.32. The NRC staff has reviewed these analyses and found them acceptable, although the Technical Specifications have not been formally modified. Therefore, the corrective actions set forth below are based upon an F_Q limit of 2.32 since the analyses provide assurance that the peak clad temperature would conform to the criteria of 10 CFR 50.46(b). The ECCS performance evaluation submitted by the Licensee was based upon a previously approved ECCS evaluation model developed by the Westinghouse Electric Corporation (Westinghouse), the designer of the facility, to conform with the requirements of the Commission's ECCS Acceptance Criteria, 10 CFR Part 50, 50.46 and Appendix K. The evaluation indicated that with a total nuclear peaking factor limited as set forth above, and with the other limits set forth in the facility's Technical Specifications, the ECCS cooling performance for the facility would conform with the criteria contained in 10 CFR 50.46(b) which govern calculated peak clad temperature, maximum cladding oxidation, maximum hydrogen generation, coolable geometry and long term cooling.

Due to the configuration of the Westinghouse reactor vessel design, a small portion of reactor inlet water which is cooler than outlet water is directed through several nozzles located on the periphery of the vessel to cool the upper portion of the vessel head. Accordingly, upper head temperatures used in evaluating ECCS performance were assumed to be equal to the reactor inlet water temperature. However, recent operating data gathered at the Connecticut Yankee facility has indicated that, contrary to this expectation, the temperature of the water in the upper head is higher than the reactor inlet water temperature, by about 60 percent of the difference between reactor inlet and reactor outlet temperature. This higher upper head water temperature would have the effect of increasing the calculated peak clad temperature in the event of a loss of coolant accident.

In a meeting with the staff on August 9, 1976, Westinghouse presented generic evaluations of the effect on calculated peak clad temperature for the worst break identified in previous calculations for each type of Westinghouse reactor and fuel design using an upper head water temperature exceeding reactor inlet water temperature by an amount equal to 75 percent of the reactor inlet—reactor outlet differential. On August 12, 1976, the staff instructed the licensee to submit an analysis similar to the Westinghouse evaluation with the clearly conservative assumption of upper head water temperature equal to reactor outlet temperature (100 percent of the reactor outlet—reactor inlet differential) and to operate the facility in accordance with the results of this analysis. The results of the evaluation submitted for the Beaver Valley Unit No. 1 reactor indicated that with this modification of the upper head water temperature the calculated peak clad temperature for the worst case break would exceed the Commission's ECCS performance criteria by about 77° F.

Extensive sensitivity studies, submitted with previous calculations in connection with assessment of Westinghouse evaluation models, have established a relationship between the reactor total nuclear peaking factor (F_Q) and calculated peak clad temperature such that if F_Q is reduced by .08 the calculated peak clad temperature for the Beaver Valley Unit No. 1 reactor would not exceed 2200 F. As directed by the NRC staff, the Licensee agreed to operate the facility with the

total nuclear peaking factor reduced by .08 to 2.24. However, subsequent to the licensee's submittal, further review of data presented by Westinghouse has led the staff to conclude that an additional reduction in F_Q over that presented by the licensee is warranted. This is based on the fact that the Westinghouse generic evaluation for plants with three reactor coolant loops, used the results from two different, but approved, ECCS models (the March 1975 and the October 1975 models). When consistent ECCS models are used the calculated peak clad temperature could increase by an additional 17 F.

After discussions with the NRC staff, on August 25, 1976, the licensee amended his previous submission to account for this additional increase in peak clad temperature, by reducing F_Q to 2.22. The NRC staff believes that the licensee's actions, under the circumstances, are appropriate and should be confirmed by NRC Order.

The staff expects that, when revised calculations for the facility are submitted using an approved evaluation model with correct input for upper head water temperature, or assuming that the upper head water temperature equals reactor vessel outlet water temperature, such calculations will demonstrate that operation with this total nuclear peaking factor would conform with the criteria of 10 CFR 50.46(b). Such revised calculations fully conforming to the requirements of 10 CFR 50.46 are to be provided for the facility as soon as possible. The additional limitations set forth in this Order will provide reasonable assurance that the public health and safety will not be endangered.

Copies of the following documents are available for public inspection in the Commission's Public Document Room, 1717 H Street, N.W., Washington, D.C. 20555 and at the Beaver Area Memorial Library, 100 College Avenue, Beaver, Pennsylvania 15009, (1) Licensee's Amendment No. 17 dated June 5, 1975, to his Application for an Operating License, (2) Facility Operating License including Appendix A (Technical Specifications) dated January 30, 1976, (3) Licensee's letters of August 18 and 25, 1976, and (4 This Order for Modification of License, In the Matter of Duquesne Light Company, Ohio Edison Company, and Pennsylvania Power Company, Beaver Valley Power Station, Unit No. 1, Docket No. 50–334.

III. Accordingly, pursuant to the Atomic Energy Act of 1954, as amended, and the Commission's Rules and Regulations in 10 CFR Parts 2 and 50, *It is Ordered*, That Facility Operating License No. DPR-66 is hereby amended by adding the following new provisions:

1. As soon as possible, the Licensee shall submit a reevaluation of ECCS cooling performance calculated in accordance with an approved Westinghouse Evaluation Model, with appropriate correction for upper head water temperature.

2. Until further authorization by the Commission, the Technical Specification limit for total nuclear peaking factor (F_Q) shall be reduced to 2.22.

For The Nuclear Regulatory Commission.

Dated in Bethesda, Md. this 27th day of August 1976.

BEN C. RUSCHE,
Director, Office of Nuclear Reactor Regulation.

[FR Doc.76–26162 Filed 9–8–76;8:45 am]

[Docket Nos. 50–250 and 50–251]

FLORIDA POWER & LIGHT CO. (TURKEY POINT PLANT UNITS NOS. 3 AND 4)

Order for Modification of License

I. The Florida Power and Light Company (the Licensee), is the holder of Facility Operating Licenses No. DPR–31 and DPR–41 which authorize the operation of the nuclear power reactors known as Turkey Point Plant Units Nos. 3 and 4 (the facilities) at steady state reactor power levels not in excess of 2200 thermal megawatts (rated power). The facilities are pressurized water reactors (PWR) located at the Licensee's site in Dade County Florida.

II. In conformance with evaluations of the performance of the facilities' Emergency Core Cooling System (ECCS) submitted by the Licensee on March 10, 1975, and supplemented by letters dated April 10, April 30, May 15 and May 21, 1975, the Technical Specifications issued June 5, 1975, for the facilities limit the reactor total nuclear peaking factor (F_Q) to 2.32. The ECCS performance evaluation submitted by the Licensee was based upon a previously approved ECCS evaluation model developed by the Westinghouse Electric Corporation (Westinghouse), the designer of the facilities, to conform with the requirements of the Commission's ECCS Acceptance Criteria, 10 CFR Part 50, § 50.46 and Appendix K. The evaluation indicated that with a total nuclear peaking factor limited as set forth above, and with the other limits set forth in the facilities' Technical Specifications, the ECCS cooling performance for the facilities would conform with the criteria contained in 10 CFR 50.46(b) which govern calculated peak clad temperature, maximum cladding oxidation, maximum hydrogen generation, coolable geometry and long term cooling.

Due to the configuration of the Westinghouse reactor vessel design, a small portion of reactor inlet water which is cooler than outlet water is directed through several nozzles located on the periphery of the vessel to cool the upper portion of the vessel head. Accordingly, upper head temperatures used in evaluating ECCS performance were assumed to be equal to the reactor inlet water temperature. However, recent operating data gathered at the Connecticut Yankee facility has indicated that, contrary to this expectation, the temperature of the water in the upper head is higher than the reactor inlet water temperature, by about 60 percent of the difference between reactor inlet and reactor outlet temperature. This higher upper head water temperature would have the effect of increasing the calculated peak clad temperature in the event of a loss of coolant accident.

In a meeting with the staff on August 9, 1976, Westinghouse presented generic evaluations of the effect on calculated peak clad temperature for the worst break identified in previous calculations for each type of Westinghouse reactor and fuel design using an upper head water temperature exceeding reactor inlet water temperature by an amount equal to 75 percent of the reactor inlet-reactor outlet differential. On August 13, 1976, the staff instructed the licensee to submit an analysis similar to the Westinghouse evaluation with the clearly conservative assumption of upper head water temperature equal to reactor outlet temperature (100 percent of the reactor outlet-reactor inlet differential) and to operate the facilities in accordance with the results of this analysis. The results of the evaluation submitted for the Turkey Point Plant reactors indicated that with this modification of the upper head water temperature the calculated peak clad temperature for the worst case break would exceed the Commission's ECCS performance criteria by about 160° F.

Extensive sensitivity studies, submitted with previous calculations in connection with assessment of Westinghouse evaluation models, have established a relationship between the reactor total nuclear peaking factor (F_Q) and calculated peak clad temperature such that if F_Q is reduced by 0.16 the calculated peak clad temperature for the Turkey Point Plant reactors would not exceed 2200°F. As directed by the NRC staff, the Licensee agreed to operate the facility with the total nuclear peaking factor reduced by 0.16 to 2.16. However, subsequent to the licensee's submittal, further review of data presented by Westinghouse has led the staff to conclude that an additional reduction in F_Q over that presented by the licensee is warranted. This is based on the fact that the Westinghouse generic evaluation for plants with three reactor coolant loops, used the results from two different, but approved, ECCS models (the March 1975 and the October 1975 models). When consistent ECCS models are used the calculated peak clad temperature could increase by an additional 50°F.

After discussions with the NRC staff, on August 24, 1976 the licensee amended his previous submission to account for this additional increase in peak clad temperature, by reducing F_Q to 2.11. The NRC staff believes that the licensee's actions, under the circumstances, are appropriate and should be confirmed by NRC Order.

The staff expects that, when revised calculations for the facility are submitted using an approved evaluation model with correct input for upper head water temperature, or assuming that the upper head water temperature equals reactor vessel outlet water temperatures, such

calculations will demonstrate that operation with this total nuclear peaking factor would conform with the criteria of 10 CFR 50.46(b). Such revised calculations fully conforming to the requirements of 10 CFR 50.46 are to be provided for the facility as soon as possible. The additional limitations set forth in this Order will provide reasonable assurance that the public health and safety will not be endangered.

Copies of the following documents are available for public inspection in the Commission's Public Document Room, 1717 H Street, N.W., Washington, D.C., 20555 and at the Environmental and Urban Affairs Library, Florida International University, Miami, Florida: (1) ECCS performance dated March 10, 1975 and supplemented by letters dated April 10, April 30, May 15 and May 21, 1975, (2) Amendments Nos. 9 and 8 to Licenses DPR–31 and DPR–41 dated June 5, 1975, (3) Letter dated August 19, 1975, from Florida Power and Light Company to Office of Nuclear Reactor Regulation and (4) This Order for Modification of License, In the Matter of Florida Power and Light Company (Turkey Point Plant, Units Nos. 3 and 4), Dockets Nos. 50–250 and 50–251.

III. Accordingly, pursuant to the Atomic Energy Act of 1954, as amended, and the Commission's Rules and Regulations in 10 CFR Parts 2 and 50, *It is ordered*, That Facility Operating Licenses Nos. DPR–31 and DPR–41 are hereby amended by adding the following new provisions:

1. As soon as possible, the Licensee shall submit a re-evaluation of ECCS cooling performance calculated in accordance with an approved Westinghouse Evaluation Model, with appropriate correction for upper head water temperature.
2. Until further authorization by the Commission, the Technical Specification limit for total nuclear peaking factor (F_Q) shall be reduced to 2.11.

Dated in Bethesda, Md. this 27th day of August, 1976.

For the Nuclear Regulatory Commission.

BEN C. RUSCHE,
Director, Office of
Nuclear Reactor Regulation.

[FR Doc.76-26156 Filed 9-8-76;8:45 am]

[Docket No. 50–315]

INDIANA AND MICHIGAN ELECTRIC CO. AND INDIANA AND MICHIGAN POWER CO. (DONALD C. COOK NUCLEAR PLANT UNIT NO. 1)

Order for Modification of License

I. Indiana & Michigan Electric Company and Indiana & Michigan Power Company (the Licensee) is the holder of Facility Operating License No. DPR–58 which authorizes the operation of a nuclear power reactor known as Donald C. Cook Nuclear Plant Unit No. 1 (the facility) at steady state reactor power levels not in excess of 3250 thermal megawatts (rated power). The facility is a pressurized water reactor (PWR) located at the Licensee's site in Berrien County, Michigan.

II. In conformance with evaluations of the performance of the Emergency Core Cooling System (ECCS) of the facility submitted by the Licensee on September 6, 1974, October 31 and December 12, 1975, January 9 and 26, 1976 and in a letter NS–CE–832 dated November 4, 1975 from C. Eicheldinger (Westinghouse) to B. C. Rusche (NRC), the Technical Specifications issued March 30, 1976 for the facility limit the reactor total nuclear peaking factor (F_Q) to 1.98. The ECCS performance evaluation submitted by the Licensee was based upon a previously approved ECCS evaluation model developed by the Westinghouse Electric Corporation (Westinghouse), the designer of the facility, to conform with the requirements of the Commission's ECCS Acceptance Criteria, 10 CFR Part 50, § 50.46 and Appendix K. The evaluation indicated that with a total nuclear peaking factor limited as set forth above, and with the other limits set forth in the facility's Technical Specifications, the ECCS cooling performance for the facility would conform with the criteria contained in 10 CFR 50.46(b) which govern calculated peak clad temperature, maximum cladding oxidation, maximum hydrogen generation, coolable geometry and long term cooling.

Due to the configuration of the Westinghouse reactor vessel design, a small portion of reactor inlet water which is cooler than outlet water is directed through several nozzles located on the periphery of the vessel to cool the upper portion of the vessel head. Accordingly, upper head temperatures used in evaluating ECCS performance were assumed to be equal to the reactor inlet water temperature. However, recent operating data gathered at the Connecticut Yankee facility has indicated that, contrary to this expectation, the temperature of the water in the upper head is higher than the reactor inlet water temperature, by about 60 percent of the difference between reactor inlet and reactor outlet temperature. This higher upper head water temperature would have the effect of increasing the calculated peak clad temperature in the event of a loss of coolant accident.

In a meeting with the staff on August 9, 1976, Westinghouse presented generic evaluations of the effect on calculated peak clad temperature for the worst break identified in previous calculations for each type of Westinghouse reactor and fuel design using an upper head water temperature exceeding reactor inlet water temperature by an amount equal to 75 percent of the reactor inlet-reactor outlet differential. On August 12, 1976, the staff instructed the licensee to submit an analysis similar to the Westinghouse evaluation with the clearly conservative assumption of upper head water temperature equal to reactor outlet temperature (100 percent of the reactor outlet-reactor inlet differential) and to operate the facility in accordance with the results of this analysis. The results of the evaluation submitted for the D.C. Cook Unit No. 1 reactor indicated that with this modification of the upper head water temperature the calculated peak clad temperature for the worst case break would not exceed the Commission's ECCS performance criteria.

The staff expects that, when revised calculations for the facility are submitted using an approved evaluation model with correct input for upper head water temperature, or assuming that the upper head water temperature equals reactor vessel outlet water temperature, such calculations will demonstrate that operation with this total nuclear peaking factor would conform to the criteria of 10 CFR 50.46(b). Such revised calculations fully conforming to the requirements of 10 CFR 50.46 are to be provided for the facility as soon as possible. The limitations presently incorporated in the Technical Specifications for the facility continue to provide reasonable assurance that the public health and safety will not be endangered.

Copies of the following documents are available for public inspection in the Commission's Public Document Room, 1717 H Street, NW., Washington, D.C., and at the Maude Preston Palenske Memorial Library, 500 Market Street, St. Joseph, Michigan 49085: (1) Licensee's ECCS submittals dated September 6, 1974, October 31 and December 12, 1975, January 9 and 26, 1976 and letter NS–CE–832 dated November 4, 1975 from C. Eicheldinger (Westinghouse) to B. C. Rushce (NRC), (2) Amendment No. 12 to Operating License DPR–58 dated March 30, 1976, (3) Licensee's letter dated August 18, 1976, and (4) This Order for Modification of License, In the Matter of Indiana & Michigan Electric Company and Indiana & Michigan Electric Company, Donald C. Cook Nuclear Plant Unit No. 1, Docket No. 50–315.

III. Accordingly, pursuant to the Atomic Energy Act of 1954, as amended, and the Commission's Rules and Regulations in 10 CFR Parts 2 and 50, *It is ordered*, That Facility Operating License No. DPR-58 is hereby amended by adding the following new provision:

As soon as possible, the Licensee shall submit a reevaluation of ECCS cooling performance calculated in accordance with an approved Westinghouse Evaluation Model, with appropriate correction for upper head water temperature.

Dated in Bethesda, Md. this 27th day of August, 1976.

For the Nuclear Regulatory Commission.

BEN C. RUSCHE,
Director, Office of
Nuclear Reactor Regulation.

[FR Doc.76-26155 Filed 9-8-76;8:45 am]

INTERNATIONAL ATOMIC ENERGY AGENCY DRAFT SAFETY GUIDE

Availability of Draft for Public Comment

The International Atomic Energy Agency (IAEA) is developing a limited

number of internationally acceptable codes of practice and safety guides for nuclear power plants. These codes and guides will be developed in the following five areas: Government Organization, Siting, Design, Operations and Quality Assurance. The purpose of these codes and guides is to provide IAEA guidance to countries beginning nuclear power programs.

The IAEA Codes of Practice and Safety Guides are developed in the following way. The IAEA receives and collates relevant existing information used by member countries. Using this collation as a starting point, an IAEA Working Group of a few experts then develops a preliminary draft. Following this, an IAEA Technical Review Committee reviews the preliminary draft and modifies it to the extent necessary to develop a draft acceptable to the IAEA Technical Review Committee. This draft Code of Practice or Safety Guide is then sent to the IAEA Senior Advisory Group which reviews and modifies the draft as necessary to reach agreement on the draft and then forwards it to the IAEA Secretariat to obtain comments from the member states.

As a part of this program Safety Guide SG–03 "Operational Limits and Conditions" has been developed and the NRC staff is soliciting comments on this Guide from the U.S. public.

An IAEA Working Group, consisting of Mr. N. Veeraraghavan of India, Mr. A. Higashi of Japan, and Mr. K. V. Seyfrit (Nuclear Regulatory Commission) of the United States developed the draft from an IAEA collation during a meeting that was held in Vienna, Austria on July 5–16, 1976.

As the next step in its development the draft Safety Guide is scheduled to be reviewed by the IAEA Technical Review Commitee on Operations at a meeting in Vienna, Austria on October 4–8, 1976. Comments received by September 20, 1976 will be useful to this review. Single copies of this draft may be obtained by a written request to the Director, Office of Standards Development, U.S. Nuclear Regulatory Commission, Washington, D.C. 20555.

(5 U.S.C. 522(a))

Dated at Rockville, Maryland this 24th day of August 1976.

For the Nuclear Regulatory Commission.

ROBERT B. MINOGUE,
Director, Office of Standards Development.

[FR Doc.76-26169 Filed 9-8-76;8:45 am]

[Docket No. 50-336]

NORTHEAST NUCLEAR ENERGY CO., ET AL.

Issuance of Amendment to Facility Operating License

Notice is hereby given that the U.S. Nuclear Regulatory Commission (the Commission) has issued Amendment No. 17 to Facility Operating License No. DPR–65 issued to Northeast Nuclear Energy Company, The Connecticut Light and Power Company, The Hartford Electric Light Company, and Western Massachusetts Electric Company, which revised Technical Specifications for operation of the Millstone Nuclear Power Station, Unit No. 2, located in the Town of Waterford, Connecticut. The amendment is effective as of the date of issuance.

The amendment will provide for a redesigned undervoltage (UV) reactor trip function for the Reactor Protective System (RPS).

The application for the amendment complies with the standards and requirements of the Atomic Energy Act of 1954, as amended (the Act), and the Commission's rules and regulations. The Commission has made appropriate findings as required by the Act and the Commission's rules and regulations in 10 CFR Ch. I, which are set forth in the license amendment. Prior public notice of this amendment was not required since the amendment does not involve a significant hazards consideration.

The Commission has determined that the issuance of this amendment will not result in any significant environmental impact and that pursuant to 10 CFR 15.5 (d)(4) an environmental impact statement, negative declaration or environmental impact appraisal need not be prepared in connection with issuance of this amendment.

For further details with respect to this action, see (1) the application for amendment dated August 4, 1976, (2) Amendment No. 17 to License No. DPR–65, and (3) the Commission's related Safety Evaluation. All of these items are available for public inspection at the Commission's Public Document Room, 1717H Street N.W., Washington, D.C. and at the Waterford Public Library, Rope Ferry Road, Waterford, Connecticut 06385.

A copy of items (2) and (3) may be obtained upon request addressed to the U.S. Nuclear Regulatory Commission, Washington, D.C. 20555, Attention: Director, Division of Operating Reactors.

Dated at Bethesda, Maryland, this 30th day of August 1976.

For the Nuclear Regulatory Commission.

GEORGE LEAR,
Chief, Operating Reactor Branch No. 3, Division of Operating Reactors.

[FR Doc.76-26165 Filed 9-8-76;8:45 am]

[Docket No. 50-336]

NORTHEAST NUCLEAR ENERGY CO., ET AL.

Issuance of Amendment to Facility Operating License

Notice is hereby given that the U.S. Nuclear Regulatory Commission (the Commission) has issued Amendment No. 13 to Facility Operating License No. DPR–65 issued to Northeast Nuclear Energy Company, The Connecticut Light and Power Company, The Hartford Electric Light Company, and Western Massachusetts Electric Company, which revised Technical Specifications for operation of the Millstone Nuclear Power Station, Unit No. 2, located in the Town of Waterford, Connecticut. The amendment is effective as of its date of issuance.

The amendment modifies the Technical Specifications to eliminate the required operability and surveillance of the Turbine Runback feature of the Engineered Safety Feature Actuation System.

The application for the amendment complies with the standards and requirements of the Atomic Energy Act of 1954, as amended (the Act), and the Commission's rules and regulations. The Commission has made appropriate findings as required by the Act and the Commission's rules and regulations in 10 CFR Ch. I, which are set forth in the license amendment. Notice of Proposed Issuance of Amendment to Facility Operating License in connection with this action was published in the FEDERAL REGISTER on July 22, 1976 (41 FR 30225). No request for a hearing or petition for leave to intervene was filed following notice of the proposed action.

The Commission has determined that the issuance of this amendment will not result in any significant environmental impact and that pursuant to 10 CFR 51.5(d)(4) an environmental statement, negative declaration or environmental impact appraisal need not be prepared in connection with issuance of this amendment.

For further details with respect to this action, see (1) the application for amendment dated May 26, 1976 and supplements dated June 14, 1976 and June 22, 1976, (2) Amendment No. 13 to License No. DPR–65, and (3) the Commission's related Safety Evaluation. All of these items are available for public inspection at the Commission's Public Document Room, 1717 H Street, NW., Washington, D.C. and at the Waterford Public Library, Rope Ferry Road, Route 156, Waterford, Connecticut 06385.

A copy of items (2) and (3) may be obtained upon request addressed to the U.S. Nuclear Regulatory Commission, Washington, D.C. 20555, Attention: Director, Division of Operating Reactors.

Dated at Bethesda, Maryland, this 31st day of August, 1976.

For the Nuclear Regulatory Commission.

GEORGE LEAR,
Chief, Operating Reactors Branch No. 3, Division of Operating Reactors.

[FR Doc.76-26166 Filed 9-8-76;8:45 am]

[Docket Nos. 50-282 and 50-306]

NORTHERN STATES POWER CO. (PRAIRIE ISLAND NUCLEAR GENERATING PLANT UNIT NOS. 1 AND 2)

Order for Modification of Licenses

I. The Northern States Power Company (the Licensee) is the holder of

Facility Operating License Nos. DPR–42 and DPR–60 which authorize the operation of nuclear power reactors known as Prairie Island Nuclear Generating Plant Unit Nos. 1 and 2 (the facilities) at steady state power levels not in excess of 1650 thermal megawatts (rated power per Unit). The facilities are pressurized water reactors (PWR) located at the Licensee's site near Redwing, Minnesota.

II. In conformance with evaluations of the performance of the Emergency Core Cooling System (ECCS) of the facilities submitted by the Licensee on April 14, 1975, April 17, 1975, July 9, 1975, October 21, 1975, January 7, 1976 and March 1, 1976, the proposed Technical Specifications submitted by the Licensee on February 2, 1976 for the facilities limit the reactors total nuclear peaking factor (F_Q) to 2.15. The ECCS performance evaluation submitted by the Licensee was based upon previously approved ECCS evaluation model developed by the Westinghouse Electric Corporation (Westinghouse), the designer of the facilities, to conform with the requirements of the Commission's ECCS Acceptance Criteria, 10 CFR Part 50, § 50.46 and Appendix K. The evaluation indicated that with a total nuclear peaking factor limited as set forth above, and with the other limits set forth in the facilities' Technical Specifications, the ECCS cooling performance for the facilities would conform with the criteria contained in 10 CFR 50.46(b) which govern calculated peak clad temperature, maximum cladding oxidation, maximum hydrogen generation, coolable geometry and long term cooling.

Due to the configuration of the Westinghouse reactor vessel design, a small portion of reactor inlet water which is cooler than outlet water is directed through several nozzles located on the periphery of the vessel to cool the upper portion of the vessel head. Accordingly, upper head temperatures used in evaluating ECCS performance were assumed to be equal to the reactor inlet water temperature. However, recent operating data gathered at the Connecticut Yankee facility has indicated that, contrary to this expectation, the temperature of the water in the upper head is higher than the reactor inlet water temperature, by about 60 percent of the difference between reactor inlet and reactor outlet temperature. This higher upper head water temperature would have the effect of increasing the calculated peak clad temperature in the event of a loss of coolant accident.

In a meeting with the staff on August 9, 1976, Westinghouse presented generic evaluations of the effect on calculated peak clad temperature for the worst break identified in previous calculations for each type of Westinghouse reactor and fuel design using an upper head water temperature exceeding reactor inlet water temperature by an amount equal to 75 percent of the reactor inlet-reactor outlet differential. On August 12, 1976, the staff instructed the licensee to submit an analysis similar to the Westinghouse evaluation with the clearly conservative assumption of upper head water temperature equal to reactor outlet temperature (100 percent of the reactor outlet-reactor inlet differential) and to operate the facilities in accordance with the results of this analysis. The results of the evaluation submitted for the Prairie Island reactors indicated that with this modification of the upper head water temperature the calculated peak clad temperature for the worst case break would not exceed the Commission's ECCS performance criteria.

The staff expects that, when revised calculations for the facilities are submitted using an approved evaluation model with correct input for upper head water temperature, or assuming that the upper head water temperature equals reactor vessel outlet water temperature, such calculations will demonstrate that operation with this total nuclear peaking factor would conform to the criteria of 10 CFR 50.46(b). Such revised calculations fully conforming to the requirements of 10 CFR 50.46 are to be provided for the facilities as soon as possible. The limitations presently incorporated in the Technical Specifications for the facilities continue to provide reasonable assurance that the public health and safety will not be endangered.

Copies of the following documents are available for public inspection in the Commission's Public Document Room, 1717 H Street, NW., Washington, D.C., 20555 and at The Environmental Conservation Library, Minneapolis Public Library, 300 Nicollet Mall, Minneapolis, Minnesota 55401: (1) the application for amendments dated February 2, 1976 and earlier filings dated April 14, 1975, April 17, 1975, July 9, 1975, October 21, 1975, January 1, 1976 and March 1, 1976, (2) letter from Northern States Power Company dated August 17, 1976, and (3) This Order for Modification of License, In the Matter of the Northern States Power Company, Prairie Island Nuclear Generating Plant Unit Nos. 1 and 2, Docket Nos. 50–282 and 50–306.

III. Accordingly, pursuant to the Atomic Energy Act of 1954, as amended, and the Commission's Rules and Regulations in 10 CFR Parts 2 and 50, *It is ordered*, That Facility Operating License Nos. DPR–42 and DPR–60 are hereby amended by adding the following new provision:

As soon as possible, the Licensee shall submit a re-evaluation of ECCS cooling performance calculated in accordance with an approved Westinghouse Evaluation Model, with appropriate correction for upper head water temperature.

Dated in Bethesda, Maryland this 27th day of August, 1976.

For the Nuclear Regulatory Commission.

BEN C. RUSCHE,
Director, Office of Nuclear Reactor Regulation.

[FR Doc.76–26154 Filed 9–8–76;8:45 am]

[Docket No. 50–344]

PORTLAND GENERAL ELECTRIC CO., ET AL.

Issuance of Amendment to Facility Operating License

The U.S. Nuclear Regulatory Commission (the Commission) has issued Amendment No. 8 to Facility Operating License No. NPF–1 issued to Portland General Electric Company, the City of Eugene, Oregon and Pacific Power and Light Company which revised the Technical Specifications for operation of the Trojan Nuclear Plant located on the west shore of the Columbia River in Columbia County, Oregon. The amendment is effective as of its date of issuance.

The amendment corrects editorial omissions and errors in Table 3.6–1 (Containment Isolation Valves) of Appendix A of the Technical Specifications.

The application for the amendment complies with the standards and requirements of the Atomic Energy Act of 1954, as amended (the Act), and the Commission's rules and regulations. The Commission has made appropriate findings as required by the Act and the Commission's rules and regulations in 10 CFR Chapter I, which are set forth in the license amendment. Prior public notice of this amendment was not required since the amendment does not involve a significant hazards consideration.

The Commission has determined that the issuance of this amendment will not result in any significant environmental impact and that pursuant to 10 CFR 51.5(d)(4) an environmental impact statement or negative declaration and environmental impact appraisal need not be prepared in connection with issuance of this amendment.

For further details with respect to this action, see (1) the application for amendment dated August 13, 1976, (2) Amendment No. 8 to License No. NPF–1, and (3) the Commission's related Safety Evaluation. All of these items are available for public inspection at the Commission's Public Document Room, 1717 H Street, NW., Washington, D.C. 20555, and at the Columbia County Courthouse, Law Library, Circuit Court Room, St. Helens, Oregon 97051.

A copy of items (2) and (3) may be obtained upon request addressed to the U.S. Nuclear Regulatory Commission, Washington, D.C. 20555, Attention: Director, Division of Operating Reactors.

Dated at Bethesda, Maryland, this 19th day of August 1976.

For the Nuclear Regulatory Commission.

A. SCHWENCER,
Chief, Operating Reactors Branch No. 1, Division of Operating Reactors.

[FR Doc.76–26167 Filed 9–8–76;8:45 am]

[Docket No. 50-344]

PORTLAND GENERAL ELECTRIC CO., ET AL. (TROJAN NUCLEAR PLANT)

Order for Modification of License

I. Portland General Electric Company, The City of Eugene, Oregon and Pacific Power and Light Company (the Licensee) are the holder of Facility Operating License No. NPF-1 which authorizes the operation of a nuclear power reactor known as Trojan Nuclear Plant (the facility) at steady state reactor power levels not in excess of 3411 thermal megawatts (rated power). The facility is a pressurized water reactor (PWR) located at the Licensee's site on the west side of the Columbia River in Columbia County, Oregon.

II. In conformance with evaluations of the performance of the Emergency Core Cooling System (ECCS) of the facility submitted by the Licensee on November 4, 1974 and September 5, 1975, the Technical Specifications issued November 21, 1975 for the facility limit the reactor total nuclear peaking factor (F_Q) to 2.32. The ECCS performance evaluation submitted by the Licensee was based upon a previously approved ECCS evaluation model developed by the Westinghouse Electric Corporation (Westinghouse), the designer of the facility, to conform with the requirements of the Commission's ECCS Acceptance Criteria, 10 CFR Part 50, § 50.46 and Appendix K. The evaluation indicated that with a total nuclear peaking factor limited as set forth above, and with the other limits set forth in the facility's Technical Specifications, the ECCS cooling performance for the facility would conform with the criteria contained in 10 CFR 50.46(b) which govern calculated peak clad temperature, maximum cladding oxidation, maximum hydrogen generation, coolable geometry and long term cooling.

Due to the configuration of the Westinghouse reactor vessel design, a small portion of the reactor inlet water which is cooler than outlet water is directed through several nozzles located on the periphery of the vessel to cool the upper portion of the vessel head. Accordingly, upper head temperatures used in evaluating ECCS performance were assumed to be equal to the reactor inlet water temperature. However, recent operating data gathered at the Connecticut Yankee facility has indicated that, contrary to this expectation, the temperature of the water in the upper head is higher than the reactor inlet water temperature, by about 60 percent of the difference between reactor inlet and reactor outlet temperature. This higher upper head water temperature would have the effect of increasing the circulated peak clad temperature in the event of a loss of coolant accident.

In a meeting with the staff on August 9, 1976, Westinghouse presented generic evaluations of the effect on calculated peak clad temperature for the worst break identified in previous calculations for each type of Westinghouse reactor and fuel design using an upper head water temperature exceeding reactor inlet water temperature by an amount equal to 75 percent of the reactor inlet-reactor outlet differential. On August 12, 1976, the staff instructed the licensee to submit an analysis similar to the Westinghouse evaluation with the clearly conservative assumption of upper head water temperature equal to reactor outlet temperature (100 percent of the reactor outlet—reactor inlet differential) and to operate the facility in accordance with the results of this analysis. The results of the evaluation submitted for the Trojan reactor indicated that with this modification of the upper head water temperature the calculated peak clad temperature for the worst case break would not exceed the Commission's ECCS performance criteria.

The staff expects that, when revised calculations for the facility are submitted using an approved evaluation model with correct input for upper head water temperature, or assuming that the upper head water temperature equals reactor vessel outlet water temperature, such calculations will demonstrate that operation with this total nuclear peaking factor would conform to the criteria of 10 CFR 50.46(b). Such revised calculations fully conforming to the requirements of 10 CFR 50.46 are to be provided for the facility as soon as possible. The limitations presently incorporated in the Technical Specifications for the facility continue to provide reasonable assurance that the public health and safety will not be endangered.

Copies of the following documents are available for public inspection in the Commission's Public Document Room, 1717 H Street NW., Washington, D.C., 20555 and at the Columbia County Courthouse, Law Library, Circuit Court, St. Helens, Oregon 97051: (1) the ECCS performance evaluations dated November 4, 1974 and September 5, 1975, (2) Facility License No. NPF-1 issued November 21, 1975, (3) the Licensee's letter dated August 18, 1976, and (4) This Order for Modification of License, In the Matter of Portland General Electric Company, The City of Eugene, Oregon, Pacific Power and Light Company, Docket No. 50-344.

III. Accordingly, pursuant to the Atomic Energy Act of 1954, as amended, and the Commission's Rules and Regulations in 10 CFR Parts 2 and 50, *It is ordered*, That Facility Operating License No. NPF-1 is hereby amended by adding the following new provision:

As soon as possible, the Licensee shall submit a reevaluation of ECCS cooling performance calculated in accordance with an approved Westinghouse Evaluation Model, with appropriate correction for upper head water temperature.

Dated in Bethesda, Maryland, this Auguest 27, 1976.

For the Nuclear Regulatory Commission.

BEN C. RUSCHE,
Director, Office of Nuclear Reactor Regulation.

[FR Doc.76-26153 Filed 9-8-76;8:45 am]

[Docket No. 50-537]

PROJECT MANAGEMENT CORP. AND TENNESSEE VALLEY AUTHORITY (CLINCH RIVER BREEDER REACTOR PLANT)

Special Meeting With Counsel

AUGUST 31, 1976.

The Licensing Board will hold a special meeting with counsel to consider all matters related to the Memorandum and Order of the Nuclear Regulatory Commision dated August 27, 1976, in connection with Contentions 10 and 11 submitted by Intervenors NRDC, *et al.* Such meeting with Counsel will be held on Thursday, September 23, 1976, at 10:00 a.m. at the Nuclear Regulatory Commission, Atomic Safety and Licensing Board Panel Office, 4th Floor, East-West Towers Bldg., 4350 East-West Highway, Bethesda, Maryland, to consider the following aspects of the Commission's Order:

1. Action consistent with the Memorandum and Order of the Commission entered August 27, 1976.
2. Schedule revisions or amendments.
3. The likelihood that the proposed CRBR project will meet its objectives within the LMFBR program, as a relevant issue.
4. Alternatives for meeting such objectives, evaluated in terms of the objectives defined in the ERDA impact statement.
(a) Alternatives sites outside the Tennessee Valley Authority service area.
5. Clarification of the subcontentions of NRDC Contention 10.
6. Limitations on discovery and cross-examination, consistent with the standards described in the Commission's Memorandum and Order.
7. Other matters reasonably related to the foregoing subjects.

Counsel are requested to have any relevant papers they desire to submit in the offices of the Licensing Board at the above address on or before 4:00 p.m., Friday, September 17, 1976.

It is so ordered.

Dated at Bethesda, Maryland, this 31st day of August, 1976.

ATOMIC SAFETY AND LICENSING BOARD.
MARSHALL E. MILLER,
Chairman.

[FR Doc.76-26170 Filed 9-8-76;8:45 am]

[Docket No. 50-376]

PUERTO RICO WATER RESOURCES AUTHORITY

Availability of Draft Environmental Statement (Spanish Translation) for North Coast Nuclear Plant, Unit No. 1

Pursuant to the National Environmental Policy Act of 1969 and the United States Nuclear Regulatory Commission's regulations in 10 CFR Part 51, notice is hereby given that a Draft Environmental Statement (Spanish translation) has been prepared by the Commission's Office of Nuclear Reactor Regulation related to the suitability of the site proposed for construction of the North Coast

Nuclear Plant, Unite No. 1. The proposed site is located on the north central coast of Puerto Rico (Islote). The Draft Environmental Statement (NUREG–0113) is available for inspection by the public in the Commission's Public Document Room at 1717 H Street, N.W., Washington, D.C., the Arecibo City Hall Library, Post Office Box 1086, Arecibo, Puerto Rico 00612 and the Etien Totti Public Library, College of Engineers, Architects and Surveyors, Orb Roosevelt Development, Hato Rey, Puerto Rico 00918. The Draft Statement is also being made available at the Puerto Rico Planning Board, P.O. Box 41119, Minillas Station, Santurce, Puerto Rico 00940. Requests for copies of the Draft Environmental Statement should be addressed to the U.S. Nuclear Regulatory Commission, Washington, D.C., 20555, Attention: Director, Division of Site Safety and Environmental Analysis.

An English language version of this Draft Environmental Statement was issued on August 23, 1976, the availability of which was published in the FEDERAL REGISTER on August 26, 1976 (41 FR 36093).

The Applicant's Environmental Report, as supplemented, submitted by Puerto Rico Water Resources Authority, is also available for public inspection at the above designated locations. Notice of availability of the Applicant's Environmental Report was published in the FEDERAL REGISTER on February 14, 1975 (40 FR 6835).

Pursuant to 10 CFR Part 51, interested persons may submit comments on the Draft Environmental Statement for the Commission's consideration. Federal, Commonwealth, and specified local agencies are being provided with copies of the Applicant's Environmental Report and the Draft Environmental Statement. Other interested persons or local agencies may obtain these documents upon request. Comments on both the English language and Spanish translation are due by October 26, 1976. Comments by Federal, Commonwealth, and local officials, or other members of the public will be made available by the Commission for public inspection at the Commission's Public Document Room in Washington, D.C., the Arecibo City Hall Library, Arecibo, Puerto Rico 00612, and the Etien Totti Public Library, College of Engineers, Architects and Surveyors, Orb Roosevelt Development, Hato Rey, Puerto Rico 00918. Upon consideration of comments submitted with respect to the Draft Environmental Statement, the Commission's staff will prepare a Final Environmental Statement, the availability of which will be published in the FEDERAL REGISTER.

Comments on the Draft Environmental Statement from interested members of the public should be addressed to U.S. Nuclear Regulatory Commission, Washington, D.C. 20555, Attention: Director, Division of Site Safety and Environmental Analysis.

Dated at Rockville, Maryland, this 31st day of August 1976.

For the Nuclear Regulatory Commission.

GEORGE W. KNIGHTON,
Chief, Environmental Projects Branch 1, Division of Site Safety and Environmental Analysis.

[FR Doc.76-26148 Filed 9-8-76;8:45 am]

REGULATORY GUIDE

Issuance and Availability

The Nuclear Regulatory Commission has issued a new guide in its Regulatory Guide Series. This series has been developed to describe and make available to the public methods acceptable to the NRC staff of implementing specific parts of the Commission's regulations and, in some cases, to delineate techniques used by the staff in evaluating specific problems or postulated accidents and to provide guidance to applicants concerning certain of the information needed by the staff in its review of applications for permits and licenses.

Regulatory Guide 1.121, "Bases for Plugging Degraded PWR Steam Generator Tubes," describes a method acceptable to the NRC staff for establishing the limiting safe conditions of tube degradation of steam generator tubing, beyond which defective tubes as established by inservice inspection should be removed from service by welding plugs at each end of the tube. This guide applies only to pressurized water reactors.

Comments and suggestions in connection with (1) items for inclusion in guides currently being developed or (2) improvements in all published guides are encouraged at any time. Public comments on Regulatory Guide 1.121 will, however, be particularly useful in evaluating the need for an early revision if received by November 5, 1976.

Comments should be sent to the Secretary of the Commission, U.S. Nuclear Regulatory Commission, Washington, D.C. 20555, Attention: Docketing and Service Section.

Regulatory guides are available for inspection at the Commission's Public Document Room, 1717 H Street NW., Washington, D.C. Requests for single copies of issued guides (which may be reproduced) or for placement on an automatic distribution list for single copies of future guides should be made in writing to the Director, Office of Standards Development, U.S. Nuclear Regulatory Commission, Washington, D.C. 20555. Telephone requests cannot be accommodated. Regulatory guides are not copyrighted and Commission approval is not required to reproduce them.

(5 U.S.C. 552(a))

Dated at Rockville, Maryland this 30th day of August 1976.

For the Nuclear Regulatory Commission.

ROBERT B. MINOGUE,
Director, Office of Standards Development.

[FR Doc.76-26168 Filed 9-8-76;8:45 am]

[Docket No. 50-244]

ROCHESTER GAS AND ELECTRIC CORP. AND R. E. GINNA NUCLEAR POWER PLANT

Order for Modification of License

I. The Rochester Gas and Electric Corporation (the Licensee), is the holder of Provisional Operating License No. DPR-18 which authorizes the operation of a nuclear power reactor known as R. E. Ginna Nuclear Power Plant (the facility) at steady state reactor power levels not in excess of 1520 thermal megawatts (rated power). The facility is a pressurized water reactor (PWR) located at the Licensee's site near Rochester, New York.

II. In conformance with evaluations of the performance of the Emergency Core Cooling System (ECCS) of the facility submitted by the Licensee on March 11, 1975, the Technical Specifications issued May 14, 1975 for the facility limit the reactor total nuclear peaking factor (F_Q) to 2.32. The ECCS performance evaluation submitted by the Licensee was based upon a previously approved ECCS evaluation model developed by Westinghouse Electric Corporation (Westinghouse), the designer of the facility, to conform to the requirements of the Commission's ECCS Acceptance Criteria, 10 CFR Part 50, § 50.46 and Appendix K. The evaluation indicated that with a total nuclear peaking factor limited as set forth above, and with the other limits set forth in the facility's Technical Specifications, the ECCS cooling performance for the facility would conform to the criteria contained in 10 CFR § 50.46(b) which govern calculated peak clad temperature, maximum cladding oxidation, maximum hydrogen generation, coolable geometry and long term cooling.

Due to the configuration of the Westinghouse reactor vessel design, a small portion of relatively cooler reactor inlet water is directed through several nozzles located on the periphery of the vessel to cool the upper portion of the head. Accordingly, upper head temperatures were assumed in evaluating ECCS performance to be equal to the reactor inlet water temperature. However, recent operating data gathered at the Connecticut Yankee facility has indicated that, contrary to this expectation, the temperature of the water in the upper head is warmer than the reactor inlet water temperature, by about some 60 percent of the reactor inlet-reactor outlet temperature differential. This increase in upper head water temperature over that used in ECCS performance calculations would have the effect of increasing the calculated peak clad temperature. This higher upper head water temperature would have the effect of increasing the calculated peak clad temperature in the event of a loss of coolant accident.

In a meeting with the staff on August 9, 1976, Westinghouse presented generic evaluations of the effect on calculated peak clad temperature for the worst break identified in previous calculations for each type of Westinghouse reactor and fuel design using an upper head

water temperature exceeding reactor inlet water temperature by an amount equal to 75% of the reactor inlet-reactor outlet differential. On August 12, 1976, the staff directed the licensee to submit an analysis similar to the Westinghouse evaluation with the clearly conservative assumption of upper head water temperature equal to reactor outlet temperature (100% of the reactor inlet-reactor outlet differential) and to operate the facility in accordance with the results of this analysis. The results of the evaluation submitted for the R. E. Ginna reactor indicated that with this modification of the upper head water temperature the calculated peak clad temperature for the worst case break would not exceed the Commission's ECCS performance criteria.

The staff expects that, when revised calculations for the facility are submitted using an approved evaluation model with correct input for upper head water temperature, or assuming that the upper head water temperature equals reactor vessel outlet water temperature, such calculations will demonstrate that operation with the total nuclear peaking factor would conform to the criteria of 10 CFR § 50.46(b). Such revised calculations fully conforming to the requirements of 10 CFR § 50.46 are to be provided for the facility as soon as possible. The limitations presently incorporated in the Technical Specifications for the facility continue to provide reasonable assurance that the public health and safety will not be endangered.

Copies of the following documents are available for public inspection in the Commission's Public Document Room, 1717 H Street, N.W., Washington, D.C., 20555 and at the Lyons Public Library, 67 Canal Street, Lyons, New York 14489, (1) Licensee letter dated March 11, 1975, (2) NRC letter dated May 14, 1975, (3) Licensee letter dated August 18, 1975, and (4) This Order for Modification of License, In the Matter of R. E. Ginna Nuclear Power Plant, Docket No. 50-244.

III. Accordingly, pursuant to the Atomic Energy Act of 1954, as amended, and the Commission's Rules and Regulations in 10 CFR Parts 2 and 50, IT IS ORDERED THAT Provisional Operating License No. DPR-18 is hereby amended by adding the following new provision:

1. As soon as possible, the Licensee shall submit a reevaluation of ECCS cooling performance calculated in accordance with an approved Westinghouse Evaluation Model, with appropriate correction for upper head water temperature.

Dated in Bethesda, Maryland this 27th day of August 1976.

For the Nuclear Regulatory Commission.

BEN C. RUSCHE,
Director, Office of Nuclear Reactor Regulation.

[FR Doc.76-26150 Filed 9-8-76;8:45 am]

[Dockets Nos. 50-280 and 50-281]

VIRGINIA ELECTRIC AND POWER CO. SURRY POWER STATION, UNITS 1 AND 2

Order for Modification of License

I. Virginia Electric and Power Company (the Licensee), is the holder of Facility Operating Licenses Nos. DPR-32 and DPR-37 which authorizes the operation of two nuclear power reactors known as Surry Power Station, Units 1 and 2 (the facility) at steady state reactor power levels not in excess of 2441 thermal megawatts (rated power). The reactors are pressurized water reactors (PWR) located at the Licensee's site in Surry County, Virginia.

II. In conformance with evaluations of the performance of the Emergency Core Cooling System (ECCS) of the facility submitted by the Licensee on April 15, 1975, as supplemented May 1, May 20, June 6, June 9 and June 11, 1975, the Technical Specifications issued June 16, 1975 for the facility limit the reactor total nuclear peaking factor (F_Q) to 2.10 for each unit. The ECCS performance evaluation submitted by the Licensee was based upon a previously approved ECCS evaluation model developed by the Westinghouse Electric Corporation (Westinghouse), the designer of the nuclear steam supply system, to conform with the requirements of the Commission's ECCS Acceptance Criteria, 10 CFR Part 50, § 50.46 and Appendix K. The evaluation indicated that with a total nuclear peaking factor limited as set forth above, and with the other limits set forth in the facility's Technical Specifications, the ECS cooling performance for the facility would conform with the criteria contained in 10 CFR § 50.46(b) which govern calculated peak clad temperature, maximum cladding oxidation, maximum hydrogen generation, coolable geometry and long term cooling.

Due to the configuration of the Westinghouse reactor vessel design, a small portion of reactor inlet water which is cooler than outlet water is directed through several nozzles located on the periphery of the vessel to cool the upper portion of the vessel head. Accordingly, upper head water temperatures used in evaluating ECCS performance were assumed to be equal to the reactor inlet water temperature. However, recent operating data gathered at the Connecticut Yankee facility has indicated that, contrary to this expectation, the temperature of the water in the upper head is higher than the reactor inlet water temperature, by about 60% of the difference between reactor inlet and reactor outlet temperature. This higher upper head water temperature would have the effect of increasing the calculated peak clad temperature in the event of a loss of coolant accident.

In a meeting with the staff on August 9, 1976, Westinghouse presented generic evaluations of the effect on calculated peak clad-temperature for the worst break identified in previous calculations for each type of Westinghouse reactor and fuel design using an upper head water temperature exceeding reactor inlet water temperature by an amount equal to 75% of the reactor inlet—reactor outlet differential. On August 13, 1976, the staff instructed the licensee to submit an analysis similar to the Westinghouse evaluation with the clearly conservative assumption of upper head water temperature equal to reactor outlet temperature (100% of the reactor outlet—reactor inlet differential) and to operate the facility in accordance with the results of this analysis. The results of the evaluation submitted for the Surry reactors indicated that with this modification of the upper head water temperature the calculated peak clad temperature for the worst case break would exceed the Commission's ECCS performance criteria by about 250°F for Surry Unit 1 and 250°F for Surry Unit 2.

Extensive sensitivity studies, submitted with previous calculations in connection with assessment of Westinghouse evaluation models, have established a relationship between the reactor total nuclear peaking factor (F_Q) and calculated peak clad temperature such that if F_Q is reduced by 0.25 for Surry Unit 1 and 0.23 for Unit 2 the calculated peak clad temperature for the Surry reactors would not exceed 2200° F.

As directed by the NRC staff, the Licensee agreed to operate the facility with the total nuclear peaking factor reduced by 0.25 to 1.85 for Surry Unit 1 and 0.23 to 1.87 for Surry Unit 2. However, subsequent to the licensee's submittal, further review of data presented by Westinghouse has led the staff to conclude that an additional reduction in F_Q over that presented by the licensee is warranted. This is based on the fact that the Westinghouse generic evaluation for plants with three reactor coolant loops, used the results from two different, but approved, ECCS models (the March 1975 and October 1975 models). When consistent ECCS models are used the calculated peak clad temperature could increase by an additional 50° F.

After discussions with the NRC staff, on August 24 and 25, 1976, the licensee amended his previous submission to account for this additional increase in peak clad temperature, by reducing F_Q to 1.80 for Surry Unit 1 and 1.82 for Surry Unit 2. The NRC staff believes that the licensee's actions, under the circumstances, are appropriate and should be confirmed by NRC Order.

The staff expects that, when revised calculations for the facility are submitted using an approved evaluation model with correct input for upper head water temperature, or assuming that the upper head water temperature equals reactor vessel outlet water temperature, such calculations will demonstrate that op-

eration with this total nuclear peaking factor would conform with the criteria of 10 CFR § 50.46(b). Such revised calculations fully conforming to the requirements of 10 CFR §50.46 are to be provided for the facility as soon as possible. The additional limitations set forth in this Order will provide reasonable assurance that the public health and safety will not be endangered.

Copies of the following documents are available for public inspection in the Commission's Public Document Room, 1717 H Street, N.W., Washington, D.C., 20555 and at the Swem Library, College of William and Mary, Williamsburg, Virginia, (1) Licensee's Appendix K Analyses submitted April 15, 1975, as supplemented May 1, May 20, June 6, June 9 and June 11, 1975, (2) ECCS Approval by License Amendment No. 7 dated June 16, 1975, (3) Letter from Licensee dated August 18, 1976, (4) Letter from Licensee dated August 26, 1976, and (5) This Order for Modification of License, In the Matter of Virginia Electric and Power Company, Surry Power Station Units 1 and 2, Dockets Nos. 50–280 and 50–281.

III. Accordingly, pursuant to the Atomic Energy Act of 1954, as amended, and the Commission's Rules and Regulations in 10 CFR Parts 2 and 50, it is ordered that Facility Operating Licenses Nos. DPR–32 and DPR–37 are hereby amended by adding the following new provisions:

1. As soon as possible, the Licensee shall submit a reevaluation of ECCS cooling performance calculated in accordance with an approved Westinghouse Evaluation Model, with appropriate correction for upper head water temperature.

2. Until further authorization by the Commission, the Technical Specification limit for total nuclear peaking factor (F_Q) shall be reduced to 1.80 for Surry Unit 1 and 1.82 for Surry Unit 2.

Dated in Bethesda, Maryland this 27th day of August 1976.

For the Nuclear Regulatory Commission.

BEN C. RUSCHE,
Director, Office of Nuclear Reactor Regulation.

[FR Doc.76–26160 Filed 9–8–76;8:45 am]

[Docket No. 50–266]

WISCONSIN ELECTRIC POWER CO. AND WISCONSIN MICHIGAN POWER CO.

Proposed Issuance of Amendment to Facility Operating License

The Nuclear Regulatory Commission (the Commission) is considering the issuance of an amendment to Facility Operating License No. DPR–24 issued to Wisconsin Electric Power Company and Wisconsin Michigan Power Company (the licensees), for operation of the Point Beach Nuclear Plant, Unit No. 1, located in the Town of Two Creeks, Manitowoc County, Wisconsin.

The amendment would revise the Technical Specifications to eliminate the fuel residence time limit and alter the core power distribution limits to allow operation of Point Beach Unit No. 1 in core Cycle 5.

Prior to issuance of the proposed license amendment, the Commission will have made the findings required by the Atomic Energy Act of 1954, as amended (the Act) and the Commission's rules and regulations.

By October 12, 1976 the licensees may file a request for a hearing and any person whose interest may be affected by this proceeding may file a request for a hearing in the form of a petition for leave to intervene with respect to the issuance of the amendment to the subject facility operating license. Petitions for leave to intervene must be filed under oath or affirmation in accordance with the provisions of Section 2.714 of 10 CFR Part 2 of the Commission's regulations. A petition for leave to intrevene must set forth the interest of the petitioner in the proceeding, how that interest may be affected by the results of the proceeding, and the petitioner's contentions with respect to the proposed licensing action. Such petitions must be filed in accordance with the provisions of this FEDERAL REGISTER notice and Section 2.714, and must be filed with the Secretary of the Commission, U.S. Nuclear Regulatory Commission, Washington, D.C. 20555, Attention: Docketing and Service Section, by the above date. A copy of the petition and/or request for a hearing should be sent to the Executive Legal Director, U.S. Nuclear Regulatory Commission, Washington, D.C. 20555, and to Mr. Bruce W. Churchill, Esq., Shaw, Pittman, Potts & Trowbridge, 1800 M Street, N.W., Washington, D.C. 20036, the attorney for the licensees.

A petition for leave to intervene must be accompanied by a supporting affidavit which identifies the specific aspect or aspects of the proceeding as to which intervention is desired and specifies with particularity the facts on which the petitioner relies as to both his interest and his contentions with regard to each aspect on which intervention is requested. Petitions stating contentions relating only to matters outside the Commission's jurisdiction will be denied.

All petitions will be acted upon by the Commission or licensing board, designated by the Commission or by the Chairman of the Atomic Safety and Licensing Board Panel. Timely petitions will be considered to determine whether a hearing should be noticed or another appropriate order issued regarding the disposition of the petitions.

In the event that a hearing is held and a person is permitted to intervene, he becomes a party to the proceeding and has a right to participate fully in the conduct of the hearing. For example, he may present evidence and examine and cross-examine witnesses.

For further details with respect to this action, see the application for amendment dated July 30, 1976, which is available for public inspection at the Commission's Public Document Room, 1717 H Street, N.W., Washington, D.C. and at the University of Wisconsin—Stevens Point Library, Stevens Point, Wisconsin 54481. The license amendment and the Safety Evaluation, when issued, may be inspected at the above locations and a copy may be obtained upon request addressed to the U.S. Nuclear Regulatory Commission, Washington, D.C. 20555, Attention: Director, Division of Operating Reactors.

Dated at Bethesda, Maryland, this 1st day of September 1976.

For the Nuclear Regulatory Commission.

GEORGE LEAR,
Chief, Operating Reactors Branch No. 3, Division of Operating Reactors.

[FR Doc.76–26147 Filed 9–8–76;8:45 am]

[Docket Nos. 50–266 50–301]

WISCONSIN ELECTRIC POWER CO. AND WISCONSIN MICHIGAN POWER CO. POINT BEACH NUCLEAR PLANT UNITS NOS. 1 AND 2

Order for Modification of License

I. The Wisconsin Electric Power Company and Wisconsin Michigan Power Company (the Licensees), are the holders of Facility Operating Licenses Nos. DPR–24 and DPR–27 which authorize the operation of two nuclear power reactors known as Point Beach Nuclear Plant, Units Nos. 1 and 2, respectively, (the facility) at steady state reactor power levels not in excess of 1518 thermal megawatts (rated power). The facility consists of two pressurized water reactor (PWR) located at the Licensee's site near Two Creeks, Manitowoc County, Wisconsin.

II. In conformance with evaluations of the performance of the Emergency Core Cooling System (ECCS) of the facility submitted by the Licensee on September 6, 1974, June 24, and October 6, 1975 and supplements dated December 6, 1974, May 7, November 5 and 26 and December 15 and 18, 1975, the Technical Specifications issued December 24, 1975 for the facility limit the reactor total nuclear peaking factor (F_Q) to 2.32. The ECCS performance evaluation submitted by the Licensee was based upon a previously approved ECCS evaluation model developed by the Westinghouse Electric Corporation (Westinghouse), the designer of the facility, to conform with the requirements of the Commission's ECCS Acceptance Criteria, 10 CFR Part 50, § 50.46 and Appendix K. The evaluation indicated that with a total nuclear peaking factor limited as set forth above, and with the other limits set forth in the facility's Technical Specifications, the ECCS cooling performance for the facility would conform with the criteria contained in 10 CFR § 50.46(b) which govern calculated peak clad temperature, maximum cladding ovidation, maximum hydrogen generation, coolable geometry and long term cooling.

Due to the configuration of the Westinghouse reactor vessel design, a small portion of reactor inlet water which is cooler than outlet water is directed through several nozzles located on the periphery of the vessel to cool the upper portion of the vessel head. Accordingly, upper head temperatures used in evaluating ECCS performance were assumed to be equal to the reactor inlet water temperature. However, recent operating data gathered at the Connecticut Yankee facility has indicated that, contrary to this expectation, the temperature of the water in the upper head is higher than the reactor inlet water temperature, by about 60% of the difference betwen reactor inlet and reactor outlet temperature. This higher upper head water temperature would have the effect of increasing the calculated peak clad temperature in the event of a loss of coolant accident.

In a meeting with the staff on August 9, 1976, Westinghouse presented generic evaluations of the effect on calculated peak clad temperature for the worst break identified in previous calculations for each type of Westinghouse reactor and fuel design using an upper head water temperature exceeding reactor inlet water temperature by an amount equal to 75% of the reactor inlet-reactor outlet differential. On August 12, 1976, the staff instructed the licensee to submit an analysis similar to the Westinghouse evaluation with the clearly conservative assumption of upper head water temperature equal to reactor outlet temperature (100% of the reactor outlet-reactor inlet differential) and to operate the facility in accordance with the results of this analysis. The results of the evaluation submitted for the Point Beach reactors indicated that with this modification of the upper head water temperature the calculated peak clad temperature for the worst case break would not exceed the Commission's ECCS performance criteria.

The staff expects that, when revised calculations for the facility are submitted using an approved evaluation model with correct input for upper head water temperature, or assuming that the upper head water temperature equal reactor vessel outlet water temperature, such calculations will demonstrate that operation with this total nuclear peaking factor would conform to the criteria of 10 CFR § 50.46(b). Such revised calculations fully conforming to the requirements of 10 CFR § 50.46 are to be provided for the facility as soon as possible. The limitations presently incorporated in the Technical Specifications for the facility continued to provide reasonable assurance that the public health and safety will not be endangered.

Copies of the following documents are available for public inspection in the Commission's Public Document Room, 1717 H Street N.W., Washington, D.C. 20555 and at the University of Wisconsin—Stevens Point Library, Stevens Point, Wisconsin: (1) the applications for amendment dated September 6, 1974, June 24 and October 6, 1975, and supplements dated December 6, 1974, May 7, November 5 and 26, and December 15 and 18, 1975, (2) Amendments Nos. 14 and 18 to License Nos. DPR–24 and DPR–27, (3) Licensees letter dated August 18, 1976, and (4) This Order for Modification of License, In the Matter of Wisconsin Electric Power Company and Wisconsin Michigan Power Company, Point Beach Nuclear Plant, Units Nos. 1 and 2, Docket Nos. 50–266 and 50–301.

III. Accordingly, pursuant to the Atomic Energy Act of 1954, as amended, and the Commission's Rules and Regulations in 10 CFR Parts 2 and 50, it is ordered that Facility Operating License Nos. DPR–24 and DPR–27 are hereby amended by adding the following new provision:

1. As soon as possible, the Licensee shall submit a re-evaluation of ECCS cooling performance calculated in accordance with an approved Westinghouse Evaluation Model, with appropriate correction for upper head water temperature.

Dated in Bethesda, Maryland this 27th day of August 1976.

For the Nuclear Regulatory Commission.

BEN C. RUSCHE,
Director, Office of
Nuclear Reactor Regulation.

[FR Doc.76-26157 Filed 9-8-76;8:45 am]

[Docket No. 50-305]

WISCONSIN PUBLIC SERVICE CORP. KEWAUNEE NUCLEAR POWER PLANT

Order for Modification of License

I. The Wisconsin Public Service Corporation (the licensee), is the holder of Facility Operating License No. DPR–43 which authorized the operation of a nuclear power reactor known as the Kewaunee Nuclear Power Plant (the facility) at steady state reactor power levels not in excess of 1650 thermal megawatts (rated power). The facility is a pressurized water reactor (PWR) located at the licensee's site in Kewaunee County, Wisconsin.

II. In conformance with evaluations of the performance of the Emergency Core Cooling System (ECCS) of the facility submitted by the Licensee on September 4, 1974, as supplemented December 2, 1974; December 23, 1974; April 1, 1975; April 18, 1975; April 22, 1975; July 8, 1975; January 22, 1976; February 10, 1976; and February 20, 1976, the Technical Specifications issued March 22, 1976 for the facility limit the reactor total nuclear peaking factor (F_Q) to 2.15. The ECCS performance evaluation submitted by the Licensee was based upon a previously approved ECCS evaluation model developed by the Westinghouse Electric Corporation (Westinghouse), the designer of the facility, to conform with the requirements of the Commission's ECCS Acceptance Criteria, 10 CFR Part 50, § 50.46 and Appendix K. The evaluation indicated that with a total nuclear peaking factor limited as set forth above, and with the other limits set forth in the facility's Technical Specifications, the ECCS cooling performance for the facility would conform with the criteria contained in 10 CFR § 5046(b) which govern calculated peak clad temperature, maximum cladding oxidation, maximum hydrogen generation, coolable geometry and long term cooling.

Due to the configuration of the Westinghouse reactor vessel design, a small portion of reactor inlet water which is cooler than outlet water is directed through several nozzles located on the periphery of the vessel to cool the upper portion of the vessel head. Accordingly, upper head temperatures used in evaluating ECCS performance were assumed to be equal to the reactor inlet water temperature. However, recent operating data gathered at the Connecticut Yankee facility has indicated that, contrary to this expectation, the temperature of the water in the upper head is higher than the reactor inlet water temperature, by about 60% of the difference between reactor inlet and reactor outlet temperature. This increase in upper head water temperature over that used in ECCS performance calculations would have the effect of increasing the calculated peak clad temperature in the event of a loss of coolant accident.

In a meeting with the staff on August 9, 1976, Westinghouse presented generic evaluations of the effect on calculated peak clad temperature for the worst break identified in previous calculations for each type of Westinghouse reactor and fuel design using an upper head water temperature exceeding reactor inlet water temperature by an amount equal to 75% of the reactor inlet-reactor outlet differential. On August 12, 1976, the staff directed the licensee to submit an analysis similar to the Westinghouse evaluation with the clearly conservative assumption of upper head water temperature equal to rector outlet temperature (100% of the reactor inlet-reactor outlet differential) and to operate the facility in accordance with the results of this analysis. The results of the evaluation submitted for the Kewaunee reactor indicated that with this modification of the upper head water temperature the calculated peak clad-temperature for the worst case break would exceed the Commission's ECCS performance criteria by about 400 F.

Extensive sensitivity studies, provided with previous calculations submitted in connection with assessment of Westinghouse evaluation models, have established a relationship between the reactor total nuclear peaking factor (F_Q) and calculated peak clad temperature such that if F_Q is reduced to 0.04, the calculated peak clad temperature for the Kewaunee reactor would not exceed 2200° F.

As directed by the NRC staff, the Licensee agreed to operate the facility with the total nuclear peaking factor reduced by 0.04 to 2.11. The staff believes that the Licensee's action, under the circum-

stances, is appropriate and that this action should be confirmed by NRC Order.

The staff expects that, when revised calculations for the facility are submitted using an approved evaluation model with correct input for upper head water temperature, or assuming that the upper head water temperature equals reactor vessel outlet water temperature, such calculations will demonstrate that operation with the total nuclear peaking factor would conform to the criteria of 10 CFR § 50.46(b). Such revised calculations fully conforming to the requirements of 10 CFR § 50.46 are to be provided for the facility as soon as possible. The additional limitations set forth in this Order will provide reasonable assurance that the public health and safety will not be endangered.

Copies of the following documents are available for public inspection in the Commission's Public Document Room, 1717 H Street, N.W., Washington, D.C., 20555 and at the Kewaunee Public Library, 314 Milwaukee Street, Kewaunee, Wisconsin, 54216, (1) Wisconsin Public Service Corporation letters dated September 4, 1974, as supplemented December 2, 1974; December 23, 1976; April 1, 1975; April 18, 1975; April 22, 1975; July 8, 1975; January 22, 1976; February 10, 1976; and February 20, 1976, (2) NRC letter dated March 22, 1976, (3) Wisconsin Public Service Corporation letter dated August 18, 1976, and (4) This Order for Modification of License, In the Matter of the Kewaunee Nuclear Power Plant, Docket No. 50-305.

III. Accordingly, pursuant to the Atomic Energy Act of 1954, as amended, and the Commission's Rules and Regulations in 10 CFR Parts 2 and 50, *It is ordered*, That Facility Operating License No. DPR-43 is hereby amended by adding the following new provisions:

1. As soon as possible, the Licensee shall submit a re-evaluation of ECCS cooling performance calculated in accordance with an approved Westinghouse Evaluation Model, with appropriate correction for upper head water temperature.

2. Until further authorization by the Commission, the Technical Specification limit for total nuclear peaking factor (F_Q) shall be reduced to 2.11.

Dated in Bethesda, Maryland this August 27, 1976.

For the Nuclear Regulatory Commission.

BEN C. RUSCHE,
Director, Office of Nuclear Reactor Regulation.

[FR Doc. 76-26152 Filed 9-8-76; 8:45 am]

[Docket No. 50-29]

YANKEE ATOMIC ELECTRIC CO.; YANKEE NUCLEAR POWER STATION (YANKEE-ROWE)

Order for Modification of License

I. Yankee Atomic Electric Company, is the holder of Facility Operating License No. DPR-3 which authorizes the operation of a nuclear power reactor known as Yankee Nuclear Power Station [Yankee-Rowe] (the facility) at steady state reactor power levels not in excess of 600 thermal megawatts (rated power). The facility is a pressurized water reactor (PWR) located at the Licensee's site in Rowe, Franklin County, Massachusetts.

II. In conformance with evaluations of the performance of the Emergency Core Cooling System (ECCS) of the facility submitted by the Licensee on February 20, 1976, the Technical Specifications issued on June 2, 1976 (Amendment No. 26), for the facility limit the allowable peak linear heat generation rate (LHGR) as set forth in Figure 8-1 of the Technical Specifications. The ECCS performance evaluation submitted by the Licensee was based upon a previously approved ECCS evaluation model developed by Exxon Nuclear Corporation (Exxon), the nuclear fuel vendor, to conform to the requirements of the Commission's ECCS Acceptance Criteria, 10 CFR Part 50, § 50.46 and Appendix K. The evaluation indicated that with the peak LHGR limited as set forth above, and with the other limits set forth in the facility's Technical Specifications, the ECCS cooling performance for the facility would conform to the criteria contained in 10 CFR § 50.46(b) which govern calculated peak clad temperature, maximum cladding oxidation, maximum hydrogen generation, coolable geometry and long term cooling.

Due to the configuration of the reactor vessel design, a small portion of relatively cooler reactor inlet water is directed through a bypass gap in the inlet nozzles to cool the upper portion of the head. Accordingly, upper head temperatures were assumed in evaluating ECCS performance to be equal to the reactor inlet water temperature. However, recent operating data gathered at the Connecticut Yankee facility has indicated that, contrary to this expectation, the temperature of the water in the uppear head is warmer than the reactor inlet water temperature, by about some 60% of the reactor inlet-reactor outlet temperature differential. This increase in upper head water temperature over that used in ECCS performance calculations would have the effect of increasing the calculated peak clad temperature. This higher upper head water temperature would have the effect of increasing the calculated peak clad temperature in the event of a loss of coolant accident.

In a meeting wiith the staff on August 9, 1976, Westinghouse, the reactor designer, presented generic evaluations of the effect on calculated peak clad temperature for the worst break identified in previous calculations for several types of Westinghouse reaction designs using an upper head water temperature exceeding reactor inlet water temperature by an amount equal to 75% of the reactor inlet-reactor outlet differential. On August 12, 1976, the staff directed the licensee to submit an analysis with the clearly conservative assumption of upper head water temperature equal to reactor outlet temperature (100% of the reactor inlet-reactor outlet differential) and to operate the facility in accordance with the results of this analysis. The results of the evaluation submitted for the Yankee-Rowe reactor indicated that with this modification of the upper head water temperature the calculated peak clad temperature for the previously established worst case break would not exceed the Commission's ECCS performance criteria if the peak LHGR were reduced by 0.35 Kw/ft. This evaluation was performed using the approved Exxon ECCS evaluation model. However, since a revised evaluation for the entire break spectrum for the facility using such an approved evaluation model with the properly corrected upper head temperature cannot be completed for some time, the staff believes that it is prudent to impose an interim penalty on allowable peak LHGR to account for uncertainties that may exist. The staff concludes that a further limitation on peak LHGR, in addition to that originally proposed by the Licensee will eliminate uncertainties resulting from the preliminary calculations thus far performed, and will assure that ECCSS performance at the facility will conform to all the criteria set forth in 10 CFR § 50.46(b).

After discussions with the NRC staff on August 26, 1976, the licensee amended his previous submission, to account for these uncertainties, by reducing the peak LHGR by another 0.5 kw/ft for a total reduction of 0.85 kw/ft. The NRC staff believes that the licensee's actions, under the circumstances, are appropriate and should be confirmed by NRC Order.

The staff expects that, when revised calculations for the facility are submitted using an approved evaluation model with correct input for upper head water temperature, or assuming that the upper head water temperature equals reactor vessel outlet water temperature, such calculations will demonstrate that operation at the reduced peak LHGR would conform to the criteria of 10 CFR § 50.46(b). Such revised calculations fully conforming to the requirements of 10 CFR § 50.46 are to be provided for the facility as soon as possible. The additional limitations set forth in this Order will provide reasonable assurance that the public health and safety will not be endangered.

Copies of the following documents are available for public inspection in the Commission's Public Document Room, 1717 H Street, NW., Washington, D.C. 20555 and are being placed in the Commission's Local Public Document Room, Greenfield Public Library, 402 Main Street, Greenfield, Massachusetts 01581, (1) Licensee letter dated February 20, 1976, (2) NRC letter dated June 2, 1976, and (3) This Order for Modification of License, In the Matter of Yankee Nuclear Power Station (Yankee-Rowe), Docket No. 50-29.

III. Accordingly, pursuant to the Atomic Energy Act of 1954, as amended, and the Commission's Rules and Regulations in 10 CFR Parts 2 and 50, IT IS ORDERED THAT Facility Operating License No. DPR-3 is hereby amended by adding the following new provisions:

1. As soon as possible, the Licensee shall

submit a re-evaluation of ECCS cooling performance calculated in accordance with an approved ECCS Evaluation Model, with appropriate correction for upper head water temperature.

2. Until further authorization by the Commission, the Technical Specification limit for allowable peak LHGR (Table 3-1 in the Technical Specifications) shall be reduced by 0.85 Kw/ft.

Dated in Bethesda, Maryland this August 27, 1976.

For the Nuclear Regulatory Commission.

BEN C. RUSCHE,
Director, Office of Nuclear Reactor Regulation.

[FR Doc.76-26149 Filed 9-8-76;8:45 am]

OFFICE OF MANAGEMENT AND BUDGET

CLEARANCE OF REPORTS

List of Requests

The following is a list of requests for clearance of reports intended for use in collecting information from the public received by the Office of Management and Budget on September 3, 1976 (44 USC 3509). The purpose of publishing this list in the FEDERAL REGISTER is to inform the public.

The list includes the title of each request received; the name of the agency sponsoring the proposed collection of information; the agency form number(s), if applicable; the frequency with which the information is proposed to be collected; the name of the reviewer or reviewing division within OMB, and an indication of who will be the respondents to the proposed collection.

Requests for extension which appear to raise no significant issues are to be approved after brief notice through this release.

Further information about the items on this daily list may be obtained from the Clearance Office, Office of Management and Budget, Washington, D.C. 20503, (202-395-4529), or from the reviewer listed.

NEW FORMS

ENERGY RESEARCH AND DEVELOPMENT ADMINISTRATION

Unit Operation Equipment Survey, single-time, Warren Topelius, 395-5872.

ACTION

Action Cost-Sharing Study Project Survey Instruments, single-time, project directors, staff, advisory council in action Project Housing, Veterans and Labor Division, Raynsford, R., 395-3532.

DEPARTMENT OF AGRICULTURE

Extension Service, Vermont woodland owner study, single-time, woodland owners, Lowry, R. L., 395-3772.

DEPARTMENT OF COMMERCE

Domestic and International Business Administration, Evaluation of DIBA Business Assistance Programs, DIB-2007P, single-time, users of DIBA services, Peterson, M. O., 395-5631.

Bureau of Census:

Reinterview Questionnaire and Reconciliation Record, AHS-1976 national sample panels 2 and 6, AHS-394, annually, households in 461 PSU design, Sunderhauf, M. B., 395-6140.

National Longitudinal Surveys, Survey of Work Experience of Young Women—1977 Questionnaire and Advance Letter, GT-471 and 47, annually, women between the ages of 14-24 in 1967, Strasser, A., 395-5867.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Office of the Secretary, Project Developmental Continuity Survey Forms, (1) Teacher Survey, (2) Parent Survey, (3) Child Rating Scale; semi-annually, experimental and comparison teachers, parents, Human Resources Division, Raynsford, R., 395-3532.

Office of Education, National Evaluation of Title I Programs for Neglected and Delinquent Children in State Institutions, OE-518, single-time, state title I coordinator, teacher, students, Human Resources Division, Raynsford, R., 395-3532.

Public Health Service, Survey of Attitudes Toward Advances in Biomedical and Behavioral Research and Technology, OASH 0105, single-time, 1600 households, national cross-section, George Hall, 395-6140.

Office of the Secretary, Evaluation of the Child and Family Resource Program, semi-annually, parents, teachers, program staff children, Human Resources Division, Reese, B. F., 395-3532.

Public Health Service, 1977-78 National Inventory of Optometrists, single-time, licensed optometrist, Richard Eisinger, Lowry, R. L. 395-6140.

DEPARTMENT OF LABOR

Employment and Training Administration, Job Corpsmember Participation in the 1976 Upward Bound Program, MA-18, single-time, all Job Corps centers, Human Resources Division, C. Louis Kincannon, 395-3532.

DEPARTMENT OF THE INTERIOR

Departmental and Other, Claim for Relocation Payments Under P.L. 91-646, on occasion, displaced persons applying for relocation benefits, Warren Topelius, 395-5872.

REVISIONS

VETERANS ADMINISTRATION

Obtaining Supplemental Information from Doctor or Hospital, FL29-551B, on occasion, doctor or hospital official, Warren Topelius, 395-5872.

DEPARTMENT OF COMMERCE

Economic Development Administration, Marketing and Capacity Information Reports, ED 220, annually, comercial and industrial firms, Marsha Traynham, 395-4529.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Office of Education:

Application for Federal Assistance (Nonconstruction Programs): Instructions for Parts B and C, Title IV, Public Law 92-318, OE 267, on occasion, Indian tribes, organization, education, agencies, Lowry, R. L., 395-3772.

Application for Federal Assistance—Title IV, Civil Rights Act, OE 296, annually, LEA's, SEA's, institutions of higher education, Lowry, R. L., 395-3772.

Social and Rehabilitation Service:

Annual Statistical Report on Hearings, SR SNCSS105, semiannually, State public assistance agencies, Sunderhauf, M. B., 395-6140.

Office of Education:

Application for Federal assistance (Nonconstruction): Instructions for Part A, Title IV, Public Law 92-318, OE 444, annually, LEA's, Lowry, R. L., 395-3772.

DEPARTMENT OF LABOR

Employment Standards Administration:

Application for a Farm Labor Contractor Certificate of Registration, WH-410, annually, agricultural workers, Warren Topelius, 395-5872.

EXTENSIONS

U.S. CIVIL SERVICE COMMISSION

Description of Significant Experience, CSC 1201, on occasion, households in any geographic area in United States, Marsha Traynham, 395-4529.

List of College Courses, CSC 1202, on occasion, households in any geographic area in United States, Marsha Traynham, 395-4529.

DEPARTMENT OF COMMERCE

Economic Development Administration:

Borrower's Request for Equity Credit, ED 266, on occasion, business entities expanding or building new facilities, Warren Topelius, 395-5872.

Status of Payments on Project Accounts, ED 268, on occasion, business entities constructing new or expanded facilities, Warren Topelius, 395-5872.

Business Loan Project Inspection and Certification of Acceptability, ED 269, on occasion, business firms expanding or building new facilities, Warren Topelius, 395-5872.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Social and Rehabilitation Service:

Annual Statistical Report on Cost Standards and Maximum and Other Limitations on Money Payments, SRS NCSS 1, annually, State public assistance agencies, Sunderhauf, M. B., 395-6140.

Office of Education:

Application for Federal Assistance (Nonconstruction Programs) Instructions for Community Education, OE 453 annually, LEA's, SEA's, IHE's, Marsha Traynham, 395-4529.

Social and Rehabilitation Service:

Administrative and Legal Actions on Questions of Suspected Fraud Under Medical Assistance Programs, SRS NCSS 1, quarterly, State medicaid (title XIX) agencies, Human Resources Division, Warren Topelius, 395-3532.

PHILLIP D. LARSEN,
Budget and Management Officer.

[FR Doc.76-26517 Filed 9-7-76;3:01 pm]

SECURITIES AND EXCHANGE COMMISSION

SMITH, BARNEY EQUITY FUND, INC. AND SMITH, BARNEY INCOME AND GROWTH FUND, INC., 1345 AVENUE OF THE AMERICAS, NEW YORK, NEW YORK 10019

[Rel. No. 9418 (812-3960)]

Notice of Filing of Application Pursuant to Section 6(c) of the Act for an Order Exempting Certain Transactions From Section 22(d) of the Act

AUGUST 26, 1976.

Notice is hereby given that Smith, Barney Equity Fund, Inc. ("Equity") and

Smith, Barney Income and Growth Fund, Inc. ("Income and Growth"), both Maryland corporations registered under the Act as open-end diversified management companies (collectively "Funds" or "Applicants"), filed an application on May 28, 1976, and amendments thereto on July 30 and August 24, 1976, pursuant to Section 6(c) of the Investment Company Act of 1940 ("Act") for an order of exemption from Section 22(d) of the Act to the extent necessary to permit the Funds to implement a schedule of sales charges which would not apply to certain classes of persons. All interested persons are referred to the application on file with the Commission for a statement of the representations therein which are summarized below.

Equity has operated since its inception, and Income and Growth since May 1, 1971, as no-load funds offering shares at net asset value without any sales charge being paid by purchasers of shares. Smith, Barney, Harris Upham & Co. Incorporated (Smith Barney), and its predecessor Smith, Barney & Co. Incorporated, have acted as distributors of the Funds' shares and Smith, Barney Advisers, Inc., a wholly-owned subsidiary of Smith Barney, acts as manager to both Funds. Smith, Barney Advisers, Inc. has sub-advisory agreements with Smith Barney.

It is proposed that, in the future, sales charges will be imposed on sales of the Funds' shares. However, all shareholders of record as of a cut-off date (to be determined) would have the right to make additional investments at net asset value at any time without the imposition of any sales charge. Persons who were not shareholders prior to the cut-off date would be subject to sales charges. However, after such a person shall have been a shareholder continuously for 24 months, he may make additional investments at net asset value without any sales charge, provided he is a shareholder at the time of purchase.

Section 22(d) of the Act provides that registered investment companies issuing redeemable securities may sell their shares only at a current offering price described in the prospectus. Section 6(c) provides, in part, that the Commission may conditionally or unconditionally exempt any person, security, or transaction, or any class or classes of persons, securities, or transactions, from any provision of the Act, if and to the extent that such exemption is necessary or appropriate in the public interest and consistent with the protection of investors and the purposes fairly intended by the policy and provisions of the Act.

The Funds have requested that the Commission issue an order pursuant to Section 6(c) of the Act for an exemption from the provisions of Section 22(d) of the Act with respect to (1) the sale of additional shares of the Funds without a sales charge to present shareholders of the Funds as of a record date to be set by the Boards of Directors of the Funds, and (2) the sale of additional shares of the Funds without a sales charge to shareholders who have become and remain shareholders for 24 consecutive months subsequent to such record date and who remain shareholders at the time of the purchase of such additional shares.

Applicants state that the distinction the proposed plan makes between existing shareholders and new shareholders is based on the difference in the cost of selling an additional share to a present shareholder and the cost of selling the first share to a non-shareholder. Applicants assert that no sales effort or explanation by salesmen is necessary for additional purchases by existing investors, and that, for new shareholders, shares purchased in the first 24 months will be available with a sales charge somewhat below that imposed by other funds with standard sales charges. With respect to group programs as permitted by Rule 22d-1 (a) and (b), which own shares prior to the cut-off date or which become and remain shareholders subsequent to the cut-off date for 24 consecutive months. Applicants contend that there is an absence of selling costs incurred in adding a new person to the persons for whose benefit such programs hold the shares, which justifies the non-imposition of a sales charge on purchases of shares for the benefit of a new person covered by such a program.

Applicants assert that the proposed plan has certain benefits for existing shareholders, new shareholders and the Funds themselves. For existing shareholders the "no-load" status of the Funds is preserved; new shareholders may invest at "no-load" after 24 months; and the Funds will have a broader and more effective sales effort to reverse a downtrend in sales and return to a positive cash flow. Finally, Applicants also contend that, by exempting the shareholder who has held shares for 24 months from future sales charges, interest by longer term holders is encouraged and continuing compensation to salesmen when their services are no longer required is eliminated.

Notice is further given that any interested person may, not later than September 20, 1976, at 5:30 p.m., submit to the Commission in writing a request for a hearing on the matter accompanied by a statement as to the nature of his interest, the reason for such request, and the issues, if any, of fact or law proposed to be controverted, or he may request that he be notified if the Commission should order a hearing thereon. Any such communication should be addressed: Secretary, Securities and Exchange Commission, Washington, D.C. 20549. A copy of such request shall be served personally or by mail upon Applicants at the address stated above. Proof of such service (by affidavit, or in the case of an attorney-at-law, by certificate) shall be filed contemporaneously with the request. As provided by Rule 0-5 of the Rules and Regulations promulgated under the Act, an order disposing of the application will be issued as of course following said date unless the Commission thereafter orders a hearing upon request or upon the Commission's own motion. Persons who request a hearing, or advice as to whether a hearing is ordered, will receive any notices and orders issued in this matter, including the date of the hearing (if ordered) and any postponements thereof.

By the Commission.

SHIRLEY E. HOLLIS,
Assistant Secretary.

[FR Doc.76-26318 Filed 9-8-76;8:45 am]

COMMISSION ON CIVIL RIGHTS

NORTH CAROLINA ADVISORY COMMITTEE

Agenda and Notice of Open Meeting

Notice is hereby given, pursuant to the provisions of the Rules and Regulations of the U.S. Commission on Civil Rights, that a planning meeting of the North Carolina Advisory Committee (SAC) to this Commission will convene at 6:00 pm. and end at 10:30 pm. on September 28, 1976, and reconvene at 9:30 am. and end at 6:00 pm. on September 29, 1976, at the Great Smokies Hilton, 1 Hilton Drive, Ashville, North Carolina 28806.

Persons wishing to attend this open meeting should contact the Committee Chairperson, or the Southern Regional Office of the Commission, Citizens Trust Bank Building, Room 362, 75 Piedmont Avenue, NE., Atlanta, Georgia 30303.

The purpose of this meeting is planning for the Migrant Project. Discussion of migrant study proposal. Reports from the jury selection and employment subcommittees.

This meeting will be conducted pursuant to the Rules and Regulations of the Commission.

Dated at Washington, D.C., September 8, 1976.

ISAIAH T. CRESWELL, Jr.,
Advisory Committee,
Management Officer.

[FR Doc.76-26659 Filed 9-8-76;12:02 pm]

VIRGINIA ADVISORY COMMITTEE

Agenda and Notice of Open Meeting

Notice is hereby given, pursuant to the provisions of the Rules and Regulations of the U.S. Commission on Civil Rights, that a press conference of the Virginia Advisory Committee (SAC) to this Commission will convene at 1:00 pm. and end at 2:00 pm. on September 30, 1976, at the U.S. Post Office Building, 101-25th Street, Newport News, Virginia 26307.

Persons wishing to attend this press conference should contact the Committee Chairperson, or the Mid-Atlantic Regional Office of the Commission, 2120 L Street, NW., Room 510, Washington, D.C. 20037.

The purpose of this conference is to release a report by the Advisory Committee on school desegregation progress in Newport News Public School Districts since 1971, which supplements a national report on school desegregation released by the Commission on August 24th.

This conference will be conducted pursuant to the Rules and Regulations of the Commission.

Dated at Washington, D.C., September 8, 1976.

ISAIAH T. CRESWELL, JR.,
Advisory Committee Management Officer.

[FR Doc.76-26659 Filed 9-8-76;12:02 pm]

INTERSTATE COMMERCE COMMISSION

[Notice No. 139]

ASSIGNMENT OF HEARINGS

SEPTEMBER 3, 1976.

Cases assigned for hearing, postponement, cancellation or oral argument appear below and will be published only once. This list contains prospective assignments only and does not include cases previously assigned hearing dates. The hearings will be on issues as presently reflected in the Official Docket of the Commission. An attempt will be made to publish notices of cancellation of hearings as promptly as possible, but interested parties should take appropriate steps to insure that they are notified of cancellation or postponements of hearings in which they are interested.

MC 136640 (Sub-No. 11), Robert L. Allen, DBA Allen Transport, now assiged October 13, 1976, at Boston, Mass. will be held on the Fifth Floor, 150 Causeway.

MC 141932 (Sub-No. 1), Polar Transport, Inc., now assigned October 14, 1976, at Boston, Mass. will be held on the Fifth Floor, 150 Causeway.

MC-F-12802, Terminal Transport Co., Inc.—Purchase—Goguen Transportation Co., Inc. and MC 22229 (Sub-No. 108), now assigned October 18, 1976, at Boston, Mass. will be held on the Fifth Floor, 150 Causeway.

H. G. HOMME, Jr.,
Acting Secretary.

[FR Doc.76-26396 Filed 9-8-76;8:45 am]

[Notice AB 6 (Sub-No. 33)]

BURLINGTON NORTHERN, INC.—ABANDONMENT BETWEEN—WAVERLY AND MOUNT HOPE IN SPOKANE COUNTY, WASHINGTON

AUGUST 27, 1976.

The Interstate Commerce Commission hereby gives notice that its Environmental Affairs Staff has concluded that the proposed abandonment by Burlington Northern Inc., of its railroad between Waverly and Mount Hope in Spokane County, Wash., a distance of 8.7 miles, if approved by the Commission, does not constitute a major Federal action significantly affecting the quality of the human environment within the meaning of the National Environmental Policy Act of 1969 (NEPA), 42 U.S.C. §§ 4321, et seq., and that preparation of a detailed environmental impact statement will not be required under section 4332(2)(C) of the NEPA.

It was concluded, among other things, that because of the small amount of traffic which would be diverted to motor carriers no significant environmental impacts will result from the abandonment of the line. The Washington Department of Game has identified the right-of-way as valuable wildlife habitat for several species and recommends that the corridor be preserved for wildlife and wildlife-oriented recreation. Inasmuch as there are no economic development plans in the area dependent upon the subject line, abandonment would not have a serious adverse effect on rural and community development.

This conclusion is contained in a staff-prepared environmental threshold assessment survey, which is available on request to the Interstate Commerce Commission, Office of Proceedings, Washington, D.C. 20423; telephone 202-275-7011.

Interested persons may comment on this matter by filing their statements in writing with the Interstate Commerce Commission, Washington, D.C., 20423, on or before October 8, 1976.

It should be emphasized that the environmental threshold assessment survey represents an evaluation of the environmental issues in the proceeding and does not purport to resolve the issue of whether the present or future public convenience and necessity permit discontinuance of the line proposed for abandonment. Consequently, comments on the environmental study should be limited to discussion of the presence or absence of environmental impacts and reasonable alternatives.

ROBERT L. OSWALD,
Secretary.

[FR Doc.76-26395 Filed 9-8-76;8:45 am]

[Notice AB 18 (Sub-No. 23)]

THE CHESAPEAKE AND OHIO RAILWAY COMPANY ABANDONMENT BETWEEN FOREST AND MCVEY IN RALEIGH COUNTY, WEST VIRGINIA

AUGUST 31, 1976.

The Interstate Commerce Commission hereby gives notice that its Environmental Affairs Staff has concluded that the proposed abandonment by the Chesapeake and Ohio Railway Company (C&O) of its line of railroad between Valuation Station 280+80.5 at or near Forest to the end of the line at Valuation Station 328+55, a distance of 0.90 miles, at or near McVey, all in Raleigh County, West Virginia, if approved by the Commission, does not constitute a major Federal action significantly affecting the quality of the human environment within the meaning of the National Environmental Policy Act of 1969 (NEPA), 42 U.S.C. §§ 4321, et seq., and that preparation of a detailed environmental impact statement will not be required under section 4332(2)(C) of the NEPA.

It was concluded, among other things, that the environmental impacts of the proposed action are considered insignificant because no traffic has been handled on the line since 1968, and, therefore, no diversion of traffic is expected. Consequently, no alterations in existing air quality, fuel consumption, or noise intrusions is expected. Also, no land use plans of an economic or industrial importance exist which are dependent upon the continued operation of the line. Although the major mineral commodity produced in the general area is coal, there is no demand for shipping along this portion of the line.

This conclusion is contained in a staff-prepared environmental threshold assessment survey, which is available on request to the Interstate Commerce Commission, Office of Proceedings, Washington, D.C. 20423; telephone 202-275-7011.

Interested persons may comment on this matter by filing their statements in writing with the Interstate Commerce Comimssion, Washington, D.C. 20423, on or before October 12, 1976.

It should be emphasized that the environmental threshold assessment survey represents an evaluation of the environmental issues in the proceeding and does not purport to resolve the issue of whether the present or future public convenience and necessity permit discontinuance of the line proposed for abandonment. Consequently, comments on the environmental study should be limited to discussion of the presence or absence of environmental impacts and reasonable alternatives.

H. G. HOMME, Jr.
Acting Secretary.

[FR Doc.76-26399 Filed 9-8-76;8:45 am]

[Notice AB 92]

THE SALT LAKE CITY UNION DEPOT AND RAILROAD COMPANY ABANDONMENT OPERATIONS SALT LAKE RAILROAD STATION, SALT LAKE CITY, UTAH

AUGUST 31, 1976.

The Interstate Commerce Commission hereby gives notice that its Environmental Affairs Staff has concluded that the proposed abandonment by the Salt Lake City Union Depot and Railroad Company of its passenger depot and track and terminal facilities in Salt Lake City, Utah, if approved by the Commission, does not constitute a major Federal action significantly affecting the quality of the human environment within the meaning of the National Environmental Policy Act of 1969 (NEPA), 42 U.S.C. §§ 4321, et seq., and that preparation of a detailed environmental impact statement will not be required under section 4332(2)(C) of the NEPA.

It was concluded, among other things, that service will continue to be provided on the line by the applicant's co-owners and, therefore, there will be no diversion of rail freight or passenger traffic. The Denver and Rio Grande Railroad Station is to be acquired for preservation purposes by the State of Utah. It is expected that the building will be adapted to another use, possibly as a museum. The historic and architectural characteristics of the building will not be altered.

This conclusion is contained in a staff-prepared environmental threshold assessment survey, which is available on request to the Interstate Commerce

Commission, Office of Proceedings, Washington, D.C. 20423; telephone 202–275–7011.

Interested persons may comment on this matter by filing their statements in writing with the Interstate Commerce Commission, Washington, D.C. 20423, on or before October 12, 1976.

It should be emphasized that the environmental threshold assessment survey represents an evaluation of the environmental issues in the proceeding and does not purport to resolve the issue of whether the present or future public convenience and necessity permit discontinuance of the line proposed for abandonment. Consequently, comments on the environmental study should be limited to discussion of the presence or absence of environmental impacts and reasonable alternatives.

H. G. HOMME, Jr.
Acting Secretary.

[FR Doc.76-26394 Filed 9-8-76;8:45 am]

[Notice AB 69 (Sub-No. 4)]

WESTERN MARYLAND RAILWAY COMPANY ABANDONMENT OF ITS FAIRMONT-BINGAMON BRANCH NEAR HENSHAW IN HARRISON COUNTY, WEST VIRGINIA

AUGUST 31, 1976.

The Interstate Commerce Commission hereby gives notice that its Environmental Affairs Staff has concluded that the proposed abandonment by the Western Maryland Railway Company (WM) of its line of railroad between Milepost 3.88 to the end of the line at Milepost 5.72, a distance of 1.84 miles, near Henshaw, all in Harrison County, West Virginia, if approved by the Commission, does not constitute a major Federal action significantly affecting the quality of the human environment within the meaning of the National Environmental Policy Act of 1969 (NEPA), 42 U.S.C. §§ 4321, et seq., and that preparation of a detailed environmental impact statement will not be required under section 4332(2)(C) of the NEPA.

It was concluded, among things, that the environmental impacts of the proposed action are considered insignificant because no traffic has been handled on the line since 1963, and, therefore, no diversion of traffic is expected. Consequently, there will be no alterations in existing air quality, fuel consumption, or noise intrusions. In addition, no land use plans of economic or industrial importance exist in the affected area which are dependent upon the continued operation of the line. Western Maryland Railway Company will continue to maintain rail service to Williams Mines, an active strip coal mining area located immediately south of the subject right-of-way. Interest has been expressed in acquiring the right-of-way for recreational use.

This conclusion is contained in a staff-prepared environmental threshold assessment survey, which is available on request to the Interstate Commerce Commission, Office of Proceedings, Washington, D.C. 20423; telephone 202–275–7011.

Interested persons may comment on this matter by filing their statements in writing with the Interstate Commerce Commission, Washington, D.C., 20423, on or before October 12, 1976.

It should be emphasized that the environmental threshold assessment survey represents an evaluation of the environmental issues in the proceeding and does not purport to resolve the issue of whether the present or future public convenience and necessity permit discontinuance of the line proposed for abandonment. Consequently, comments on the environmental study should be limited to discussion of the presence or absence of environmental impacts and reasonable alternatives.

H. G. HOMME, Jr.,
Acting Secretary.

[FR Doc.76-26398 Filed 9-8-76;8:45 am]

[Notice No. 24]

MOTOR CARRIER BOARD TRANSFER PROCEEDINGS

The following publications include motor carrier, water carrier, broker, and freight forwarder transfer applications filed under Section 212(b), 206(a), 211, 312(b), and 410(g) of the Interstate Commerce Act.

Each application (except as otherwise specifically noted) contains a statement by applicants that there will be no significant effect on the quality of the human environment resulting from approval of the application.

Protests against approval of the application, which may include a request for oral hearing, must be filed with the Commission within 30 days after the date of this publication. Failure seasonably to file a protest will be construed as a waiver of opposition and participation in the proceeding. A protest must be served upon applicant's representative(s), or applicants (if no such representative is named), and the protestant must certify that such service has been made.

Unless otherwise specified, the signed original and six copies of the protest shall be filed with the Commission. All protests must specify with particularity the factual basis and the section of the Act, or he applicable rule governing the proposed transfer which protestant believes would preclude approval of the application. If the protest contains a request for oral hearing, the request shall be supported by an explanation as to why the evidence sought to be presented cannot reasonably be submitted through the use of affidavits.

The operating rights set forth below are in synopses form, but are deemed sufficient to place interested persons on notice of the proposed transfer.

No. MC–FC–76651, filed August 27, 1976. Transferee: RAPID FREIGHT SYSTEMS, 1819 S. Soto St., Los Angeles, Calif. 90023. Transferor: Intercity Delivery Service, Inc., Internal Revenue Truck & Delivery Service, Inc., Internal Revenue Service, Successor-in-Interest, 16941 So. Reegan, Carson, Calif. 90746. Applicants' Representative: Donald Murchison, Attorney-at-Law, 9454 Wilshire Blvd., No. 400, Beverly Hills, Calif. 90212. Authority sought for purchase by transferee of the operating rights of transferor, as set forth in Certificate of Registration No. MC 99877 (Sub-No. 1), issued October 17, 1963, as follows: General commodities, between points within the Los Angeles Basin Territory, Calif. Transferee presently holds no authority from this Commission. Application has not been filed for temporary authority under Section 210a(b).

No. MC–FC–76710, filed August 19, 1976. Transferee: DAVID ALEXANDER CARSON, 1306 Speaker Drive, Auburndale, Florida 33823. Transferor: Glosson Motor Lines, Inc., P.O. Box 1328, Lexington, North Carolina 27292. Applicant's Attorney: John P. McMahon, 100 East Broad Street, Suite 1800, Columbus, Ohio 43215. Authority sought for purchase by transferee of a portion of the operating rights of transferor, as set forth in Certificate No. MC 41255 (Sub-No. 64), issued October 10, 1966, as follows: specified commodities, from, to and between specified points in Massachusetts, Florida, Georgia, Louisiana, North Carolina, South Carolina, Tennessee, Virginia, Alabama, Mississippi, New York, New Jersey, Virginia, Rhode Island, Delaware, Pennsylvania, Maryland, Connecticut, Maine, New Hampshire, Vermont, West Virginia and Washington, D.C. Transferee presently holds no authority from this Commission. Application has not been filed for temporary authority under Section 210a(b).

No. MC–FC–76711, filed August 19, 1976. Transferee: ERNEST L. SECCOMB, JR. AND ERNEST M. KINGSBURY, a partnership, doing business as Kitto's Transfer & Storage, 700 East Front Street, Butte, Montana 59701. Transferor: Ernest L. Seccomb and Ernest M. Kingsbury, a partnership, doing business as Kitto's Transfer & Storage, 700 East Front Street, Butte, Montana 59701. Applicants' representative: Ernest L. Seccomb, 700 East Front Street, Butte, Montana 59701. Authority sought for purchase by transferee of the operating rights of transferor, as set forth in Certificates No. MC 70176 and No. MC 70176 (Sub-No. 3), issued August 2, 1967 and February 16, 1971, respectively, as follows: Heavy machinery, between points in Silver Bow County, Mont., on the one hand, and, on the other, points in Montana within 100 miles of Butte, Mont., equipment, materials and supplies, used or useful in the control of forest fires, between Butte, Mont., and points within 250 miles of Butte, general commodities, between Butte, Mont., on the one hand, and, on the other, points in Silver Bow County, Mont., and general commodities, with certain exceptions, between points in Silver Bow County, Mont., other than Butte, Mont.; and used household goods,

between specified counties in Montana. Transferee presently holds no authority from this Commission. Application has not been filed for temporary authority under Section 210a(b).

H. G. HOMME, Jr.,
Acting Secretary.

[FR Doc.76-26392 Filed 9-8-76;8:45 am]

Office of Proceedings

[Notice No. 116]

MOTOR CARRIER TEMPORARY AUTHORITY APPLICATIONS

SEPTEMBER 2, 1976.

Important Notice: The following are notices of filing of applications for temporary authority under Section 210a(a) of the Interstate Commerce Act provided for under the provisions of 49 CFR 1131.3. These rules provide that an original and six (6) copies of protests to an application may be filed with the field official named in the FEDERAL REGISTER publication no later than the 15th calendar day after the date the notice of the filing of the application is published in the FEDERAL REGISTER. One copy of the protest must be served on the applicant, or its authorized representative, if any, and the protestant must certify that such service has been made. The protest must identify the operating authority upon which it is predicated, specifying the "MC" docket and "Sub" number and quoting the particular portion of authority upon which it relies. Also, the protestant shall specify the service it can and will provide and the amount and type of equipment it will make available for use in connection with the service contemplated by the TA application. The weight accorded a protest shall be governed by the completeness and pertinence of the protestant's information.

Except as otherwise specifically noted, each applicant states that there will be no significant effect on the quality of the human environment resulting from approval of its application.

A copy of the application is on file, and can be examined at the Office of the Secretary, Interstate Commerce Commission, Washington, D.C., and also in the ICC Field Office to which protests are to be transmitted.

MOTOR CARRIERS OF PROPERTY

No. MC 112963 (Sub-No. 62TA), filed August 25, 1976. Applicant: ROY BROS. INC., 764 Boston Road, Pinehurst, Mass. 01866. Applicant's representative: Leonard E. Murphy (same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Molten sulphur*, in bulk, in tank vehicles, from Bucksport, Maine, to Everett, Mass., for 180 days. Applicant has also filed an underlying ETA seeking up to 90 days of operating authority. Supporting shipper: Freeport Sulphur Company, P.O. Box 61520, New Orleans, La. 70161. Send protests to: D. W. Hammons, District Supervisor, Interstate Commerce Commission, 150 Causeway St., Room 501, Boston, Mass. 02114.

No. MC 113908 (Sub-No. 381TA), filed August 25, 1976. Applicant: ERICKSON TRANSPORT CORP., 2105 E. Dale St., P.O. Box 3180 G.S.S., Springfield, Mo. 65804. Applicant's representative: B. B. Whitehead (same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Fertilizer and deicer*, from Viroqua, Wis., to points in Arkansas, Colorado, Kentucky, Missouri, Montana, Oklahoma, Tennessee and Wyoming, for 180 days. Supporting shipper: Howard Johnson Enterprises, Railroad Ave., Viroqua, Wis. 54665. Send protests to: John V. Barry, District Supervisor, Interstate Commerce Commission, Bureau of Operations, 600 Federal Bldg., 911 Walnut St., Kansas City, Mo. 64106.

No. MC 114045 (Sub-No. 447TA), filed August 25, 1976. Applicant: TRANS-COLD EXPRESS, INC., P. O. Box 61228, D/FW Airport, Tex. 75261. Applicant's representative: J. B. Stuart (same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Food, food products and food ingredients* in mechanically refrigerated equipment (except in bulk), from the plant and warehouse facilities of Archer Daniels Midland Company, located in Decatur, Ill., to points in Arkansas, Louisiana, Texas, Oklahoma and New Mexico, for 180 days. Applicant has also filed an underlying ETA seeking up to 90 days of operating authority. Supporting shipper: Archer Daniels Midland Company, P. O. Box 1470, Decatur, Ill. 62525. Send protests to: Opal M. Jones, Transportation Assistant, Interstate Commerce Commission, 1100 Commerce St., Room 13C12, Dallas, Tex. 75242.

No. MC 110525 (Sub-No. 1164TA), filed August 26, 1976. Applicant: CHEMICAL LEAMAN TANK LINES, INC., 520 E. Lancaster Ave., P.O. Box 200, Downingtown, Pa. 19335. Applicant's representative: Thomas J. O'Brien (same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Liquid chemicals*, in bulk, in tank vehicles, from the plantsite of Nalco Chemical Co., at Sugarland, Tex., to points in Courtland and Decatur, Ala.; Miami, Ariz.; Armorel and El Dorado, Ark.; Dania and Pensacola, Fla.; Dry Branch and Jonesboro, Ga.; Muncie and Whiting, Ind.; Tyrone, N. Mex.; and Ahoskie and Kinston, N.C.; and to points in Illinois, Kansas, Louisiana, Mississippi, Missouri, Oklahoma, Kentucky and Wyoming, for 180 days. Supporting shipper: Nalco Chemical Company, 2901 Butterfield Road, Oak Brook, Ill. Send protests to: Monica A. Blodgett, Transportation Assistant, Interstate Commerce Commission, 600 Arch St., Room 3238, Philadelphia, Pa. 19106.

No. MC 110563 (Sub-No. 188TA), filed August 26, 1976. Applicant: COLDWAY FOOD EXPRESS, INC., P.O. Box 747, 113 N. Ohio Ave., Ohio Bldg., Sidney, Ohio 45365. Applicant's representative: John L. Maurer (same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Bread crumbs, or cubes, salad dressing preparations, dry and mixes, dips, dry*, (except in bulk or frozen), from the plantsite and storage facilities of The Clorox Company and/or of the Grocery Store Products Company, located in Kennett Square and West Chester, Pa., to points in Illinois, Indiana, Kentucky, Michigan, Missouri, Ohio and Wisconsin, for 180 days. Supporting shipper: The Clorox Company, 1221 Broadway, Oakland, Calif. 94612. Send protests to: Keith D. Warner, District Supervisor, Interstate Commerce Commission, Bureau of Operations, 313 Federal Office Bldg., 234 Summit St., Toledo, Ohio 43604.

No. MC 110563 (Sub-No. 189TA), filed August 27, 1976. Applicant: COLDWAY FOOD EXPRESS, INC., P.O. Box 747, 113 N. Ohio Ave., Ohio Bldg., Sidney, Ohio 45365. Applicant's representative: Victor J. Tambascia (same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Foodstuffs*, in vehicles equipped with mechanical refrigeration (except commodities in bulk, in tank vehicles), from the plantsite and/or warehouse facilities of Kraftco Corporation, at Champaign, Ill., to points in Maine, New Hampshire, Vermont, New York, Massachusetts, Rhode Island, Connecticut, Pennsylvania, New Jersey, Delaware, Virginia, Maryland, and the District of Columbia. Restriction: Restricted to the transportation of traffic originating at the origin point and destined to the named destination points, for 180 days. Applicant has also filed an underlying ETA seeking up to 90 days of operating authority. Supporting shipper: Kraftco Corporation, 500 Peshtigo Court, Chicago, Ill. 60690. Send protests to: Keith D. Warner, District Supervisor, Bureau of Operations, 313 Federal Office Bldg., 234 Summit St., Toledo, Ohio 43604.

No. MC 115904 (Sub-No. 58TA), filed August 23, 1976. Applicant: GROVER TRUCKING CO., 1710 West Broadway, Idaho Falls, Idaho. Applicant's representative: Irene Warr, 430 Judge Bldg., Salt Lake City, Utah 84111. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Mineral fiber, mineral fiber products and insultating materials*, from Pueblo, Colo., to points in Idaho, for 180 days. Supporting shipper: Intermountain Gas Company, P.O. Box 7608, Boise, Idaho 83707. Send protests to: Barney L. Hardin, District Supervisor, Interstate Commerce Commission, 550 West Fort, Box 07, Boise, Idaho 83724.

No. MC 123233 (Sub-No. 59TA), filed August 25, 1976. Applicant: PROVOST CARTAGE INC., 7887 Rue Grenache, Ville D'Anjou 437, P.Q. Canada HLJ 1C4. Applicant's representative: J. P. Vermette, 7887 2E Ave., Ville D'Anjou, P.Q.,

Canada. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Silica sand*, in bulk, in tank vehicles, from McConnellsville, N.Y., to the International Boundary Line between the United States and Canada, located near Alexandria Bay, N.Y., restricted to the transportation of traffic destined to points in the Province of Quebec, for 90 days. Applicant has also filed an underlying ETA seeking up to 90 days of operating authority. Support shipper: W. R. Cuthbert Ltd., 47 Duke St., Montreal, P.Q., Canada. Send protests to: David Demers, District Supervisor, 87 Stat St., P.O. Box 548, Montpelier, Vt. 05602.

No. MC 123255 (Sub-No. 78TA), filed August 26, 1976. Applicant: B & L MOTOR FREIGHT, INC., 140 Everett Ave., Newark, Ohio 43055. Applicant's representative: C. F. Schnee, Jr. (same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Glass containers*, from Cliffwood, N.J., to points in New York, for 180 days. Supporting shipper: Midland Glass Company, Inc., P.O. Box 557, Cliffwood, N.J. 07721. Send protests to: Frank L. Calvary, District Supervisor, Interstate Commerce Commission, 220 Federal Bldg., and U.S. Courthouse, 85 Marconi Blvd., Columbus, Ohio 43215.

No. MC 123255 (Sub-No. 79TA), filed August 26, 1976. Applicant: B & L MOTOR FREIGHT, INC., 140 Everett Ave., Newark, Ohio 43055. Applicant's representative: C. F. Schnee, Jr. (same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Container and container ends*, from the warehouse site of the National Can Corporation, at Sharonville, Ohio, to LaCrosse, Wis., and Evansville, Ind., for 180 days. Supporting shipper: National Can Corporation, 8101 West Higgins Road, Chicago, Ill. 60631. Send protests to: Frank L. Calvary, District Supervisor, Interstate Commerce Commission, 220 Federal Bldg., and U.S. Courthouse, 85 Marconi Blvd., Columbus, Ohio 43215.

No. MC 123255 (Sub-No. 80 TA), filed August 26, 1976. Applicant: B & L MOTOR FREIGHT, INC., 140 Everett Ave., Newark, Ohio 43055. Applicant's representative: C. F. Schnee, Jr. (same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Glass containers*, from Baltimore, Md.; Milford, Mass.; Cliffwood, N.J.; and Brockway, Clarion, Connellsville, Oil City, and Washington, Pa., to the Miller Brewing Company, at South Volney, N.Y., for 180 days. Supporting shipper: Miller Brewing Company, 4000 West State St., Milwaukee, Wis. 53208. Send protests to: Frank L. Calvary, District Supervisor, Interstate Commerce Commission, 220 Federal Bldg., and U.S. Courthouse, 85 Marconi Blvd., Columbus, Ohio 43215.

No. MC 128746 (Sub-No. 28 TA), filed August 10, 1976. Applicant: D'AGATA NATIONAL TRUCKING CO., 3224-44 South 61st St., Philadelphia, Pa. 19153. Applicant's representative: Edward J. Kiley, 1730 M St., NW, Suite 501, Washington, D.C. 20036. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Glass containers*, from the plantsite and storage facilities of Midland Glass Co., Inc., located at or near Cliffwood, N.J., to points in New York, for 180 days. Supporting shipper: Midland Glass Co., Inc., P.O. Box 557, Cliffood, N.J. 07721. Send protests to: Monica A. Blodgett, Transportation Assistant, Interstate Commerce Commission, 600 Arch St., Room 3238, Philadelphia, Pa. 19106.

No. MC 129624 (Sub-No. 7 TA), filed August 20, 1976. Applicant: ROUTE MESSENGERS OF PENNSYLVANIA, INC., 2425 Bambridge St., Philadelphia, Pa. 19146. Applicant's representative: Alan Kahn, 1920 Two Penn Center Plaza, Philadelphia, Pa. 19102. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Drugs, pharmaceuticals and health care products*, between the facilities of E. R. Squibb, Inc., in Somerset, Somerset County, N.J., on the one hand, and, on the other, points in Bucks, Chester, Delaware, Montgomery, and Philadelphia Counties, Pa., and New Castle County, Del., for 180 days. Supporting shipper: E. R. Squibb, Inc., 5 Georges Road, New Brunswick, N.J. 08902. Send protests to: Monica A. Blodgett, Transportation Assistant, Interstate Commerce Commission, 600 Arch St., Room 3238, Philadelphia, Pa. 19106.

No. MC 133796 (Sub-No. 36 TA), filed August 27, 1976. Applicant: GEORGE APPEL, 249 Carverton Road, Trucksville, Pa. 18708. Applicant's representative: John W. Frame, Box 626, 2207 Old Gettysburg Road, Camp Hill, Pa. 17011. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Hair curlers, shampoos, cream rinses, bobby pins, waterproof plastic capes, towels, brooms, nail files, scissors, notions and novelties* (except fireworks); *materials and supplies* used in the manufacture of the commodities described above; *and such merchandise* as is dealt in by variety stores (except commodities in bulk), originating at the plantsite of Wilson Manufacturing Corporation, and Hugh H. Wilson Company, at Sunbury, Pa., and destined to Carrollton, Tex., La Mirada and South San Francisco, Calif., for 180 days. Applicant has also filed an underlying ETA seeking up to 90 days of operating authority. Supporting shipper: Wilson Manufacturing Corporation, Hugh H. Wilson Company, Packer St., Sunbury, Pa. 17801. Send protests to: Paul J. Kenworthy, District Supervisor, Bureau of Operations, Interstate Commerce Commission, 314 U.S. Post Office Bldg., Scranton, Pa. 18503.

No. MC 134084 (Sub-No. 3 TA), filed August 26, 1976. Applicant: CLIFFORD M. SHROCK, 940 Blaine St., Woodburn, Oreg. 97071. Applicant's representative: Robert R. Hollis, 400 Pacific Bldg., Portland, Oreg. 97204. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Lumber*, from points in Clackamas County, Oreg., to Portland, Oreg., and points in Clark and Cowlitz Counties, Wash., for 180 days. Applicant has also filed an underlying ETA seeking up to 90 days of operating authority. Supporting shippers: Avison Lumber Co., P.O. Box 597, Molalla, Oreg. 97038. Brazier Forest Products, Inc., P.O. Box 5, Molalla, Oreg. 97038. Send protests to: A. E. Odoms, District Supervisor, Bureau of Operations, Interstate Commerce Commission, 114 Pioneer Courthouse, 555 S. W. Yamhill St., Portland, Oreg. 97204.

No. MC 134349 (Sub-No. 20 TA), filed August 26, 1976. Applicant: B. L. T. CORPORATION, 405 Third Ave., Brooklyn, N.Y. 11215. Applicant's representative: Eugene M. Malkin, Suite 6193, 5 World Trade Center, New York, N.Y. 10048. Authority sought to operate as a *contract carrier*, by motor vehicle, over irregular routes, transporting: *Small live animals, birds, fish and foods, medicines, toys, books, accessories and supplies related to their care and treatment and such other commodities* as are dealt in or used by a manufacture and distributor thereof, between Harrison, Jersey City and Bloomfield, N.J.; and Tampa, Fla., on the one hand, on the other, Birmingham, Leeds, Tuscaloosa, Geneva and Anniston, Montgomery, Ala.; Van Buren, Ark.; Denver and Grand Junction, Colo.; Jacksonville, Tampa, Hialeah, Miami, Hallendale, Largo and Ocala, Fla.; Atlanta, Albany, Forest Park, Morrow, Decatur and Douglas, Ga.; Addison, Berkely, Chicago, Elk Grove and Rock Island, Ill.; Fort Wayne, Indianapolis, Evansville and Marion, Ind.; Davenport, Grinnel and Urbandale, Iowa; Topeka, Wichita and Olathe, Kans.; Louisville, Ky.; New Orleans, Harahan, Kenner, La Combe and Metairie, La.; Baltimore, Brentwood, Elkridge, Beltsville, Columbia City, Jessup, Silver Springs, Timonium and Landover, Md.; Grand Rapids, Ferndale, Monroe, Warren, Detroit, Hastings, Novi, Bay City, Romulus and Keego Harbor, Mich.; Minneapolis, Edina, Marshall and Hopkins, Minn.; Jackson and Indianola, Miss.; Independence, Kansas City, St. Louis, Hazelwood and Desloge, Mo.; Omaha and Lincoln, Nebr.; Ashboro, Charlotte, Hickory, Kernersville, Winston Salem, and Greenville, N.C.; Cincinnati, Dayton, Middleburg Heights, Toledo, Cleveland, Fairfield, Sharonville, Youngstown, Columbus, Loveland, Solon, Bedford Heights, Bellefontaine, N. Lima, Vanwert and Findlay, Ohio; Oklahoma City, Tulsa and Muskogee, Okla.; Allentown, Dunmore, Leetsdale, Sunbury, Carnegie, Harrisburg, Pittsburgh, Monroeville, Flifton Heights, Lancaster, Robesonia, E. Butler, Parkersburg and Shiremanstown, Pa., Greenville and Charleston Heights, S.C.; Chattanooga, Memphis, Nashville and Bristol, Tenn.; Arlington, Kilgore, Mesquite, Dallas, Lubbock, Beaumont, Grand Prairie, San Antonio, Amarillo, Houston, Fort Worth and Garland, Tex.; Norfolk,

Richmond, Salem, Newington and Roanoke, Va.; Milwaukee, Wausau and Waukesha, Wis., under a continuing contract with The Hartz Mountain Corporation, for 180 days. Applicant has also filed an underlying ETA seeking up to 90 days of operating authority. Supporting shipper: The Hartz Mountain Corporation, 700 South Fourth St., Harrison, N.J. 07029. Send protests to: Maria B. Kejss, Transportation Assistant, Interstate Commerce Commission, 26 Federal Plaza, New York, N.Y. 10007.

No. MC 135658 (Sub-No. 2 TA), filed August 27, 1976. Applicant: ROCK RIVER CARTAGE, INC., R.R. No. 2, P.O. Box 430, Rock Falls, Ill. 61071. Applicant's representative: Robert T. Lawley, 300 Reisch Bldg., Springfield, Ill. 62701. Authority sought to operate as a *contract carrier*, by motor vehicle, over irregular routes, transporting: *Refractory materials and products* (except in bulk), for the account of Northwestern Steel and Wire Company, from Lake County, Ind., to Sterling, Ill., under a continuing contract with Northwestern Steel and Wire Company, for 180 days. Applicant has also filed an underlying ETA seeking up to 90 days of operating authority. Supporting shipper: Northwestern Steel and Wire Company, Lanny J. Nunz, Chief Rate Analyst, 121 Wallace St., Sterling, Ill. 61081. Send protests to: Patricia A. Roscoe, Transportation Assistant, Interstate Commerce Commission, Everett McKinley Dirksen Bldg., 219 S. Dearborn St., Room 1386, Chicago, Ill. 60604.

No. MC 136220 (Sub-No. 36 TA), filed August 27, 1976. Applicant: ROY SULLIVAN, doing business as SULLIVAN TRUCKING CO., P.O. Box 2164, Ponca City, Okla. 74601. Applicant's representative: G. Timothy Armstrong, 6161 North May Ave., Oklahoma City, Okla. 73112. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Aggregate* (in bulk in dump vehicles), from the plantsite of Arkansas Lightweight Aggregate Corporation, near West Memphis, Ark., to points in Kentucky and Tennessee, for 180 days. Applicant has also filed an underlying ETA seeking up to 90 days of operating authority. Supporting shipper: Arkansas Lightweight Aggregate Corporation, P.O. Box 157, West Memphis, Ark. 72301. Send protests to: Joe Green, District Supervisor, Room 240 Old Post Office Bldg., 215 Northwest Third St., Oklahoma City, Okla. 73102.

No. MC 139460 (Sub-No. 20 TA), filed August 24, 1976. Applicant: FORT EDWARD EXPRESS CO., INC., Route 9, Saratago Road, Fort Edward, N.Y. 12828. Applicant's representative: J. Fred Relyea (same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Wollastonite*, in bulk, in tank vehicles, from Willsboro, N.Y. (Essex County), to Blanchester, Ohio, for 180 days. Supporting shipper: Interpace Corporation, Willsboro, N.Y. 12996. Send protests to: Robert A. Radler, District Supervisor, 518 Federal Bldg., P.O. Box 1167, Albany, N.Y. 12201.

No. MC 139923 (Sub-No. 19 TA), filed August 24, 1976. Applicant: MILLER TRUCKING CO., 105 S. 8th St., Stroud, Okla. 74079. Applicant's representative: Wilburn L. Williamson, 280 National Foundation Life Bldg., 3535 NW. 58th St., Oklahoma City, Okla. 73112. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Food, food products and food ingredients*, in mechanically refrigerated equipment (except in bulk), from the plantsite and warehouse facilities of Archer Daniels Midland Company, at or near Decatur, Ill., to points in Arkansas, Louisiana, New Mexico, Oklahoma and Texas, for 180 days. Applicant has also filed an underlying ETA seeking up to 90 days of operating authority. Supporting shipper: Archer Daniels Midland Company, P.O. Box 1470, Decatur, Ill. 62525. Send protests to: Joe Green, District Supervisor, Room 240 Old Post Office Bldg., 215 Northwest Third St., Oklahoma City, Okla. 73102.

No. MC 139923 (Sub.-No. 21TA), filed August 26, 1976. Applicant: MILLER TRUCKING CO., INC., 105 S. 8th St., Stroud, Okla. 74079. Applicant's representative: Jack H. Blanshan, Suite 200, 205 West Touhy Ave., Park Ridge, Ill. 60068. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Cranberry products, fruit juices and table sauces* (except commodities in bulk), from the plantsite and warehouse facilities of or utilized by Ocean Spray Cranberries, Inc., located at or near Kenosha, Wis., and North Chicago, Ill., to Kansas City, Mo., and points in its Commercial Zone, and to points in Kansas, Oklahoma and Texas, for 180 days. Applicant has also filed an underlying ETA seeking up to 90 days of operating authority. Supporting shipper: Ocean Spray Cranberriers, Inc., 7800 South 60th Ave., Kenosha, Wis. 53140. Send protests to: Joe Green, District Supervisor, Room 240 Old Post Office Bldg., 215 Northwest Third St., Oklahoma City, Okla. 73102.

No. MC 142309TA, filed August 25, 1976. Applicant: MARY PACKER AND JOHN COOLEN, doing business as, PACKER & COOLEN TRUCKING, Route 1, Box 725, Coos Bay, Oreg. 97420. Applicant's representative: Mary Packer (same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Veneer and used machinery*, from Willow Creek, Calif., to the Grants Pass, Medford, White City and Glendale, Oreg. area; and from Brookings, Oreg., to the Grants Pass, Medford, White City and Glendale, Oreg., area, for 180 days. Supporting shippers: Willow Creek, Inc., Willow Creek, Calif. Fourply, Inc., P.O. Drawer AN, Brookings, Oreg. 97415. Send protests to: A. E. Odoms, District Supervisor, Bureau of Operations, Interstate Commerce Commission, 114 Pioneer Courthouse, 555 SW. Yamhill St., Portland, Oreg. 97204.

No. MC 142340 (Sub-No. 1TA), filed August 23, 1976. Applicant: HERBERT F. CLARK, JR., INC., R.D. 2, Box 357 D, Selkirk, N.Y. 12158. Applicant's representative: Neil D. Breslin, 99 Washington Ave., Suite 1111, Albany, N.Y. 12210. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Scrap metal*, in dump vehicles, (1) from Albany, N.Y., to Newark, N.J.; Jersey City, N.J.; North Haven, Conn.; and Port of Entry at Niagara Falls, N.Y.; and (2) from Village of Colonie (Albany County), N.Y., to Newark, N.J., and Jersey City, N.J., for 180 days. Supporting shippers: V. T. E. Industries, Foot of Binghamton St., Albany, N.Y. 12202. Empire Alloys Corp., Foot of First St., Colonie, N.Y. 12205. Send protests to: Robert A. Radler, District Supervisor, P.O. Box 1167, Albany, N.Y. 12201.

No. MC 142358 (Sub-No. 1TA), filed August 23, 1976. Applicant: J. J. GILLAM TRUCKING COMPANY, INC., 1028 Sinnock Ave., P.O. Box 297, Moberly, Mo. 65270. Applicant's representative: Thomas P. Rose, Jefferson, Bldg., P.O. Box 205, Jefferson City, Mo. 65101. Authority sought to operate as a *contract carrier*, by motor vehicle, over irregular routes, transporting: *Coal*, in bulk, in dump vehicles, from points in Howard County, Mo., to Quincy, Ill., under a continuing contract with Universay Coal and Energy Company, Inc., for 180 days. Applicant has also filed an underlying ETA seeking up to 90 days of operating authority. Supporting shipper: Universal Coal and Energy Company, Inc., 1102 E. Broadway, Columbia, Mo. 65201. Send protests to: Vernon V. Coble, District Supervisor, Interstate Commerce Commission, 600 Federal Bldg., 911 Walnut St., Kansas City, Mo. 64106.

No. MC 142380TA, filed August 26, 1976. Applicant: GART, INC., 35 Brown St., Washington, N.J. 07882. Applicant's representative: Robert B. Pepper, 168 Woodbridge Ave., Highland Park, N.J. 08904. Authority sought to operate as a *contract carrier*, by motor vehicle, over irregular routes, transporting: (1) *Clay* (except in bulk), from Skillman, N.J., to points in Connecticut, Kentucky, Maryland, Massachusetts, New York, Ohio, Pennsylvania, Tennessee, Virginia, Washington, D.C., and West Virginia and (2) *Talc, materials and supplies* used in the manufacturing or ceramics (except in bulk), from the above destination states to Skillman, N.J., under a continuing contract with Standard Clay Mines, for 180 days. Applicant has also filed an underlying ETA seeking up to 90 days of operating authority. Supporting shipper: Standard Clay Mines, Camp Meeting, Skillman, N.J. 08558. Send protests to: Joel Morrows, District Supervisor, Interstate Commerce Commission, Bureau of Operations, 9 Clinton St., Room 618, Newark, N.J. 07102.

No. MC 142381TA, filed August 26, 1976. Applicant: WAYNE E. BELL, doing business as WAYNE BELL, Box 34,

Colusa, Ill. 62329. Applicant's representative: Edward G. Pree, 904–5 Myers Bldg., Springfield, Ill. 62701. Authority sought to operate as a *contract carrier*, by motor vehicle, over irregular routes, transporting: *Dry animal and poultry feed and feed ingredients*, in open top vehicles, from points in Iowa on or south of U.S. Highway 30 and on or east of U.S. Highway 69; and from Hannibal, Mexico, Montgomery City, Marshall and Smithton, Mo.; and from Kansas City, Kans., to the facilities of Cargill, Inc., at or near Carthage, Ill., under a continuing contract with Cargill, Inc., Nutrena Feed Division, for 180 days. Supporting shipper: Cargill, Inc., Nutrena Feed Division, Fred K. Coerper, General Traffic Manager, Cargill Bldg., Minneapolis, Minn. 55402. Send protests to: Patricia A. Roscoe, Transportation Assistant, Interstate Commerce Commission, Everett McKinley Dirksen Bldg., 219 S. Dearborn St., Room 1386, Chicago, Ill. 60604.

By the Commission.

[SEAL] GORDON H. HOMME, JR.,
Acting Secretary.

[FR Doc.76-26390 Filed 9-8-76;8:45 am]

[Notice No. 117]

MOTOR CARRIER TEMPORARY AUTHORITY APPLICATIONS

SEPTEMBER 3, 1976.

Important notice: The following are notices of filing of applications for temporary authority under Section 210a(a) of the Interstate Commerce Act provided for under the provisions of 49 CFR 1131.3. These rules provide that an original and six (6) copies of protests to an application may be filed with the field official named in the FEDERAL REGISTER publication no later than the 15th calendar day after the date the notice of the filing of the application is published in the FEDERAL REGISTER. One copy of the protest must be served on the applicant, or its authorized representative, if any, and the protestant must certify that such service has been made. The protest must identify the operating authority upon which it is predicated, specifying the "MC" docket and "Sub" number and quoting the particular portion of authority upon which it relies. Also, the protestant shall specify the service it can and will provide and the amount and type of equipment it will make available for use in connection with the service contemplated by the TA application. The weight accorded a protest shall be governed by the completeness and pertinence of the protestant's information.

Except as otherwise specifically noted, each applicant states that there will be no significant effect on the quality of the human environment resulting from approval of its application.

A copy of the application is on file, and can be examined at the Office of the Secretary, Interstate Commerce Commission, Washington, D.C., and also in the ICC Field Office to which protests are to be transmitted.

MOTOR CARRIERS OF PROPERTY

No. MC 56679 (Sub-No. 88TA), filed August 26, 1976. Applicant: BROWN TRANSPORT CORP., 125 Milton Ave., SE., Atlanta, Ga. 30315. Applicant's representative: R. J. Reynolds, III, 1400 Candler Bldg., Atlanta, Ga. 30303. Authority sought to operate as a *common carrier*, by motor vehicle, over regular routes, transporting: *General commodities* (except those of unusual value, classes A and B explosives, household goods as defined by the Commission, commodities in bulk and those requiring special equipment); (1) between Atlanta, Ga., and Cartersville, Ga., serving no intermediate points, but serving the termini of Atlanta, Ga., and Cartersville, Ga., and all points within their respective commercial zones; from Atlanta, Ga., to Cartersville, Ga., over U.S. Highway 41 (also over all completed portions of Interstate Highway 75 between Atlanta, Ga., and Cartersville, Ga., and over all roads and portions of roads connecting completed portions of Interstate Highway 75 to U.S. Highway 41) and return over the same route. Restriction: No point may be served by operating over Interstate Highway 75 that is not also authorized for service over U.S. Highway 41; (2) between Cartersville, Ga., and Chattanooga, Tenn., serving (a) the termini of Cartersville, Ga., and Chattanooga, Tenn., and all points within their respective commercial zones; and (b) all intermediate points between Cartersville, Ga., and Chattanooga, Tenn., and all places within the commercial zones of each of said intermediate points; from Cartersville, Ga., to Chattanooga, Tenn., over U.S. Highway 41 (also over all completed portions of Interstate Highway 75 between Cartersville, Ga., and Chattanooga, Tenn., and over all roads and portions of roads connecting completed portions of Interstate Highway 75 to U.S. Highway 41); and return over the same route. Restriction: No point may be served by operating over Interstate Highway 75 that is not also authorized for service over U.S. Highway 41.

(3) Serving the plantsite of E. T. Barwick Industries, Inc., near the intersection of Georgia Highways 143 and 193 at or near Hedges, Ga., located in Walker County, Ga., as an off-route point in connection with carrier's authorized regular-route operations described above between Atlanta and Cartersville, Ga., and between Cartersville, Ga., and Chattanooga, Tenn.; and (4) between Chattanooga, Tenn., and Knoxville, Tenn., serving no intermediate points, but serving the termini of Chattanooga, Tenn., and Knoxville, Tenn., and all points within their respective commercial zones; from Chattanooga, Tenn., to Knoxville, Tenn., over Interstate Highway 75, and return over the same route. Applicant intends to tack its existing authority with MC 56679 Subs 2, 9, 10, 15, 37, 43, 72, and 85. Applicant also intends to interline at Atlanta, Ga., Chattanooga, Tenn., and Knoxville, Tenn., for 180 days. Applicant has also filed an underlying ETA seeking up to 90 days of operating authority. Supporting shippers: There are approximately 70 statements of support attached to the application, which may be examined at the Interstate Commerce Commission in Washington, D.C., or copies thereof which may be examined at the field office named below. Send protests to: Sara K. Davis, Transportation Assistant, Bureau of Operations, Interstate Commerce Commission, 1252 W. Peachtree St. NW., Room 546, Atlanta, Ga. 30309.

No. MC 95376 (Sub-No. 13TA), filed August 26, 1976. Applicant: McVEY TRUCKING, INC., Route No. 1, Oakwood, Ill. 61858. Applicant's representative: Robert T. Lawley, 300 Reisch Bldg., Springfield, Ill. 62701. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Dry animal and poultry feed, dry animal and poultry mineral mixtures, animal and poultry tonics, insecticides* (other than agricultural) *and premiums and advertising matter relating to such products*, from Danville, Ill., to points in Kentucky, restricted to traffic originating at the plantsite and facilities of Shur-Grain Feed Division, William Davies Co., Inc., at Danville, Ill., for 180 days. Applicant has also filed an underlying ETA seeking up to 90 days of operating authority. Supporting shipper: Shur-Grain Feed Division of William Davies Co., Inc., W. L. Lavery, General Manager, 628 E. Fairchild St., Danville, Ill. 61832. Send protests to: Patricia A. Roscoe, Transportation Assistant, Interstate Commerce Commission, Everett McKinley Dirksen Bldg., 219 S. Dearborn St., Room 1386, Chicago, Ill. 60604.

No. MC 110420 (Sub-No. 760TA), filed August 27, 1976. Applicant: QUALITY CARRIERS, INC., P.O. Box 186, Pleasant Prairie, Wis. 53158. Applicant's representative: Joseph K. Reber (same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Can coating, paint, and resins*, from Milwaukee, Wis., to points in California, for 180 days. Supporting shipper: PPF Industries, Inc., One Gateway Center, Pittsburgh, Pa. 15222. Send protests to: Gail Daugherty, Transportation Assistant, Interstate Commerce Commission, Bureau of Operations, 135 West Wells St., Room 807, Milwaukee, Wis. 53203.

No. MC 119619 (Sub-No. 90TA), filed August 26, 1976. Applicant: DISTRIBUTORS SERVICE CO., 2000 W. 43rd St., Chicago, Ill. 60609. Applicant's representative: Bruce J. Robbins, One Lafrak City Plaza, Flushing, N.Y. 11368. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Meats, meat products, and meat by-products, and articles distributed by meat packinghouses*, as described in Sections A and C of Appendix I to the report in *Descriptions in Motor Carrier Certificates*, 61 M.C.C. 209 and 766 (except hides and commodities in bulk), from the plantsite and storage facilities of Elcona Foods, Inc., located at Elkhart, Ind., to points in Connecticut, Delaware, Illinois, Iowa, Kansas, Ken-

tucky, Maine, Maryland, Massachusetts, Michigan, Minnesota, Missouri, Nebraska, New Hampshire, New Jersey, New York, Ohio, Pennsylvania, Rhode Island, Vermont, Virginia, West Virginia, Wisconsin, and the District of Columbia. Restriction: Restricted to traffic originating at the named origin and destined to the named destinations, for 180 days. Applicant has also filed an underlying ETA seeking up to 90 days of operating authority. Supporting shipper: Elcona Foods, Inc., Keith A. Gary, Sales Supervisor, 24402 CR 45, Elkhart, Ind. 46514. Send protests to: Patricia A. Roscoe, Transportation Assistant, Interstate Commerce Commission, Everett McKinley Dirksen Bldg., 219 S. Dearborn St., Room 1386, Chicago, Ill. 60604.

No. MC 123061 (Sub-No. 83TA), filed August 27, 1976. Applicant: LEATHAM BROTHERS, INC., 46 Orange St. Salt Lake City, Utah 84104. Applicant's representative: Harry D. Pugsley, 315 East 2nd South, Salt Lake City, Utah 84111. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Boxes and sheets*, corrugated or not corrugated, K.D.F., from the plantsite of Boise Cascade Corp., in or near Nampa, Idaho, to North Salt Lake, Utah, for 180 days. Applicant has also filed an underlying ETA seeking up to 90 days of operating authority. Supporting shipper: Boise Cascade Corporation, P.O. Box 7747, Boise, Idaho 83707. Send protests to: Lyle D. Helfer, District Supervisor, Interstate Commerce Commission, Bureau of Operations, 5301 Federal Bldg., 125 South State St., Salt Lake City, Utah 84138.

No. MC 125023 (Sub-No. 41TA), filed August 25, 1976. Applicant: SIGMA-4 EXPRESS, INC., 3825 Beech Ave., P.O. Box 9117, Erie, Pa. 16504. Applicant's representative: Richard G. McCurdy (same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Malt beverages*, in containers, from Chicago, Ill., to points in Massachusetts, New York, and New Jersey (Boston, Lawrence, New Bedford, Nonquitt, and Williamsett, Mass.; Albany, Brooklyn, Buffalo, Rochester, Utica, N.Y.; and Hammonton, Lynhurst, Newark, and Orange, N.J.), for 180 days. Applicant has also filed an underlying ETA seeking up to 90 days of operating authority. Supporting shipper: Peter Hand Brewing Company, 1000 W. North Ave., Chicago, Ill. 60622. Send protests to: John J. England, District Supervisor, Interstate Commerce Commission, 2111 Federal Bldg., 1000 Liberty Ave., Pittsburgh, Pa. 15222.

No. MC 128007 (Sub-No. 90TA), filed August 27, 1976. Applicant's representative: Hofer, Inc., P.O. Box 583, 4032 Parkview Drive, Pittsburg, Kans. 66762. Applicant's representative: Larry E. Gregg, 641 Harrison, Topeka, Kans. 66603. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: (1) *Clay, clay products, related articles, fitting and jointing materials*, from Pittsburg, Kans., to points in Alabama, Arizona, Arkansas, California, Colorado, Florida, Georgia, Illinois, Indiana, Iowa, Kentucky, Louisiana, Michigan, Minnesota, Mississippi, Missouri, Nebraska, New Mexico, Ohio, Oklahoma, South Dakota, Tennessee, Texas, Wisconsin, and Wyoming; and (2) *clay, clay products*, fittings, equipment, materials, and supplies, used or useful in the manufacturing, packaging, transporting, and distributing of clay products and jointing materials, from the plantsites and/or storage facilities of W. S. Dickey Clay Manufacturing Co., at or near Bradenton, Fla.; Bessemer, Ala.; Texarkana, Texas-Arkansas; San Antonio, Tex.; Meridian, Miss.; and St. Louis, Mo., to the plantsite and/or storage facility of W. S. Dickey Clay Manufacturing Co., at or near Pittsburg, Kans., for 180 days. Supporting shipper: Dickey Clay Manufacturing Company, P.O. Box 6, Pittsburg, Kans. 66762. Send protests to: M. E. Taylor, District Supervisor, Interstate Commerce Commission, 501 Petroleum Bldg., Wichita, Kans. 67202.

No. MC 134922 (Sub-No. 186TA) (Amendment), filed July 22, 1976, published in the FEDERAL REGISTER issue of August 5, 1976, and republished as amended this issue. Applicant: B. J. MCADAMS, INC., Route 6, Box 15, North Little Rock, Ark. 72118. Applicant's representative: Bob McAdams (same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Such merchandise* as is sold and used by wholesale, retail and discount stores and *chemicals*, in vehicles equipped with mechanical refrigeration (except foodstuffs, alcoholic beverages, commodities in bulk and those which because of size or weight require the use of special equipment), from Muskegon and Greenville, Mich.; Brockway, Pa.; Corning, N.Y.; Cumberland, Md.; and Jackson, Miss., to points in Idaho, Washington, Oregon, California, Nevada, Arizona and Utah and from Memphis, Tenn., to points in Nevada, for 180 days. Supporting shipper: Triple 5 Tire Center, Inc., Vice President of Operations, 412 Madison St., Petaluma, Calif. 94952. Send protests to: William H. Land, Jr., District Supervisor, 3108 Federal Office Bldg., 700 West Capitol, Little Rock, Ark. 72201. The purpose of this republication is to delete Brazoria County, Tex., and to change the name of the supporting shipper;

No. MC 136315 (Sub-No. 11TA), filed August 27, 1976. Applicant: OLEN BURRAGE TRUCKING, INC., Route 9, Box 22–A, Philadelphia, Miss. 39350. Applicant's representative: Fred W. Johnson, Jr., 1500 Deposit Guaranty Plaza, P.O. Box 22628, Jackson, Miss. 39205. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: (1) *Lumber and lumber products*, from the facilities of Weyerhaeuser Company, Lamar County, Ala., to points in Florida, Illinois, Indiana, Iowa, Kansas, Kentucky, Maryland, Michigan, Minnesota, Missouri, North Carolina, Ohio, Oklahoma, Pennsylvania, South Carolina, Tennessee, Texas and Wisconsin; and (2) *Equipment, materials and supplies* (except in bulk), from points in the above named states to the facilities of Weyerhaeuser Company, in Lamar County, Ala., for 180 days. Applicant has also filed an underlying ETA seeking up to 90 days of operating authority. Supporting shipper: Weyerhaeuser Company, P.O. Box 1060, Hot Springs, Ark. 71901. Send protests to: Alan C. Tarrant, District Supervisor, Interstate Commerce Commission, Room 212, 145 East Amite Bldg., Jackson, Miss. 39201.

No. MC 138274 (Sub-No. 35TA) filed August 27, 1976. Applicant: SHIPPERS BEST EXPRESS, INC., 2151 North Redwood Road, Salt Lake City, Utah 84116. Applicant's representative: Chester Zyblut, 366 Executive Bldg., 1030 Fifteenth St., NW., Washington, D.C. 20005. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Foods stuffs*, in vehicles equipped with mechanical refrigeration, from Richmond and Clearfield, Utah, to Omaha, Nebr.; Springdale, Ark.; Sumter, S.C.; Salisbury, Md. for 180 days. Applicant has also filed an underlying ETA seeking up to 90 days of operating authority. Supporting shipper: Peperidge Farm, Inc., P.O. Box 145, Richmond, Utah 84333. Send protests to: Lyle D. Helfer, District Supervisor, Interstate Commerce Commission, 5301 Federal Bldg., Bureau of Operations, 125 South State St., Salt Lake City, Utah 84138.

No. MC 142350 (Sub-No. 1 TA), filed August 27, 1976. Applicant: MALT TRANSPORT, INC., P.O. Box 1488, Springfield, Mass. 01101. Applicant's representative: William P. Sullivan, 1818 H St., NW., Washington, D.C. 20006. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: (1) *Malt beverages (beer) and related advertising materials*, from South Volney, N.Y., to points in Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island and Vermont; and (2) *Returned empty malt beverage containers*, from points in Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island and Vermont, to South Volney, N.Y., for 90 days. Applicant has also filed an underlying ETA seeking up to 90 days of operating authority. Supporting shipper: Miller Brewer Company, 4000 West State St., Milwaukee, Wis. 53201. Send protests to: James D. Perry, Jr., District Supervisor, 436 Dwight St., Room 338, Springfield, Mass. 01103.

No. MC 142376TA, filed August 27, 1976. Applicant: BILLY A. LAMBERT TRUCKING, Route 3, Box 220B, Staunton, Va. 24401. Authority sought to operate as a *contract carrier*, by motor vehicle, over irregular routes, transporting: *Stone*, in bulk, in dump vehicles, from the plantsite of Harry T. Campbell & Sons Quarry, located at or near Westminster, Md., to Black Marble Quarry,

in Harrisonburg, Va., under a continuing contract with The Frazier Quarry, Inc., for 180 days. Supporting shipper: The Frazier Quarry, Inc., P.O. Box 695, Harrisonburg, Va. 22801. Send protests to: Danny R. Beeler, District Supervisor, Bureau of Operations, Interstate Commerce Commission, P.O. Box 210, Roanoke, Va. 24011.

No. MC 142378TA, filed August 26, 1976. Applicant: CENTRAL DISPATCH, INC., 650 Manhattan St., Harvey, La. 70058. Applicant's representative: Harold R. Ainsworth, 2307 American Bank Bldg., New Orleans, La. 70103. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Engine or motor parts and equipment and parts thereof* used in ships and ocean going vessels for the operation, maintenance and safety of such ships and vessels, between points in the Parishes of Plaquemines, St. Bernard, Orleans, Jefferson, St. Charles, St. John the Baptist, St. James, Ascension, Iberville, East Baton Rouge, West Baton Rouge, Calcasieu Parish, Louisiana, Harrison County, Miss., Orange and Jefferson Counties, Tex., Bay Town, Houston, Galveston, Corpus Christie, Texas City and Freeport, Tex., restricted to traffic moving in foreign commerce and under U.S. Custom bond, for 180 days. Applicant has also filed an underlying ETA seeking up to 90 days of operating authority. Supporting shippers: There are approximately 21 statements of support attached to the application, which may be examined at the Interstate Commerce Commission in Washington, D.C., or copies thereof which may be examined at the field office named below. Send protests to: Ray C. Armstrong, Jr., District Supervisor, 9038 Federal Bldg., 701 Loyola Ave., New Orleans, La. 70113.

No. MC 143279TA, filed August 27, 1976. Applicant: TULOMA, INC., 2901 Dawson Road, Tulsa, Okla. 74110. Applicant's representative: C. L. Phillips, Room 248—Classen Terrace Bldg., 1411 N. Classen, Oklahoma City, Okla. 73106. Authority sought to operate as a *contract carrier*, by motor vehicle, over irregular routes, transporting: *Copper articles, rods, cathodes and ingots*, on flat bed trailers, from Port of Catoosa, Okla., to Shawnee, Okla., under a continuing contract with Wolverine, UOP Inc., for 180 days. Supporting shipper: Wolverine, UOP Inc., F. R. Petru, Traffic Supervisor, 2901 Dawson Road, Tulsa, Okla. 74110. Send protests to: Joe Green, District Supervisor, Room 240 Old Post Office Bldg., 215 NW. Third, Oklahoma City, Okla. 73102.

By the Commission.

GORDON H. HOMME, Jr.,
Acting Secretary.

[FR Doc.76-26391 Filed 9-8-76;8:45 am]

[Notice No. MC-C-4000 (Sub-No. 6)]

MOTOR TRANSPORTATION OF PASSENGERS INCIDENTAL TO TRANSPORTATION BY AIRCRAFT

Chicago O'Hare Airport Terminal Area; Petition To Extend Exempt Zone

Petitioner: Hammond Yellow and Checker Cab, Inc., doing business as, Airport Limousine Service, Hammond, Ind., Petitioner's representative: Donald W. Smith, Suite 2465, One Indiana Square, Indianapolis, Ind. 46204. By the instant petition, filed May 17, 1976, the above named petitioner requests the Commission to reopen the proceeding in MC-C-4000, 95 M.C.C. 526 at pages 538-539, for the purpose of redefining the limits of the zone within which may be performed motor transportation of passengers having an immediately prior or subsequent movement by air, pursuant to section 203(b)(7a) of the Interstate Commerce Act, within the Chicago O'Hare International Airport air terminal area so as to include all points in Lake and Porter Counties, Ind. The limits of terminal areas at airports within which such transportation may be performed under the section 203(b)(7a) exemption were defined on July 17, 1964, in Motor Transportation of Passengers Incidental to Transportation by Aircraft, 95 M.C.C. 526, at pages 538-539 (49 CFR 1047.45). Petitioner here seeks to have the exemption redefined to include all points in Lake and Porter Counties, Ind.

Petitioner states that it has been conducting passenger terminal operations for a number of years but has found that numerous passengers utilizing the Chicago O'Hare facilities for transportation do, in fact, originate at various points in Lake and Porter Counties which are beyond the exempt area.

No oral hearing is contemplated at this time but any interested person wishing to make representations in favor of or in opposition to the relief sought by the petition may do so by submitting written statements. All such persons, including motor carriers, air carriers, shippers and receivers of freight, and others, whether or not subject to the Commission's jurisdiction, are invited to submit representations setting forth any facts or argument pertinent to the proper scope of the exempt zone surrounding the O'Hare International Airport at Chicago, Ill.

An original and 15 copies, where possible, of representations containing data, views, or arguments shall be filed with the Commission on or before November 8, 1976. One copy of each representation should be served upon petitioner's representative shown above.

Written material or suggestions submitted will be available for public inspection at the Offices of the Interstate Commerce Commission, 12th & Constitution, Washington, D.C., during regular business hours.

Notice to the general public of the matter herein under consideration will be given by depositing a copy of this notice in the Office of the Secretary of the Commission for public inspection and by filing a copy thereof with the Director, Office of the Federal Register.

By the Commission.

H. GORDON HOMME, Jr.,
Acting Secretary.

[FR Doc.76-26400 Filed 9-8-76;8:45 am]

[Volume No. 47]

SEPTEMBER 3, 1976.

Permanent authority petitions and applications; finance matters (including temporary authorities); railroad abandonments; alternate route deviation letter-notices; and intrastate applications concurrently seeking authority on interstate or foreign commerce.

PETITIONS FOR MODIFICATION, INTERPRETATION OR REINSTATEMENT OF OPERATING RIGHTS AUTHORITY

The following petitions seek modification or interpretation of existing operating rights authority, or reinstatement of terminated operating rights authority.

An original and one copy of protests to the granting of the requested authority must be filed with the Commission on or before October 12, 1976. Such protest shall comply with Special Rule 247(d) of the Commission's General Rules of Practice (49 CFR 1100.247)[1] and shall include a concise statement of protestant's interest in the proceeding and copies of its conflicting authorities. Verified statements in opposition should not be tendered at this time. A copy of the protest shall be served concurrently upon petitioner's representative, or petitioner if no representative is named.

No. MC 121630 (Sub-No. 3) (Notice of Filing of Petition to Remove Restriction), filed May 17, 1976. Petitioner: LEMORE TRANSPORTATION, INC., doing business as: ROYAL TRUCKING CO., 1420 Royal Industrial Way, P.O. Box 6085, Concord, Calif. 94524. Petitioner's representative: Raymond A. Greene, Jr., 100 Pine St., Suite 2550, San Francisco, Calif. 94111. Petitioner holds a motor *common carrier* Certificate in No. MC 121630 (Sub-No. 3), issued July 26, 1976, authorizing transportation over irregular routes, of (1) *Dry commodities*, in bulk, in dump or hopper-type vehicles (except earth, sand, loam, gravel, stone, cement, asphalt, and cement or asphalt mixes), between points in Solano, Contra Costa and Alameda Counties, Calif., on the one hand, and, on the other, Pitts-

[1] Copies of Special Rule 247 (as amended) can be obtained by writing to the Secretary, Interstate Commerce Commission, Washington, D.C. 20423.

burg, Benicia, Selby, Richmond, Oakland, and Alameda, Calif.; and (2) *General commodities* (except (a) commodities of unusual value, (b) classes A and B explosives, (c) household goods as defined by the Commission, (d) commodities requiring special equipment, (e) commodities in vehicles equipped with mechanical refrigeration, (f) liquids, compressed gases, commodities in semiplastic form, and commodities in suspension in liquids, in bulk, in tank vehicles, (g) earth, sand, loam, gravel, stone, cement, asphalt and cement or asphalt mixes, in bulk, in dump or hopper-type vehicles, (h) logs, and (i) fresh fruits and vegetables), between points in San Francisco, Alameda, and Contra Costa County, Calif., which are on and east of California Highway 82, those points in Santa Clara County, Calif., which are on, north, and west of California Highways 17 and 82, and those points in Solano County, Calif., which are bounded by a line beginning at the junction of Interstate Highway 680 and the Solano-Contra Costa, Calif., County line, and extending along Interstate Highway 680 to junction Interstate Highway 80, thence extending along Interstate Highway 80 to junction of the Solano-Contra Costa, Calif., County line, and thence extending along the Solano-Contra Costa, Calif., County line to the point of beginning (i.e. the junction of said county line and Interstate Highway 680), including points on the said line, restricted in (1) and (2) above, to or from San Francisco, Calif., to the transportation of traffic having a prior or subsequent movement by water.

By the instant petition, petitioner seeks to delete the restriction from the above authority.

No. MC 140540 (Sub-No. 1) (Notice of filing of petition for modification of permit), filed August 19, 1976. Petitioner: L. MONTGOMERY, INC., 4 Tilton Ave., Red Bank, N.J. 07721. Petitioner's representative: Robert B. Pepper, 168 Woodbridge Ave., Highland Park, N.J. 08904. Petitioner holds a motor *contract carrier* Permit in No. MC 140540 (Sub-No. 1), issued March 2, 1976, authorizing transportation over irregular routes, of *styrofoam products, plastic lids, plastic tumblers, plastic plates, and plastic utensils*, from the facilities of Thompson Industries Co., located at New Shrewsbury, N.J., to points in Connecticut, Delaware, Maryland, New York, and Pennsylvania, under a continuing contract, or contracts, with Thompson Industries Co.

By the instant petition, petitioner seeks (1) to modify the commodity description by submitting "styroproducts" in lieu of "styrofoam products"; (2) to add Alexander, Va. and Milford, N.H. as additional origin points; and (3) to add Alexander, Va., Milford, N.H., and New Shrewsbury, N.J. as additional destination points to the above authority.

MOTOR CARRIER, BROKER, WATER CARRIER AND FREIGHT FORWARDER OPERATING RIGHTS APPLICATIONS

The following applications are governed by Special Rule 247 of the Commission's *General Rules of Practice* (49 CFR § 1100.247). These rules provide, among other things, that a protest to the granting of an application must be filed with the Commission within 30 days after the date of notice of filing of the application is published in the FEDERAL REGISTER. Failure to seasonably to file a protest will be construed as a waiver of opposition and participation in the proceeding. A protest under these rules should comply with section 247(d)(3) of the rules of practice which requires that it set forth specifically the grounds upon which it is made, contain a detailed statement of protestant's interest in the proceeding (including a copy of the specific portions of its authority which protestant believes to be in conflict with that sought in the application, and describing in detail the method—whether by joinder, interline, or other means—by which protestant would use such authority to provide all or part of the service proposed), and shall specify with particularity the facts, matters, and things relied upon, but shall not include issues or allegations phrased generally. Protests not in reasonable compliance with the requirements of the rules may be rejected. The original and one copy of the protest shall be filed with the Commission, and a copy shall be served concurrently upon applicant's representative, or applicant if no representative is named. If the protest includes a request for oral hearing, such requests shall meet the requirements of section 247(d)(4) of the special rules, and shall include the certification required therein.

Section 247(f) further provides, in part, that an applicant who does not intend timely to prosecute its application shall promptly request dismissal thereof, and that failure to prosecute an application under procedures ordered by the Commission will result in dismissal of the application.

Further processing steps will be by Commission order which will be served on each party of record. Broadening amendments will not be accepted after the date of this publication except for good cause shown, and restrictive amendments will not be entertained following publication in the FEDERAL REGISTER of a notice that the proceeding has been assigned for oral hearing.

Each applicant states that there will be no significant effect on the quality of the human environment resulting from approval of its application.

No. MC 4966 (Sub-No. 20), filed August 2, 1976. Applicant: JONES TRANSFER COMPANY, 300 Jones Avenue, Monroe, Mich. 48161. Applicant's representative: Thomas M. Hummer (same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *General commodities* (except those of unusual value, Classes A and B explosives and household goods as defined by the Commission), serving the plantsite and facilities of Molmec, Inc., located at Fowlerville, Mich., as an off-route point in connection with applicant's existing regular route operations.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at either Detroit, Mich., Chicago, Ill. or Washington, D.C.

No. MC 8535 (Sub-No. 58), filed August 3, 1976. Applicant: GEORGE TRANSFER AND RIGGING COMPANY, INCORPORATED, P.O. Box 500, Interstate 83 at Route 439, Parkton, Md. 21120. Applicant's representative: John Guandolo, 1000 16th St., N.W., Washington, D.C. 20036. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Paper, paper articles, paperboard and paperboard articles* (except commodities in bulk), from Chesapeake and Lynchburg, Va., to points in Connecticut, Delaware, Kentucky, Maine, Maryland, Massachusetts, New Hampshire, New Jersey, New York, North Carolina, Ohio, Pennsylvania, Rhode Island, South Carolina, Vermont, Virginia, West Virginia, and the District of Columbia.

NOTE.—Common control may be involved. If a hearing is deemed necessary, applicant requests it be held at Washington, D.C.

No. MC 11207 (Sub-No. 375), filed July 30, 1976. Applicant: DEATON, INC., 317 Avenue W., P.O. Box 938, Birmingham, Ala. 35201. Applicant's representative: Kim D. Mann, 702 World Center Building, 918 Sixteenth Street, N.W., Washington, D.C. 20006. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Roofing and roofing materials*, from the plantsite and facilities of Masonite Corporation located in Pulaski County, Ark., to points in Alabama, Florida, Georgia, Kentucky, Louisiana, Mississippi, and Tennessee.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at either Little Rock, Ark. or Memphis, Tenn.

No. MC 22195 (Sub-No. 168), filed August 2, 1976. Applicant: DAN DUGAN TRANSPORT COMPANY, 41st & Grange Avenue, Sioux Falls, S. Dak. 57105. Applicant's representative: Fred Fischer (same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Anhydrous ammonia*, in bulk, in tank vehicles, from the storage facilities of Farmland Industries, Inc. located at or near Barnesville and Benson, Minn., to points in Minnesota, Montana, North Dakota, South Dakota and Wisconsin.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at either Kansas City, Mo. or Sioux Falls, S. Dak.

No. MC 29886 (Sub-No. 332), filed July 28, 1976. Applicant: DALLAS & MAVIS FORWARDING CO., INC., 4000 West Sample Street, South Bend, Ind. 46619. Applicant's representative: Paul F. Sullivan, 711 Washington Building, Washington, D.C. 20005. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Van delivery vehicles and motor homes*, in truckaway and driveaway service, from Forest City, Iowa to points in Illinois, Indiana, Michigan, Ohio and Wisconsin.

NOTE.—Common control may be involved. If a hearing is deemed necessary, the applicant requests that it be held at either Chicago, Ill., or Washington, D.C.

No. MC 29910 (Sub-No. 173), filed July 29, 1976. Applicant: ARKANSAS-BEST FREIGHT SYSTEM, INC., 301 South 11th Street, Fort Smith, Ark. 72901. Applicant's representative: Don A. Smith, P.O. Box 43, Fort Smith, Ark. 72901. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: (1) *Fencing, fencing materials, wire and wire products*, from Van Buren, Ark., to Reno, Nev., and points in Alabama, Georgia, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Mississippi, Missouri, Nebraska, Ohio, Oklahoma, Tennessee and Texas; and (2) *steel wire carriers*, from Reno, Nev., to Van Buren, Ark.

NOTE.—Common control may be involved. If a hearing is deemed necessary, the applicant requests it be held at either Kansas City, Mo. or Washington, D.C.

No. MC 36556 (Sub-No. 31), filed August 2, 1976. Applicant: BLACKMON TRUCKING INC., P.O. Box 186, Somers, Wis. 53171. Applicant's representative: Fred H. Figge (same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Inedible animal feed ingredients*, frozen, from the plantsite and storage facilities of Bydalek Fur Farms Inc. located in Kenosha County, Wis., to points in Illinois and Indiana.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at either Chicago, Ill. or Milwaukee, Wis.

No. MC 42487 (Sub-No. 854), filed July 29, 1976. Applicant: CONSOLIDATED FREIGHTWAYS CORPORATION OF DELAWARE, 175 Linfield Drive, Menlo Park, Calif. 94025. Applicant's representative: V. R. Oldenburg, P.O. Box 5138, Chicago, Ill. 60680. Authority sought to operate as a *common carrier*, by motor vehicle, over regular routes, transporting: *General commodities* (except those of unusual value, Classes A and B explosives, livestock, household goods as defined by the Commission, commodities in bulk, assembled automobiles, and those requiring special equipment): Serving Central City, Iowa, as an off-route point in connection with carrier's regular route operations.

NOTE.—Common control may be involved. If a hearing is deemed necessary, applicant requests it be held at Des Moines, Iowa.

No. MC 44735 (Sub-No. 29), filed August 2, 1976. Applicant: KISSICK TRUCK LINES, INC., 7101 East 12th St., Kansas City, Mo. 64126. Applicant's representative: John E. Jandera, 641 Harrison St., Topeka, Kans. 66603. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Pipe and pipe fittings, couplings, connectors, and accessories* (except iron and steel pipe), from the plantsite of Armco Steel Corporation located at or near Springfield, Ill., to points in Iowa, Kansas, Missouri and Nebraska.

NOTE.—If a hearing is deemed necessary the applicant requests a consolidated hearing but does not specify a location.

No. MC 44735 (Sub-No. 30), filed July 30, 1976. Applicant: KISSICK TRUCK LINES, INC., 7101 East 12th Street, Kansas City, Mo. 64126. Applicant's representative: John E. Jandera, 641 Harrison Street, Topeka, Kans. 66603. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Plastic pipe, plastic conduit, plastic and iron fittings* and *connections, valves, hydrants, and gaskets and related commodities*, used in the installation of plastic pipe and plastic conduit (except commodities as described in *Mercer Extension Oilfield Commodities*, 74 M.C.C. 459), from the plantsite and storage facilities of The Clow Corporation, located at or near Columbia, Mo., to points in Arizona, California, Colorado, Idaho, Kansas, Minnesota, Montana, Nebraska, Nevada, New Mexico, North Dakota, Oklahoma, Oregon, South Dakota, Texas, Utah, Washington, Wisconsin, and Wyoming.

NOTE.—Applicant requests a consolidated hearing with other similar filed applications, but does not specify a location.

No. MC 51146 (Sub-No. 474), filed July 30, 1976. Applicant: SCHNEIDER TRANSPORT, INC. 2661 South Broadway, Green Bay, Wis. 54304. Applicant's representative: Neil A. DuJardin, P.O. Box 2298, Green Bay, Wis. 54306. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: (1) *Paper and paper products, and printed matter*, between Marlin, Tex., on the one hand, and, on the other, points in Illinois, Indiana, Iowa, Ohio, Kentucky, Michigan Minnesota, and Wisconsin; and (2) *paper and paper products, and carbon paper ink* in semi-solid (non-fluid) form, between Brenham, Tex., on the one hand, and, on the other, points in Illinois Indiana, Iowa, Ohio, Kentucky, Michigan, Minnesota, and Wisconsin.

NOTE.—Common control may be involved. If a hearing is deemed necessary, the applicant requests it be held at Chicago, Ill.

No. MC 52704 (Sub-No. 131), filed August 2, 1976. Applicant: GLENN McCLENDON TRUCKING COMPANY, INC., P.O. Drawer "H", LaFayette, Ala. 36862. Applicant's representative: Archie B. Culbreth, Suite 246, 1252 West Peachtree St., N.W., Atlanta, Ga. 30309. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Glass containers and their equipment of caps, covers and tops*, from the warehouse facilities utilized by Laurens Glass Company located at or near Greenville and Mauldin, S.C., to points in Alabama, Arkansas, Delaware, Florida, Georgia, Kentucky, Indiana, Louisiana, Maryland, Mississippi, North Carolina, Tennessee, Texas, Virginia and West Virginia.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at Atlanta, Ga.

No. MC 57697 (Sub-No. 3), filed July 30, 1976. Applicant: LESTER SMITH TRUCKING, INC., 11460 West 44th Avenue, West Ridge, Colo. 80033. Applicant's representative: David J. Lister, P.O. Box 1125, Arvada, Colo. 80001. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Construction equipment, farm machinery and used farm equipment*, between points in Colorado, Iowa, Kansas, Missouri, Nebraska, and Wyoming.

NOTE.—Common control may be involved. If a hearing is deemed necessary, the applicant requests it be held at Denver, Colo. or Omaha, Nebr.

No. MC 61231 (Sub-No. 94), filed August 2, 1976. Applicant: ACE LINES, INC., 4143 East 43rd St., Des Moines, Iowa 50317. Applicant's representative: William L. Fairbank, 1980 Financial Center, Des Moines, Iowa 50309. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Pipe, pipe fittings and couplings, connectors and accessories for pipe* (except iron or steel pipe), from the plantsite of Armco Steel Corporation located at or near Springfield, Ill., to points in Iowa, Kansas, Missouri, and Nebraska.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at either Kansas City, Mo. or Springfield, Ill.

No. MC 61396 (Sub-No. 313), filed August 2, 1976. Applicant: HERMAN BROS. INC., 2565 St. Marys Avenue, P.O. Box 189, Omaha, Nebr. 68101. Applicant's representative: John E. Smith, II (same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Anhydrous ammonia*, in bulk, in tank vehicles, from the storage facilities of Farmland Industries located at or near Barnesville and Benson, Minn., to points in Minnesota, North Dakota, Montana, South Dakota and Wisconsin.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at either Kansas City, Mo. or Omaha, Nebr.

No. MC 69116 (Sub-No. 186), filed August 2, 1976. Applicant: SPECTOR FREIGHT SYSTEM, INC., 1050 Kingery Highway, Bensenville, Ill. 60106. Applicant's representative: Edward G. Bazelon, 39 South La Salle Street, Chicago, Ill. 60603. Authority sought to operate as a *common carrier*, by motor vehicle, over regular routes, transporting: *General commodities* (except those of unusual value, Classes A and B explosives, household goods as defined by the Commission, commodities in bulk and those requiring special equipment), serving the plantsite and warehouse facilities of Aerofin Corporation, located at or near Amherst, Va., as an off-route point in connection with applicant's previously authorized regular route operations.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at Richmond, Va. or Washington, D.C.

No. MC 80430 (Sub-No. 158), filed July 27, 1976. Applicant: GATEWAY TRANSPORTATION CO., INC., 455 Park Plaza Drive, La Crosse, Wis. 54601. Applicant's representative: Drew L. Carraway, 501 Perpetual Bldg., 1111 E Street, NW., Washington, D.C. 20004. Authority sought to operate as a *common carrier*, by motor vehicle, over regular routes, transporting: *General commodities* (except those of unusual value, Classes A and B explosives, household goods as defined by the Commission, commodities in bulk, and those requiring special equipment), (1) Between Iuka, Miss. and Memphis, Tenn. serving all intermediate points on U.S. Highway 72 from Iuka to junction Mississippi Highway 15: From Iuka, Miss. over U.S. Highway 72 to Memphis, Tenn., and return over the same route; (2) Between Columbus, Miss. and Corinth, Miss. serving all intermediate points: (a) From Columbus over U.S. Highway 45 to Corinth, Miss., and return over the same route: and (b) From Columbus over U.S. Highway 82 to junction U.S. Highway Alternate 45, thence over U.S. Highway Alternate 45 to junction U.S. Highway 45 and return over the same route: (3) Between Columbus, Miss. and Brownfield, Miss. serving all intermediate points:

From Columbus, Miss., over U.S. Highway 82 to junction Mississippi Highway 15, thence over Mississippi Highway 15 to Brownfield, Miss., and return over the same route; (4) Between Columbus, Miss. and Iuka, Miss. serving all intermediate points: From Columbus, Miss. over U.S. Highway 45 to junction Mississippi Highway 25 to Iuka, Miss., and return over the same route; (5) Between junction Mississippi Highway 15 with Mississippi Highway 32, and junction Mississippi Highway 32 with U.S. Highway Alternate 45 serving all intermediate points: From junction Mississippi Highway 15 and Mississippi Highway 32, thence over Mississippi Highway 32 to junction Mississippi Highway 32 and U.S. Highway Alternate 45, and return over the same route; and (6) Between Tremont, Miss. and Atlanta, Ga., serving no intermediate points: From Tremont, Miss. over U.S. Highway 78 to junction U.S. Highway 278 via Hamilton, Ala. thence over U.S. Highway 278 to junction Alabama Highway 5 via Natural Bridge, Ala., thence over Alabama Highway 5 to junction U.S. Highway 78 via Jasper, Ala., thence over U.S. Highway 78 to Atlanta, Ga., and return over the same route serving all points in that part of Mississippi bounded on the east by the Mississippi-Alabama State line, on the north by the Mississippi-Tennessee State line, on the west by Mississippi Highway 15, and on the south by U.S. Highway 82, including points on the indicated portions of Mississippi Highway 15 and U.S. Highway 82, as off route points in connection with applicant's regular route operations requested above.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at Tupelo, Miss. and Orlando, Fla.

No. MC 82492 (Sub-No. 135), filed July 30, 1976. Applicant: MICHIGAN & NEBRASKA TRANSIT CO., INC., P.O. Box 2853, 2109 Olmstead Road, Kalamazoo, Mich. 49003. Applicant's representative: William C. Harris (same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Petroleum products*, in containers, from Karns City, Pa., to points in Michigan.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at Washington, D.C.

Mo. MC 82841 (Sub-No. 181), filed August 2, 1976. Applicant: HUNT TRANSPORTATION, INC., 1077 "I" St., Omaha, Nebr. 68127. Applicant's representative: Donald L. Stern, 530 Univac Bldg., 7100 West Center Rd., Omaha, Nebr. 68106. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Cement asbestos pipe, fittings and accessories* necessary for the installation thereof, from Van Buren, Ark., to points in Colorado, Idaho, Iowa, Kansas, Minnesota, Montana, Nebraska, North Dakota, South Dakota, Utah, Wisconsin and Wyoming.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at St. Louis, Mo.

No. MC 82841 (Sub-No. 182), filed August 2, 1976. Applicant: HUNT TRANSPORTATION, INC., 10770 "I" St., Omaha, Nebr. 68127. Applicant's representative: Donald L. Stern, 530 Univac Bldg., 7100 West Center Rd., Omaha, Nebr. 68106. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: (1) *Lead and alloys*, from Omaha, Nebr., to points in the United States (except Alaska and Hawaii); (2) *materials and supplies* (except in bulk) used in the manufacture and distribution of lead alloys, from points in the United States (except Alaska and Hawaii), to Omaha, Nebr.; and (3) *dore bullion*, from Omaha, Nebr. and Tacoma, Wash., to Armarillo, Tex., restricted in (1), (2), and (3) above to the transportation of shipments originating at or destined to the facilities of Asarco, Incorporated, located at Omaha, Nebr.; Tacoma, Wash.; and Amarillo, Tex.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at St. Louis, Mo.

No. MC 82841 (Sub-No. 183), filed August 2, 1976. Applicant: HUNT TRANSPORTATION, INC., 10770 "I" St., Omaha, Nebr. 68127. Applicant's representative: Donald L. Stern, 530 Univac Bldg., 7100 W. Center Rd., Omaha, Nebr. 68106. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Pipe and pipe fittings, couplings, connectors and accessories* (except iron and steel pipe), from the plantsite of Armco Steel Corporation located at or near Springfield, Ill., to points in Iowa, Kansas and Nebraska.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at either Kansas City, Mo. or Springfield, Ill.

No. MC 87909 (Sub-No. 25), filed July 29, 1976. Applicant: ARROW MOTOR FREIGHT LINE, INC., 2125 Commercial Street, Waterloo, Iowa 50702. Applicant's representative: John P. Rhodes (same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over regular routes, transporting: *General commodities* (except those of unusual value, Classes A and B explosives, household goods as defined by the Commission, commodities in bulk, and those requiring special equipment), between Minneapolis-St. Paul, Minn., and points in their respective commercial zones, and Rochester, Minn., as an alternate route for operating convenience only in connection with carrier's presently authorized regular route operations, serving no intermediate points, and serving Rochester, Minn., for joinder purposes only: From Minneapolis-St. Paul, Minn., over Minnesota Highway 55 to junction U.S. Highway 52, thence over U.S. Highway 52 to Rochester, Minn., and return over the same route.

NOTE.—Common control may be involved. If a hearing is deemed necessary, the applicant requests it be held at either Minneapolis, Minn. or Washington, D.C.

No. MC 94350 (Sub-No. 366), filed July 30, 1976. Applicant: TRANSIT HOMES, INC., P.O. Box 1628, Greenville, S.C. 29602. Applicant's representative: Mitchell King, Jr., (same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Trailers*, designed to be drawn by passenger automobiles, in initial movements, *and buildings* in sections, mounted on wheeled undercarriages, from points in Columbia and Leon Counties, Fla., to points in Alabama, Arkansas, Georgia, Louisiana, Mississippi, North Carolina, South Carolina, and Tennessee.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at Jacksonville, Fla.

No. MC 103051 (Sub-No. 376), filed August 4, 1976. Applicant: FLEET TRANSPORT COMPANY, INC., 934 44th Avenue, North, Nashville, Tenn. 37209. Applicant's representative: Russell E. Stone, P.O. Box 90408, Nashville, Tenn. 37209. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Ferrous sulfamate*, from Eufaula, Ala., to Dunbarton, S.C.

NOTE.—If a hearing is deemed necessary, applicant requests it be held at Atlanta, Ga., or Nashville, Tenn.

No. MC 103051 (Sub-No. 377), filed Aug. 4, 1976. Applicant: FLEET TRANS-

PORT COMPANY, INC., 934 44th Avenue, North, Nashville, Tenn. 37209. Applicant's representative: Russell E. Stone, P.O. Box 90408, Nashville, Tenn. 37209. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Dry slag*, in bulk, in tank or hopper type vehicles, from Carrollton, Ga., to Ozark, Ala.

NOTE.—If a hearing is deemed necessary, applicant requests it be held at Atlanta, Ga., or Nashville, Tenn.

No. MC 106195 (Sub-No. 9), filed July 28, 1976. Applicant: CLARK BROS. TRANSFER, INC., 800 North First St., P.O. Box 388, Norfolk, Nebr. 68701. Applicant's representative: Michael J. Ogborn, P.O. Box 82028, Lincoln, Nebr. 68501. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: (1) *Iron and steel articles*, as described in *Descriptions in Motor Carrier Certificates*, 61 M.C.C. 209 and 767, from Chicago, Alton and Sterling, Ill.; Kansas City and St. Louis, Mo.; and Wilton Junction, Iowa, to Norfolk, Nebr.; and (2) *ferrous scrap metal*, from points in Colorado, Illinois, Iowa, Kansas, Minnesota, South Dakota, Wyoming, and points in that part of Missouri on and north of Interstate Highway 70, to the Nucor Steel Mill located at or near Norfolk, Nebr.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at Omaha, Nebr.

No. MC 106398 (Sub-No. 746), filed August 2, 1976. Applicant: NATIONAL TRAILER CONVOY, INC., 525 South Main, Tulsa, Okla. 74103. Applicant's representative: Irvin Tull (Same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Single wide and double wide mobile homes*, in initial movements, in truckaway service, from Adams County, Colo., to points in the United States (except Alaska and Hawaii).

NOTE.—Common control may be involved. If a hearing is deemed necessary, the applicant requests it be held at Denver, Colo.

No. MC 106398 (Sub-No. 747), filed August 2, 1976. Applicant: NATIONAL TRAILER CONVOY, INC., 525 South Main, Tulsa, Okla. 74103. Applicant's representative: Irvin Tull (Same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Mobile homes*, in initial movements, in truckaway service, from Wood County, Wis., to points in the United States (except Alaska and Hawaii).

NOTE.—Common control may be involved. If a hearing is deemed necessary, the applicant requests it be held at Milwaukee, Wis.

No. MC 106398 (Sub-No. 749), filed August 2, 1976. Applicant: NATIONAL TRAILER CONVOY, INC., 525 South Main, Tulsa, Okla. 74103. Applicant's representative: Irvin Tull (Same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Mobile homes*, in initial movements, in truckaway service, from points in Cumberland and Montgomery Counties, Tenn., to points in the United States (except Alaska and Hawaii).

NOTE.—Common control may be involved. If a hearing is deemed necessary, the applicant requests it be held at Nashville, Tenn.

No. MC 106398 (Sub-No. 751), filed Aug. 2, 1976. Applicant: NATIONAL TRAILER CONVOY, INC., 525 South Main, Tulsa, Okla. 74103. Applicant's representative: Irvin Tull (same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Mobile homes*, irrespective of their intended use, in initial movements, in truckaway service, from points in Pulaski and White Counties, Ark., to points in the United States (except Alaska and Hawaii).

NOTE.—Dual operations and common control may be involved. If a hearing is deemed necessary, applicant requests it be held at Little Rock, Ark.

No. MC 106398 (Sub-No. 752), filed August 2, 1976. Applicant: NATIONAL TRAILER CONVOY, INC., 525 South Main, P.O. Box 3329, Tulsa, Okla. 74103. Applicant's representative: Irvin Tull (same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Mobile homes*, irrespective of their intended use, in initial movements, in truckaway service, from points in Lincoln, Montgomery, and Vance Counties, N.C., to points in the United States (except Alaska and Hawaii).

NOTE.—Common control and dual operations may be involved. If a hearing is deemed necessary, applicant requests it be held at Charlotte, N.C.

No. MC 106433 (Sub-No. 10), filed August 5, 1976. Applicant: ANTRIM TRANSPORTATION CO., INC., 7–11 Suffern Place, Suffern, N.Y. 10901. Applicant's representative: John L. Alfano, 550 Mamaroneck Avenue, Harrison, N.Y. 10528. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Glass containers*, from the plantsite of Midland Glass Company, Inc., located at or near Cliffwood, N.J., to points in New York; and (2) *returned shipments*, from points in New York, to the origin point named in (1) above.

NOTE.—Common control may be involved. If a hearing is deemed necessary, the applicant requests it be held at New York.

No. MC 106775 (Sub-No. 41), filed July 29, 1976. Applicant: ATLAS TRUCK LINE, INC., 761 San Jacinto Bldg., P.O. Box 9848, Houston, Tex. 77015. Applicant's representative: Thomas Harper, P.O. Box 43, Fort Smith, Ark. 72901. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: (1) *Fencing, fencing materials, wire and wire products;* and (2) *steel wire carriers*, (a) from Van Buren, Ark., to points in Alabama, Georgia, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Mississippi, Missouri, Nebraska, Ohio, Oklahoma, Tennessee, Texas and Reno, Nev.; and (b) from Reno, Nev., to Van Buren, Ark.

NOTE.—Common control may be involved. If a hearing is deemed necessary, the applicant requests that it be held at either Kansas City, Mo., or Washington, D.C.

No. MC 107403 (Sub-No. 982, filed August 3, 1976. Applicant: MATLACK, INC., Ten West Baltimore Avenue, Lansdowne, Pa. 19050. Applicant's representative: John Nelson (same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Sulphur hexafluoride*, in bulk, in shipper provided trailers, from Metropolis, Ill., to East Chicago, Ind.

NOTE.—Common control may be involved. If a hearing is deemed necessary, the applicant requests it be held at Washington, D.C.

No. MC 107496 (Sub-No. 1040), filed August 2, 1976. Applicant: RUAN TRANSPORT CORPORATION, 3200 Ruan Center, 666 Grand Avenue, Des Moines, Iowa 50309. Applicant's representative: E. Check, P.O. Box 855, Des Moines, Iowa 50304. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Plaster and plaster products*, in bulk, in tank vehicles, from the facilities of Georgia Pacific Corporation located at or near Fort Dodge, Iowa, to points in Ohio.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at either Chicago, Ill. or Des Moines, Iowa.

No. MC 107515 (Sub-No. 1018), filed August 2, 1976. Applicant: REFRIGERATED TRANSPORT CO., INC., P.O. Box 308, Forest Park, Ga. 30050. Applicant's representative: Alan E. Serby, 3379 Peachtree Road, N.E., Suite 375, Atlanta, Ga. 30326. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Paper, paper articles and paper products*, from the plantsite and warehouse facilities of Union Camp Corporation, located at or near Franklin, Va., to points in Chicago, Ill., and its Commercial Zone; Indiana on and north of U.S. Highway 40; Michigan on and south of Michigan Highway 21, and points in Ohio.

NOTE.—Common control may be involved. If a hearing is deemed necessary, the applicant requests it be held at Washington, D.C.

No. MC 107544 (Sub-No. 127), filed August 2, 1976. Applicant: LEMMON TRANSPORT COMPANY, INCORPORATED, P.O. Box 580, Marion, Va. 24354. Applicant's representative: Harry C. Ames, Jr., 666 Eleventh Street, N.W., Washington, D.C. 20001. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Natural latex*, in bulk, in tank vehicles, from Charleston, S.C., to points in Alabama, Connecticut, Delaware, Florida, Georgia, Illinois, Indiana, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, New Hampshire, New Jersey, New York, North Carolina,

Ohio, Oklahoma, Pennsylvania, Rhode Island, South Carolina, Tennessee, Texas, Vermont, Virginia, West Virginia, Wisconsin and the District of Columbia.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at either Washington, D.C. or Roanoke, Va.

No. MC 107715 (Sub-No. 9), filed August 2, 1976. Applicant: DUQAL, LTD., 3308 Bandini Boulevard, Los Angeles, Calif. 90023. Applicant's representative: David P. Christianson, 606 South Olive, Suite 825, Los Angeles, Calif. 90014. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Potting soil and pesticides* (except in bulk), *and pottery* in mixed loads with feeds and fertilizers, from points in and south of Fresno, Inyo, Monterey and San Benito Counties, Calif., to points in Arizona.

NOTE.—Common control may be involved. If a hearing is deemed necessary, the applicant requests it be held at Los Angeles, Calif.

No. MC 107993 (Sub-No. 47), filed August 2, 1976. Applicant: J. J. WILLIS TRUCKING CO., 2608 Electronic Lane, Dallas, Tex. 75220. Applicant's representative: James W. Hightower, 136 Wynnewood Professional Bldg., Dallas, Tex. 75224. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Cement asbestos pipe, fittings, and couplings*, from the plantsite and storage facilities of Cement Asbestos Products Company located at or near Van Buren, Ark., to points in Arizona, California, Colorado, North Dakota and Utah.

NOTE.—Common control may be involved. If a hearing is deemed necessary, the applicant requests it be held at either St. Louis, Mo. or Dallas, Tex.

No. MC 109692 (Sub-No. 40), filed August 2, 1976. Applicant: GRAIN BELT TRANSPORTATION CO., INC., 340 North James, Kansas City, Kans. 66118. Applicant's representative: Tom B. Kretsinger, 910 Brookfield Bldg., 101 West Eleventh, Kansas City, Mo. 64105. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Pipe and pipe fittings, couplings, connectors, and accessories* (except iron and steel pipe), from the plantsite of Armco Steel Corporation located at or near Springfield, Ill., to points in Iowa, Kansas, Missouri, and Nebraska.

NOTE.—Common control may be involved. If a hearing is deemed necessary, the applicant requests it be held at either Kansas City or Springfield, Mo.

No. MC 110144 (Sub-No. 18), filed July 30, 1976. Applicant: JACK C. ROBINSON, doing business as ROBINSON FREIGHT LINES, 3600 Paper Mill Road, P.O. Box 10234, Knoxville, Tenn. 37919. Applicant's representative: Warren A. Goff, 5100 Poplar Avenue, 2008 Clark Tower, Memphis, Tenn. 38137. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *General commodities* (except those of unusual value, Classes A and B explosives, commodities in bulk, household goods as defined by the Commission, and commodities requiring special equipment), between points in Tennessee on and east of U.S. Highway 27, on the one hand, and, on the other, points in Bradley, McMinn, Meigs and Monroe Counties, Tenn.

NOTE.—Common control may be involved. If a hearing is deemed necessary, the applicant requests it be held at either Cleveland or Athens, Tenn.

No. MC 110191 (Sub-No. 28), filed July 23, 1976. Applicant: TURNER'S EXPRESS, INC., 1300 Shelton Avenue, Norfolk, Va. 23502. Applicant's representative: D. L. Turner (same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *General commodities* (except commodities in bulk and Classes A and B explosives), between Norfolk, Va. and its Commercial Zone, and Chesapeake, Nansemond, Portsmouth, Virginia Beach, Va. and their Commercial Zones, and points in Accomack, James City, Northampton, and York Counties, Va. and points in Camden, Currituck, Gates and Pasquotank Counties, N.C.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at either Norfolk, Va. or Washington, D.C.

No. MC 110563 (Sub-No. 186), filed Aug. 3, 1976. Applicant: COLDWAY FOOD EXPRESS, INC., P.O. Box 747, Sidney, Ohio 45365. Applicant's representative: Joseph M. Scanlan, 111 W. Washington, Chicago, Ill. 60602. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: (A) *Compressed fireplace logs and related advertising materials and display racks*, in mixed loads with compressed fireplace logs, from Suffolk, Va., to points in Alabama, Connecticut, Delaware, Florida, Georgia, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Mississippi, New Hampshire, New Jersey, New York, North Carolina, Pennsylvania, Rhode Island, South Coralina, Tennessee, Vermont, Virginia, West Virginia, and the District of Columbia; and (B) *compressed fireplace logs, char and charcoal briquettes, and wood blocks, woodchips, sawdust, fuel lighting, liquids, flavoring sticks or pellets, vermiculite* (other than crude), *perlite* (other than crude), and *related advertising materials and display racks*, when shipped with char and charcoal briquetts, and fireplace logs, from Marion, Ohio, to points in Alabama, Arkansas, Connecticut, Delaware, Florida, Georgia, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Nebraska, New Hampshire, New Jersey, New York, North Carolina, North Dakota, Ohio, Oklahoma, Pennsylvania, Rhode Island, South Carolina, South Dakota, Tennessee, Texas, Vermont, Virginia, West Virginia, Wisconsin, and the District of Columbia.

NOTE.—If a hearing is deemed necessary, applicant requests it be held at Columbus, Ohio.

No. MC 111045 (Sub-No. 131), filed Aug. 2, 1976. Applicant: REDWING CARRIERS, INC., P.O. Box 426, Tampa, Fla. 33601. Applicant's representative: J. V. McCoy (same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Sodium sulphate and sodium sulfite and mixtures thereof*, dry, in bulk, in tank vehicles, from Montgomery, Ala., to points in Alabama, Connecticut, Delaware, Illinois, (except the East St. Louis Commercial Zone), Indiana, Kentucky, Maine, Maryland, Massachusetts, Michigan, Missouri (except the St. Louis Commercial Zone), New Hampshire, New Jersey, New York, North Carolina, Ohio, Oklahoma, Pennsylvania, Rhode Island, South Carolina, Tennessee, Texas, (except points in Brazoria, Chambers, Fort Bend, Galveston, Liberty, Montgomery and Paris Counties), Vermont, Virginia, West Virginia, and the District of Columbia, restricted to traffic originating at the plantsite and storage facilities of Reichhold Chemicals, Inc., at Montgomery, Ala., and destined to the destination territory described above.

NOTE.—Common control may be involved. If a hearing is deemed necessary, applicant requests it be held at either Birmingham or Montgomery, Ala.

No. MC 111045 (Sub-No. 132), filed August 4, 1976. Applicant: REDWING CARRIERS, INC., P.O. Box 426, Tampa, Fla. 33601. Applicant's representative: J. V. McCoy (same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Products of corn, cane and beets, and blends* of said commodities, in bulk, from the plantsite and warehouse facilities of The Amalgamaize Company, located at or near Decatur, Ala., to points in the United States (except Alaska and Hawaii).

NOTE.—Common control may be involved. If a hearing is deemed necessary, the applicant requests it be held at either Mobile or Montgomery, Ala.

No. MC 111231 (Sub-No. 202), filed July 29, 1976. Applicant: JONES TRUCK LINES, INC., 610 East Emma Avenue, Springdale, Ark. 72764. Applicant's representative: Don A. Smith, P.O. Box 43, Fort Smith, Ark. 72901. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: (1) *Fencing, fencing materials, wire and wire products*, from Van Buren, Ark., to Reno, Nev., and points in Alabama, Georgia, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Mississippi, Missouri, Nebraska, Ohio, Oklahoma, Tennessee, and Texas; and (2) *steel wire carriers*, from Reno, Nev., to Van Buren, Ark.

NOTE.—Common control may be involved. If a hearing is deemed necessary, the applicant requests it be held at either Kansas City, Mo. or Washington, D.C.

No. MC 111729 (Sub-No. 673), filed August 3, 1976. Applicant: PUROLATOR COURIER CORP., 3333 New Hyde Park Road, New Hyde Park, N.Y. 11040. Applicant's representative: John M. Delany (same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Cut flowers, decorative greens, and green plants*, when moving at the same time and in the same vehicle with commodities the transportation of which is subject to economic regulation, between points in Arizona, restricted to traffic having an immediately prior or subsequent movement by air or motor vehicle.

NOTE.—Applicant holds contract carrier authority in MC 112750 and subs thereunder, therefore dual operations may be involved. Common control may also be involved. If a hearing is deemed necessary, the applicant requests it be held at Washington, D.C.

No. MC 111729 (Sub-No. 674), filed August 4, 1976. Applicant: PUROLATOR COURIER CORP., 3333 New Hyde Park Road, New Hyde Park, N.Y. 11040. Applicant's representative: John M. Delany (same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Business papers, records, audit and accounting media* of all kinds, *and blue prints*, (1) between Richmond, Va., on the one hand, and, on the other, Bristol, Chattanooga, Cleveland, Dyersburg, Harriman, Jackson, Knoxville, Memphis, Morristown, Nashville, and Shelbyville, Tenn., and Dover, Del.; and (2) between Monroe, Mich., on the one hand, and, on the other, Monett, Mo., Harrisburg, Va. and Wausau, Wis.

NOTE.—Applicant holds contract carrier authority in No. MC 112750 and subs thereunder, therefore dual operations may be involved. Common control may also be involved. If a hearing is deemed necessary, the applicant requests it be held at Washington, D.C.

No. MC 112304 (Sub-No. 110), filed August 4, 1976. Applicant: ACE DORAN HAULING & RIGGING CO., a Corporation, 1601 Blue Rock Street, Cincinnati, Ohio 45223. Applicant's representative: John D. Herbert (same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Plastic pipe or conduit, and fittings, connections, valves, hydrants, gaskets, materials, and supplies*, used in the installation thereof, from the plantsite and shipping facilities of the Clow Corporation, at or near Pell City, Ala., to points in Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, Oklahoma, South Dakota, Texas, and Wisconsin.

NOTE.—Common control may be involved. If a hearing is deemed necessary, applicant requests it be held at Washington, D.C., or Chicago, Ill.

No. MC 113325 (Sub-No. 145 (Amendment), filed July 1, 1976, published in the FEDERAL REGISTER issue of July 29, 1976, and republished as amended this issue. Applicant: SLAY TRANSPORTATION CO., INC., 2001 South Seventh St., St. Louis, Mo. 63104. Applicant's representative: T. M. Tahan (same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Liquid chemicals*, in bulk, in tank vehicles, from the facilities of Chemical Interchange Co. located at or near Blytheville, Ark.; Depue, Marseilles, and Wood River, Ill.; Flint, Grand Rapids, Kalamazoo, Mt. Clemens, Port Huron, and Warren, Mich.; and Louisiana, Mo.; and points within 5 miles of each of the named points, to points in Arkansas, Illinois, Indiana, Kentucky, Michigan, Missouri, Tennessee, and Wisconsin.

NOTE.—The purpose of this republication is to indicate the amended origin territory. If a hearing is deemed necessary, the applicant requests it be held at St. Louis, Mo.

No. MC 114045 (Sub-No. 446), filed July 27, 1976. Applicant: TRANS-COLD EXPRESS, INC., P.O. Box 61228, D/FW Airport, Tex. 75261. Applicant's representative: J. B. Stuart (same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Linoleum and adhesive materials*, in vehicles equipped with mechanical refrigeration, from Salem, N.J., to Corpus Christi, Laredo, and San Antonio, Tex.

NOTE.—Common control may be involved. If a hearing is deemed necessary, the applicant requests it be held at either Chicago, Ill. or Dallas, Tex.

No. MC 114211 (Sub-No. 278), filed July 21, 1976. Applicant: WARREN TRANSPORT, INC. 324 Manhard Street, P.O. Box 420, Waterloo, Iowa 50704. Applicant's representative: Daniel Sullivan, 327 South La Salle, Chicago, Ill. 60604. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Lumber, lumber products, millworks, forest products and such commodities* as are manufactured or distributed by lumber mills and lumber yards, from points in the United States (except Alaska and Hawaii), to ports of entry on the International Boundary line between the United States and Canada, located at or near Pembina and Dunseith, N. Dak., and Noyes, Minn., restricted to traffic moving to the Provinces of Manitoba, Saskatchewan and Alberta, Canada.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at either Fargo, N. Dak. or Minneapolis, Minn., with similar application of Arnold Bros. Transport, Ltd.

No. MC 114211 (Sub-No. 280), filed August 2, 1976. Applicant: WARREN TRANSPORT, INC., 324 Manhard St., P.O. Box 420, Waterloo, Iowa 50704. Applicant's representative: Daniel Sullivan, 327 South LaSalle St., Chicago, Ill. 60604. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Lumber, lumber products and pallets*, from the plantsite and facilities of Smith Pallet Company, Inc. located at or near Hatfield, Ark., to points in the United States (except Alaska and Hawaii).

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at either Fort Smith or Little Rock, Ark.

No. MC 114211 (Sub-No. 281), filed July 29, 1976. Applicant: WARREN TRANSPORT, INC., 324 Manhard St., P.O. Box 420, Waterloo, Iowa 50704. Applicant's representative: Daniel Sullivan, 327 South LaSalle St., Chicago, Ill. 60604. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Plywood, hardboard, fiberboard, gypsum board, particleboard, moldings, beams, laminated products and building materials*, from Boise, Idaho, to points in the United States (except Alaska and Hawaii).

NOTE.—If a hearing is deemed necessary, the applicant requests a consolidated hearing at either Boise or Pocatello, Idaho.

No. MC 114293 (Sub-No. 4), filed August 4, 1976. Applicant: SOUTHARD TRUCKING CO., INC., P.O. Box 326, Clinton, Ind. 47842. Applicant's representative: Robert W. Loser, 1009 Chamber of Commerce Bldg., Indianapolis, Ind. 46204. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Crushed limestone*, from points in Clark County, Ill., to points in Clay, Park, Sullivan, Vermillion and Vigo Counties, (a New York corporation).

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at either Indianapolis, Ind., or Chicago, Ill.

No. MC 115495 (Sub-No. 31), filed July 26, 1976. Applicant: UNITED PARCEL SERVICE, INC., 300 North 2nd Street, St. Charles, Ill. 60174. Applicant's representative: S. Harrison Kahn, 733 Investment Bldg., 1511 K Street, NW., Washington, D.C. 20005. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *General commodities* (except those of unusual value, classes A and B explosives, household goods as defined by the Commission, commodities in bulk and commodities requiring special equipment), (1) Between the premises of Montgomery Ward's Catalog Houses in Oakland, Calif.; Denver, Colo.; Chicago, Ill.; St. Paul, Minn.; Kansas City, Mo.; Portland, Oreg.; and Ft. Worth, Tex.; on the one hand, and, on the other, points in Arizona, Arkansas, Alabama, California, Colorado, Florida, Georgia, Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Michigan, Minnesota, Montana, Mississippi, Missouri, New Mexico, Nebraska, Nevada, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, South Carolina, South Dakota, Tennessee, Texas, Utah, Washington, Wisconsin, and Wyoming. (2) Between points in Pennsylvania, Virginia, and West Virginia within ten miles of the Pennsylvania-Ohio, Virginia-Kentucky, Virginia-North Carolina, Virginia-Tennessee, and the West Virginia-Kentucky States lines, on the one hand, and, on the other, points in Arizona, Arkansas, Alabama, California, Colorado, Florida, Georgia, Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Lou-

isiana, Michigan, Minnesota, Montana, Mississippi, Missouri, New Mexico, Nebraska, Nevada, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, South Carolina, South Dakota, Tennessee, Texas, Utah, Washington, Wisconsin, and Wyoming, restricted to packages originating at, or destined to the premises of Montgomery Ward's Catalog Houses in Oakland, Calif.; Denver, Colo.; Chicago, Ill.; Baltimore, Md.; St. Paul, Minn.; Kansas City, Mo.; Albany, N.Y.; Portland, Oreg.; and Ft. Worth, Tex.; and further restricted to packages having an immediately prior or, subsequent movement by United Parcel Service, Inc. a New York corporation.

(3) Between the premises of Sears, Roebuck and Co. Catalog Merchandise Distribution Centers and their associated warehouses in Los Angeles, Calif.; Jacksonville, Fla.; Atlanta, Ga.; Chicago and Elk Grove Village, Ill.; Minneapolis, Minn.; Kansas City, Mo.; Greensboro, N.C.; Columbus, Ohio; Memphis, Tenn.; Dallas, Tex.; and Seattle, Wash.; on the one hand, and, on the other, points in Arizona, Arkansas, Alabama, California, Colorado, Florida, Georgia, Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Michigan, Minnesota, Montana, Mississipi, Missouri, New Mexico, Nebraska, Nevada, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, South Carolina, South Dakota, Tennessee, Texas, Utah, Washington, Wisconsin; and Wyoming and (4) Between points in Pennsylvania, Virginia, and West Virginia, within ten miles of the Pennsylvania-Ohio, Virginia-Kentucky, Virginia-North Carolina, Virginia-Tennessee, and West Virginia-Kentucky States lines, on the one hand, and on the other, points in Arizona, Arkansas, Alabama, California, Colorado, Florida, Georgia, Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Michigan, Minnesota, Montana, Mississippi, Missouri, New Mexico, Nebraska, Nevada, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, South Carolina, South Dakota, Tennessee, Texas, Utah, Washington, Wisconsin and Wyoming, restricted to packages originating at, or destined to the premises of Sears, Roebuck and Co. Catalog Merchandise Distribution Centers and their associated warehouses in Los Angeles, Calif; Jacksonville, Fla.; Atlanta, Ga.; Chicago, and Elk Grove Village, Ill.; Boston, Mass.; Minneapolis, Minn.; Kansas City, Mo.; Greensboro, N.C.; Columbus, Ohio; Philadelphia, Pa.; Memphis, Tenn.; Dallas, Tex.; and Seattle, Wash.; and further restricted to packages having an immediately prior or subsequent movement by United Parcel Service, Inc., (a New York corporation).

Restrictions: (a) No service shall be rendered in the transportation of any package or article weighing more than 50 pounds or exceeding 108 inches in length and girth combined, and each package or article shall be considered as a separate and distinct shipment. (b) No service shall be provided in the transportation of packages or articles weighing in the aggregate more than 100 pounds from one consignor at one location to one consignee at one location on any one day.

NOTE.—Applicant holds contract carrier authority in MC 13426 and subs thereunder, therefore dual operations may be involved. Common control may also be involved. If a hearing is deemed necessary, the applicant requests it be held at New York, N.Y.

No. MC 116200 (Sub-No. 9), filed July 26, 1976. Applicant: UNITED PARCEL SERVICE, INC., 643 West 43rd Street, New York, N.Y. 10036. Applicant's representative: S. Harrison Kahn, 733 Investment Bldg., 1511 K Street, NW., Wasington, D.C. 20005. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *General commodities* (except those of unusual value, Classes A and B explosives, household goods as defined by the Commission, commodities in bulk and commodities requiring special equipment), (1) between the premises of Montgomery Ward's Catalog Houses in Albany, N.Y., and Baltimore, Md., on the one hand, and on the other, points in Connecticut, Delaware, Maine, Maryland, Massachusetts, New York, New Jersey, New Hampshire, Pennsylvania, Rhode Island, Vermont, Virginia, West Virginia, and the District of Columbia. (2) between points in Connecticut, Delaware, Maryland, Massachusetts, New Jersey, New York, New Hampshire, Pennsylvania, Rhode Island, Vermont, Virginia, West Virginia, and the District of Columbia, restricted to packages originating at, or destined to the premises of Montgomery Ward Catalog Houses in Baltimore, Md.; Albany, N.Y.; Chicago, Ill.; Denver, Colo.; Ft. Worth, Tex.; Kansas City, Mo.; Oakland, Calif.; Portland, Oreg.; and St. Paul, Minn., and further restricted to packages having an immediately prior or subsequent movement by United Parcel Service, Inc. (an Ohio Corporation).

(3) Between the premises of Sears, Roebuck and Co. Catalog Merchandise Distribution Centers and their associated warehouses in Philadelphia, Pa. and Boston, Mass., on the one hand, and on the other, points in Connecticut, Delaware, Maine, Maryland, Massachusetts, New York, New Jersey, New Hampshire, Pennsylvania, Rhode Island, Vermont, Virginia, West Virginia and the District of Columbia; and (4) between points in Connecticut, Delaware, Maine, Maryland, Massachusetts, New York, New Jersey, New Hampshire, Pennsylvania, Rhode Island, Vermont, Virginia, West Virginia, and the District of Columbia, restricted to packages originating at, or destined to the premises of Sears, Roebuck and Co. Catalog Merchandise Distribution Centers and their associated warehouses in Philadelphia, Pa.; Boston, Mass.; Greensboro, N.C.; Atlanta, Ga.; Jacksonville, Fla.; Memphis, Tenn.; Columbus, Ohio; Chicago and Elk Grove Village, Ill.; Minneapolis, Minn.; Kansas City, Mo.; Dallas, Tex.; Los Angeles, Calif. and Seattle, Wash., and further restricted to packages having an immediately prior or subsequent movement by United Parcel Service, Inc. (an Ohio Corporation). Restrictions: (a) No service shall be rendered in the transportation of any package or article weighing more than 50 pounds or exceeding 108 inches in length and girth combined, and each package or article shall be considered as a separate and distinct shipment; and (b) No service shall be provided in the transportation of packages or articles weighing in the aggregate more than 100 pounds from one consignor at one location to one consignee at one location on any one day.

NOTE.—Applicant holds contract carrier authority in MC 63063 and subs thereunder, therefore dual operations may be involved. Common control may also be involved. If a hearing is deemed necessary, the applicant requests it be held at New York, N.Y.

No. MC 117119 (Sub-No. 589), filed July 29, 1976. Applicant: WILLIS SHAW FROZEN EXPRESS, INC., P.O. Box 188, Elm Springs, Ark. 72728. Applicant's representative: L. M. McLean (Same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Processed edible flour* (except commodities in bulk), (1) from the plantsite of Modern Maid Food Products located at Vernon, Calif., to the plantsite of Modern Maid Food Products located at Ponchatoula, La.; (2) from the plantsite of Modern Maid Food Products located at Ponchatoula, La., to Brownsville and Amarillo, Tex.; and (3) from the plantsite of Modern Maid Food Products located at Ponchatoula, La., to Miami, Fla.

NOTE.—Common control may be involved. If a hearing is deemed necessary, the applicant requests that it be held at New Orleans, La.

No. MC 117119 (Sub-No. 590), filed July 29, 1976. Applicant: WILLIS SHAW FROZEN EXPRESS, INC., P.O. Box 188, Elm Springs, Ark. 72728. Applicant's representative: L. M. McLean (Same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: (A) *Frozen foods*, from the facilities of Morton Frozen Foods located at Crozet, Va., to the facilities of Morton Frozen Foods located at Russellville, Ark.; (B) *frozen foods*, from Buffalo, N.Y., to the facilities of Morton Frozen Foods located at Russellville, Ark.; and (C) *prepared flour* (except in bulk), from Minneapolis, Minn., to the facilities of Morton Frozen Foods located at Russellville, Ark., restricted in (A), (B) and (C) to traffic originating at the named origins points and destined to the named destination points.

NOTE.—Common control may be involved. If a hearing is deemed necessary, the applicant requests that it be held at Washington, D.C.

No. MC 117765 (Sub-No. 211), filed July 30, 1976. Applicant: HAHN TRUCK LINE, INC., 5315 NW. 5th St., P.O. Box 75218, Oklahoma City, Okla. 73107. Applicant's representative: R. E. Hagan (same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes,

transporting: *Scrap or waste paper, paper, and paper products,* for recycling, from points in Iowa and Nebraska, to the plantsite of United States Gypsum Company, at North Kansas City, Mo.

NOTE.—If a hearing is deemed necessary, applicant requests it be held at Oklahoma City, Okla.

No. MC 117820 (Sub-No. 9), filed August 2, 1976. Applicant: AURELIA TRUCKING CO., a corporation, 2136 Pine Grove Avenue, Port Huron, Mich. 48060. Applicant's representative: Robert D. Schuler, 100 West Long Lake Road, Suite 102, Bloomfield Hills, Mich. 48013. Authority sought to operate as a *common carrier,* by motor vehicle, over irregular routes, transporting: *Processed fish,* in containers, in vehicles equipped with mechanical refrigeration, from the plantsite of Vita Food Products, Inc., located in Chicago, Ill., to points in Maryland, Massachusetts, New Jersey, New York, Ohio, and Pennsylvania.

NOTE.—Applicant holds contract carrier authority in MC 141918 and subs thereunder, therefore, dual operations may be involved. If a hearing is deemed necessary, the applicant requests it be held at either Chicago, Ill., or Washington, D.C.

No. MC 117940 (Sub-No. 184), filed July 30, 1976. Applicant: NATIONWIDE CARRIERS, INC., P.O. Box 104, Maple Plain, Minn. 55359. Applicant's representative: Allan L. Timmerman (same address as applicant). Authority sought to operate as a *common carrier,* by motor vehicle, over irregular routes, transporting: *Genreal commodities* (except foodstuffs, those of unusual value, explosives, commodities in bulk, household goods, and those requiring special equipment), (1) from points in Connecticut, Delaware, Maine, Maryland, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont, Virginia, and West Virginia, to points in Arizona, Arkansas, California, Colorado, Idaho, Iowa, Kansas, Missouri, Montana, Nebraska, Nevada, New Mexico, Oklahoma, Oregon, South Dakota, Texas, Utah, Washington, and Wyoming; and (2) from points in Illinois, Indiana, Michigan, Minnesota, Ohio, and Wisconsin, to points in Arizona, Arkansas, California, Colorado, Idaho, Iowa, Kansas, Missouri, Montana, Nebraska, Nevada, New Mexico, Oklahoma, Oregon, South Dakota, Texas, Utah, Washington, and Wyoming, restricted to shipments originating at the above named origins and destined to the facilities of or utilized by Gamble Skogmo, Inc., and its subsidiaries, at the above named destinations.

NOTE.—Applicant holds contract carrier authority in MC 114789 and subs thereunder, therefore, dual operations may be involved. Common control may also be involved. If a hearing is deemed necessary, the applicant requests it be held at Detroit, Mich.

No. MC 118202 (Sub-No. 60), filed July 27, 1976. Applicant: SCHULTZ TRANSIT, INC., P.O. Box 503, Winona, Minn. 55987. Applicant's representative: Val M. Higgins, 1000 First National Bank Building, Minneapolis, Minn. 55402. Authority sought to operate as a *common carrier,* by motor vehicle, over irregular routes, transporting: (a) *Candy and cherries,* from Winona, Minn., to Atlanta, Ga.; Boston, Mass.; Charlotte, N.C., and points in Illinois, Indiana, Kentucky, Michigan, New Jersey, New York, Ohio, and Pennsylvania, restricted to shipments originating at the plantsites of and warehouse facilities utilized by Schuler Cholcolates, Inc.; located at Winona, Minn., and destined to the destination points named above; (b) *new furniture,* in containers, from Arcadia, Wis., to points in Alabama, Colorado, Florida, Georgia, Illinois, Indiana, Iowa, Kansas, Kentucky, Maryland, Michigan, Minnesota, Missouri, Nebraska, New Jersey, New York, North Carolina, North Dakota, Ohio, Pennsylvania, South Carolina, South Dakota, Virginia, Wisconsin, and the District of Columbia, restricted to shipments originating at the plantsites of and warehouse facilities utilized by Ashley Furniture Corporation, located at Arcadia, Wis., and destined to the destination points named above; (c) *radio, phonograph, television, and stereo cabinets, record changer bases, and speaker boxes,* (1) from Winona and Red Wing, Minn., to points in that part of the New York, New York Commercial Zone as defined in *Commercial Zones and Terminals Areas,* 111 M.C.C. 123, within which local operations may be conducted pursuant to the partial exemption of Section 203(b)(8) of the Interstate Commerce Act ("The Exempt Zone") and to Los Angeles, Calif.

(2) from Winona and Red Wing, Minn,. to Seattle, Wash.; Jessup, Md., and points in Massachusetts, (3) from Red Wing and Winona, Minn., to Atlanta, Ga.; Dallas, Tex.; and Miami and Tampa, Fla.; and (4) from Arcadia, Wis., to Chatsworth, City of Industry, and Pacoima, Calif.; Miami, Fla.; Atlanta, Ga.; Boston, Braintree, Cambridge, and Framingham, Mass.; Bayonne and Jersey City, N.J.; Brooklyn and Glendale, N.Y.; and Dallas, Tex., restricted in (1), (2), (3), and (4) above to shipments originating at the plantsites of and warehouse facilities utilized by Winona Industrial Sales Corp. at said named origins and destined to the destination points named above; (d) (1) *radio, phonograph, and stereo cabinets, record changer bases, and speaker boxes,* from Chetek, Wis., to Paterson, N.J.; Batavia, N.Y.; Smithfield, N.C.; Indianapolis, Ind.; Sioux City, Iowa; and Los Angeles, Calif.; and points in Kings County, N.Y.; (2) new furniture, in containers, from Chetek, Wis., to points in the United States (except Alaska and Hawaii), restricted in (1) and (2) above to shipments originating at the plantsites of and warehouse facilities utilized by A. B. C. Chetek, Inc., located at Chetek, Wis.

(e) (1) *general commodities* (except those of unusual value, classes A and B explosives, household goods as defined by the Commission, commodities in bulk, and those requiring special equipment), from Winona, Minn., to points in the United States (except Alaska and Hawaii); and (2) *general commodities* (except those of unusual value, classes A and B explosives, household goods as defined by the Commission, commodities in bulk and those requiring special equipment), from points in Connecticut, Delaware, Illinois, Indiana, Iowa, Massachusetts, Maryland, Michigan, Missouri, New Jersey, New York, Ohio, Pennsylvania, West Virginia, and Wisconsin, to Winona, Minn., restricted in (1) above to shipments originating at the plantsites of and warehouse facilities utilized by Watkins Products, Inc., located at Winona, Minn., and restricted in (2) above to shipments originating in the origin territory named above and destined to Watkins Products, Inc., located at Winona, Minn.

NOTE.—Applicant states that the purpose of this application is to convert presently held permits as a contract carrier authority to certificates as a common carrier and to eliminate the issue of dual operations in pending and furture applications. Applicant presently holds extensive authority as a a common carrier. If a hearing is deemed necessary, the applicant requests that it be held at Minneapolis or St. Paul, Minn.

No. MC 118535 (Sub-No. 88), filed August 2, 1976. Applicant: TIONA TRUCK LINE, INC., 111 South Prospect, Butler, Mo. 64730. Applicant's representative: Wilburn L. Williamson, 280 National Foundation Life Bldg., 3535 NW. 58th St., Oklahoma City, Okla. 73112. Authority sought to operate as a *common carrier,* by motor vehicle, over irregular routes, transporting: *Minerals, mineral mixtures, feed and fertilizer materials* and *compounds and ingredients thereof,* from Galena, Kans., to points in Arkansas, Colorado, Illinois, Indiana, Iowa, Kentucky, Louisiana, Michigan, Minnesota, Mississippi, Missouri, Nebraska, New Mexico, North Dakota, Ohio, Oklahoma, South Dakota, Tennessee, Texas, and Wisconsin.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at Kansas City, Mo.

No. MC 118561 (Sub-No. 19), filed July 29, 1976. Applicant: HERBERT B. FULLER, doing business as FULLER TRANSFER COMPANY, 212 East Street, Maryville, Tenn. 37801. Applicant's representative: Robert E. Tate, P.O. Box 517, Evergreen, Ala. 36401. Authority sought to operate as a *common carrier,* by motor vehicle, over irregular routes, transporting: (1) *Foodstuffs* (except commodities in bulk, in tank vehicles), in mechanically refrigerated equipment, in mixed loads with meats, meat products, meat by-products, and articles distributed by meat packinghouses, from the plantsite of Oscar Mayer & Co., Inc., at or near Goodlettsville, Tenn., to points in Alabama, Arkansas, Florida, Georgia, Kentucky, Louisiana, Mississippi, North Carolina, South Carolina, Virginia, and West Virginia; and (2) *materials, equipment, and supplies* (except commodities in bulk), used in the manufacture, sale,

or distribution of foodstuffs, meats, meat products, meat by-products, and articles distributed by meat packinghouses, from points in Alabama, Arkansas, Florida, Georgia, Kentucky, Louisiana, Mississippi, North Carolina, South Carolina, Virginia, and West Virginia, to the plantsite and storage facilities utilized by Oscar Mayer & Co., Inc., at or near Goodlettsville, Tenn., restricted in Part (1) above, to shipments originating at the named facilities and destined to points in States named.

NOTE.—If a hearing is deemed necessary, applicant requests it be held at Nashville, Tenn., or Washington, D.C.

No. MC 119632 (Sub-No. 70), filed July 29, 1976. Applicant: REED LINES, INC., 634 Ralston Avenue, Defiance, Ohio 43512. Applicant's representative: John P. McMahon, 100 East Broad Street, Columbus, Ohio 43215. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: (1) *Food and food products* (except commodities in bulk), from the plantsite and storage facilities of Ovaltine Products Company, located at or near Villa Park, Ill., to points in Connecticut, Delaware, Indiana, Kentucky, Maryland, the Lower Peninsula of Michigan, New Jersey, New York, Ohio, Pennsylvania, West Virginia, and the District of Columbia; and (2) *materials, equipment, and supplies* used or useful in the manufacturing, production, packaging, and distribution of the commodities described in (1) above (except commodities in bulk), from points in Connecticut, Delaware, Indiana, Kentucky, Maryland, the Lower Peninsula of Michigan, New Jersey, New York, Ohio, Pennsylvania, West Virginia, and the District of Columbia, to the plantsite and storage facilities of Ovaltine Products Company, located at or near Villa Park, Ill.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at either Columbus, Ohio, or Chicago, Ill.

No. MC 119789 (Sub-No. 296), filed August 4, 1976. Applicant: CARAVAN REFRIGERATED CARGO, INC., P.O. Box 6188, Dallas, Tex. 75222. Applicant's representative: James K. Newbold, Jr. (same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Sheet steel and plastic water coolers, plastic cooling boxes, plastic articles, hardware, paper drinking cups*, and *plastic faucets*, from Winfield, Kans., to points in Alabama, Arizona, California, Colorado, Florida, Georgia, Kentucky, Louisiana, Mississippi, Montana, Nevada, North Carolina, Oregon, South Carolina, Tennessee, Utah, Virginia, Washington, and Wyoming.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at either Wichita, Kans., or Dallas, Tex.

No. MC 119988 (Sub-No. 96), filed July 22, 1976. Applicant: GREAT WESTERN TRUCKING CO., INC., Highway 103 East, P.O. Box 1384, Lufkin, Tex. 75901. Applicant's representative: Paul D. Angenend, P.O. Box 2207, Austin, Tex. 78768. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: (1) *Paper, paper products, advertising matter, printed matter, and steel and paper cores*, from Brookfield and New Berlin, Wis., to points in the United States (except Alaska and Hawaii); and (2) *materials, equipment, and supplies* used in the manufacture and distribution of the commodities named in (1) above, on return.

NOTE.—Applicant holds contract carrier authority in No. MC 140271 and subs thereunder, therefore, dual operations may be involved. If a hearing is deemed necessary, the applicant requests it be held at either Milwaukee, Wis., Dallas, Tex., or Washington, D.C.

No. MC 119988 (Sub-No. 97), filed July 28, 1976. Applicant: GREAT WESTERN TRUCKING CO., INC., Highway 103 East, P.O. Box 1384, Lufkin, Tex. 75901. Applicant's representative: Clayte Binion, 1108 Continental Life Building, Fort Worth, Tex. 76102. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: (1) *Paper, paper products, and wood pulp;* and (2) *materials and supplies* used in the manufacture or conversion of those commodities specified in (1) above, between points in Washington and West Feliciana Parishes, La., on the one hand, and, on the other, points in the United States (except Alaska and Hawaii), restricted in (1) and (2) above against the transportation of commodities in bulk, in tank vehicles.

NOTE.—Applicant holds contract carrier authority in MC 140271 and subs thereunder; therefore, dual operations may be involved. If a hearing is deemed necessary, the applicant requests it be held at either New Orleans or Baton Rouge, La.

No. MC 121496 (Sub-No. 2), filed July 22, 1976. Applicant: CANGO CORP., 110 Milam Building, Suite 2900, Houston, Tex. 77002. Applicant's representative: Eugene T. Liipfert, 1660 L Street, NW., Washington, D.C. 20036. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Petroleum products*, in bulk, in tank vehicles, including, but not limited to (1) petroleum products listed in Appendix XIII to the report in *Descriptions in Motor Carrier Certificates*, 61 M.C.C. 206 (1952), and (2) acetic anhydride; acetylene; acrylonitrile; aromatic distillate; alkyl-pyridine; aqua ammonia; butylene; butylene glycol; captan; chloroform; commercial cyclohexane; cyanhydrine; D.D.T. (technical); diallyl phthalate; dichloroisopropyl ether; diethanollamine; diethylene glycol; dimethyl formamide; dimethylamine; dinonyl phenol; dipropylene glycol; durene; ethane; ethyl chloride; "ethyl" fluid; ethylene amines; ethylene dibromide; ethylene oxide; ethylidene dichloride; formalin; gasoline, synthetic; glycerin; glycerol dichlorohydrin; hexane; iso-butane; iso-pentane; isopropyl alcohol; ketone, methyl vinyl pyridine; liquid elemental sulphur; liquid latex; liquid sulphur; methyl chloroform; methyl chloride; methyl ethyl ketone; methyl ethyl-pyridine; methyl isobutyl carbinol; methyl isobutyl ketone; methylene chloride; methylethyl benzene; nonyl phenol; octanes; orthoxylene; paraformaldehyde; paraxylene; perchlorethylens; polyethylene glycol; polyglycol; polythene; polyvinyl chloride; propyl formcel; propylene dichloride; propylene glycol; propylene oxide; propionic acid; pseudocumene; solvesse 100 and 150; styrene-butadiene latex; tetraethylene glycol; tetrapropylene; trichlorethane; triethanolamine; triethylene glycol; and tripropylene glycol; (a) Between points Texas (except Brooks, Cameron, Chambers, El Paso, Hidalgo, Jefferson, Jim Hogg, Kenedy, Kleberg, Newton, Orange, Starr, Willacy and Zapata Counties, Tex.) (b) from points in Brooks, Cameron, Chambers, El Paso Hidalgo, Jefferson, Jim Hogg, Kenedy, Kleberg, Newton, Orange, Starr, Willacy and Zapata Counties, Tex., to points in Texas.

NOTE.—Applicant states that the purpose of this application is to convert its Certificate of Registration to a Certificate of Public Convenience and Necessity. If a hearing is deemed necessary, the applicant requests it be held at Houston, Tex.

No. MC 121664 (Sub-No. 15), filed August 4, 1976. Applicant: G. A. HORNADY, CECIL M. HORNADY AND B. C. HORNADY, doing business as, HORNADY BROTHERS TRUCK LINE, P.O. Box 846, Monroeville, Ala. 36460. Applicant's representative: Gerald D. Colvin, Jr., 630 Frank Nelson Building, Birmingham, Ala. 35203. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transportings *Cement, lime and mortar mix*, from the facilities of National Cement Company, Inc., located at or near Ragland, Ala., and the facilities of Martin Marietta Cement, Southern Division, located at or near Roberta, Ala., to points in Florida, Georgia, Mississippi, Louisiana, Tennessee, North Carolina and South Carolina.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at either Birmingham or Mobile, Ala.

No. MC 123383 (Sub-No. 79), filed August 3, 1976. Applicant: BOYLE BROTHERS, INC., RD 2, Box 329 C, Medford, N.J. 08055. Applicant's representative: Chester A. Zyblut, 366 Executive Building, 1030 Fifteenth Street, NW., Washington, D.C. 20005. Authority sought to operate as a *common carrier, by* motor vehicle, over irregular routes, transporting: *General commodities* (except those of unusual value, Classes A and B explosives, household goods as defined by the Commission, commodities in bulk and commodities requiring special equipment), from the plantsite and storage facilities of Armstrong Cork Company located at E. Hempfield Township (Lancaster County), Pa., to points in Connecticut, Delaware, Maryland, Massachusetts, New Jersey, New York, Rhode Island, Virginia and District of Columbia, and *refused and rejected shipments* on return.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at Washington, D.C.

No. MC 123675 (Sub-No. 3), filed June 24, 1976. Applicant: ELI I. SOLDIER AND JAMES J. SOLDIER, a partnership, doing business as SOLDIER BROS. AUTO BODY TRANSIT LINES, 614 Paine Avenue, Toledo, Ohio 43605. Applicant's representative: Arthur R. Cline, 420 Security Building, Toledo, Ohio 43604. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Railway passenger car seats*, set up, wrapped, from Toledo, Ohio, to Philadelphia, Pa.

NOTE.—If a hearing is deemed necessary, applicant requests it be held at Columbus, Ohio, or Lansing, Mich.

No. MC 12374 (Sub-No. 24), filed July 28, 1976. Applicant: BULTER TRUCKING CO., P.O. Box 88, Woodland, Pa. 16881. Applicant's representative: Christian V. Graf, 407 North Front Street, Harrisburg, Pa. 17101. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Furnace lining scrap or refuse* from points in Alabama, Georgia, Illinois, Indiana, Kentucky, Maryland, Michigan, Missouri, New Jersey, New York, Ohio, Pennsylvania, and West Virginia, to the plantsites of North American Refractories Co., located at or near Ironton, Ohio; White Cloud, Mich.; Mt. Union, Curwensville, Womelsdorf and Little Gap, Pa., and Farber, Mo.

NOTE.—If a hearing is deemed necessary, the applicant requests that it be held at either Washington, D.C. or Harrisburg, Pa.

No. MC 124004 (Sub-No. 34), filed August 5, 1976. Applicant: RICHARD DAHN, INC., 620 West Mountain Road, Sparta, N.J. 07871. Applicant's representative: George A. Olsen, 69 Tonnele Ave., Jersey City, N.J. 07306. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Animal and poultry feed and animal poultry and pet feed ingredients and cracklings*, (1) between points in Delaware, Maryland and Virginia, on the one hand, and, on the other, points in North Carolina and South Carolina; (2) from points in New York, New Jersey and Pennsylvania, to points in South Carolina; (3) from points in Virginia, to points in Illinois, Indiana, Michigan, Minnesota, and Ohio and Wisconsin; and (4) from Silver City, N.C., Zanesville, Ohio, and Atlanta, Ga., to points in Connecticut, Delaware, Maryland, Massachussets, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Vermont.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at either Washington, D.C. or New York, N.Y.

No. MC 124211 (Sub-No. 278), filed August 2, 1976. Applicant: HILT TRUCK LINE, INC., P.O. Box 988, D.T. S., Omaha, Nebr. 68101. Applicant's representative: Thomas L. Hilt (Same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Junk, and scrap, rubber, plastic, rubber and plastic products, and cellular products, and waste materials* (except liquids, in bulk), between points in the United States, including Alaska, but excluding Hawaii.

NOTE.—Common control may be involved. If a hearing is deemed necessary, the applicant requests it be held at either Omaha, Nebr. or Washington, D.C.

No. MC 124896 (Sub-No. 15) (Correction) filed June 29, 1976, published in the FR issue of August 5, 1976, and republished, in part, as corrected this issue. Applicant: WILLIAMSON TRUCK LINES, INC., Thorne and Ralson Streets, P.O. Box 3485, Wilson, N.C. 27893. Applicant's representative: Jack H. Blanshan, 205 West Touhy Avenue, Suite 200, Park Ridge, Ill. 60068. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Peanuts, roasted peanuts and peanut products* (except in bulk, in tank vehicles), (5) from the facilities of Carolina Peanuts of Robersonville, Inc., located at or near Robersonville, N.C., to points in Alabama, Arkansas, Arizona, California, Colorado, Connecticut, Delaware, Florida, Georgia, Illinois, Iowa, Indiana, Kansas, Kentucky, Louisiana, Maine, Maryland Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Nebraska, New Hampshire, Nevada, New Jersey, New Mexico, New York, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, Tennessee, Texas, Utah, Vermont, Virginia, Washington, West Virginia, Wisconsin and the District of Columbia.

NOTE.—The purpose of this republication in part is to correct the territorial description in (5), which was previously published in error. If a hearing is deemed necessary, the applicant requests it be held at Washington, D.C.

No. MC 125023 (Sub-No. 40), filed July 28, 1976. Applicant: SIGMA-4 EXPRESS, INC., P.O. Box 9117, Erie, Pa. 16504. Applicant's representative: Paul F. Sullivan, 711 Washington Bldg., Washington, D.C. 20005. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: (1) *Malt beverages*, in containers, from Utica, N.Y., to points in Delaware, Maryland, North Carolina, Virginia and the District of Columbia; and (2) *empty malt beverage containers* in the reverse direction or on return.

NOTE.—If a hearing is deemed necessary, the applicant requests that it be held at Washington, D.C.

No. MC 126736 (Sub-No. 90), filed August 2, 1976. Applicant: FLORIDA ROCK & TANK LINES, INC., P.O. Box 1559, 155 East 21st Street, Jacksonville, Fla. 32206. Applicant's representative: Martin Sack, Jr., 1754 Gulf Life Tower, Jacksonville, Fla. 32207. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Ground dolomitic limestone* and *ground calcium limestone*, in bulk, in dump trailers, from points in Jackson County, Fla., to points in Alabama and Georgia.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at Jacksonville, Fla.

No. MC 127337 (Sub-No. 17), filed July 30, 1976. Applicant: CHET'S TRANSPORT, INC., Charlotte, Maine 04666. Applicant's representative: Lawrence E. Lindeman, Suite 1032, Pennsylvania Bldg., 425 13th St. NW., Washington, D.C. 20004. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Paper articles and plastic articles* (except in bulk, in tank vehicles), from Richmond, Va., and Woburn, Mass., to ports of entry on the International Boundary line between the United States and Canada, located in Maine, restricted to the transportation of shipments destined to points in the provinces of New Brunswick, Nova Scotia, Prince Edward Island, and Newfoundland, Canada.

NOTE.—If a hearing is deemed necessary, applicant requests it be held at Boston, Mass.

No. MC 128273 (Sub-No. 233), filed July 30, 1976. Applicant: MIDWESTERN DISTRIBUTION, INC., P.O. Box 189, 121 Humboldt St., Fort Scott, Kans. 66701. Applicant's representative: Elden Corban (same address as applicant). Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Plumbing fittings, fixtures, materials, equipment and supplies*, from Ferguson, Ky., to points in the United States (except Alaska, Hawaii, and Kentucky).

NOTE.—If a hearing is deemed necessary, applicant requests it be held at Washington, D.C.

No. MC 128570 (Sub-No. 19), filed July 30, 1976. Applicant: BROOKS ARMORED CAR SERVICE, INC., 13 East 35th Street, Wilmington, Del. 19899. Applicant's representative: Charles Ephraim, Suite 600, 1250 Connecticut Ave., NW, Washington, D.C. 20036. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Audit and accounting media, computerized billing forms, business documents and records related thereto*, between King of Prussia, Pa., on the one hand, and, on the other, points in New Castle, Kent and Sussex Counties, Del.

NOTE.—Applicant holds contract carrier authority in MC 115601 and subs thereunder, therefore dual operations may be involved. Common control may also be involved. If a hearing is deemed necessary, applicant requests it be held at Philadelphia, Pa.

No. MC 129923 (Sub-No. 12), filed July 6, 1976. Applicant: SHIPPERS TRANSPORTS, INC., 5005 Wheeler St., West Memphis, Ark. 72301. Applicant's representative: Edward G. Grogan, Suite 2020, First National Bank Bldg., Memphis, Tenn. 38103. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Peanuts*, roasted, in containers, (except in bulk), from Sylvester, Ga., to

points in the United States (except Alaska and Hawaii).

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at either Washington, D.C. or Atlanta, Ga.

No. MC 133095 (Sub-No. 104), filed July 27, 1976. Applicant: TEXAS CONTINENTAL EXPRESS, INC., P.O. Box 434, Euless, Tex. 76039. Applicant's representative: K. Edward Wolcott, 1600 First Federal Building, Atlanta, Ga. 30303. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Chain saws, generators, pumps and lawn and garden equipment, related materials, accessories and supplies*, from Gastonia, N.C., to points in the United States in and west of Kansas, Nebraska, North Dakota, Oklahoma, South Dakota, and Texas (except Alaska and Hawaii).

NOTE.—Applicant holds contract carrier authority in MC 136032 and subs thereunder, therefore dual operations may be involved. If a hearing is deemed necessary, the applicant requests that it be held at either Charlotte, N.C. or Washington, D.C.

No. MC 133363 (Sub-No. 7), filed July 21, 1976. Applicant: WILLIAM T. HARRIS AND THEATRIS HARRIS, doing business as: HARRIS BROS. CO., 1317 49th St., Philadelphia, Pa. 19143. Applicant's representative: Morris J. Levin, 1620 Eye St., NW. Washington, D.C. 20006. Authority sought to operate as a *contract carrier*, by motor vehicle, over irregular routes, transporting: *Insulated wire and lead terminals*, between the plants of Keystone Cable Corp. located in Philadelphia, Pa.; Detroit, Mich.; Dallas, Tex.; and Atlanta, Ga., under a continuing contract, or contracts, with Keystone Cable Corp.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at either Philadelphia, Pa. or Washington, D.C.

No. MC 134449 (Sub-No. 10), filed July 30, 1976. Applicant: LESTER V. MOZNIK, 3753 Grandview Highway, Burnaby 2, British Columbia, Canada. Applicant's representative: Michael D. Duppenthaler, Rm 515, 607 Third Avenue, Seattle, Wash. 98104. Authority sought to operate as a *contract carrier*, by motor vehicle, over irregular routes, transporting: *Pretzels*, from Visalia, Calif., to the ports of entry on the International Boundary line between the United States and Canada, located at or near Blaine, Lynden, and Sumas, Wash.; Eastport, Idaho; and Sweetgrass, Mont., restricted to shipments destined to Vancouver, B.C., and Calgary and Edmonton, Alberta, Canada, under contract with California Pretzel Co.

NOTE.—If a hearing is deemed necessary, applicant requests it be held at Seattle, Wash., or Los Angeles, Calif.

No. MC 134472 (Sub-No. 9), filed August 2, 1976. Applicant: RICHARD KUSTERMANN, doing business as KUSTERMANN TRUCK SERVICE, R.R. #2, Highland, Ill. 62249. Applicant's representative: Robert T. Lawley, 300 Reisch Building, Springfield, Ill. 62701. Authority sought to operate as a *contract carrier*, by motor vehicle, over irregular routes, transporting: (1) *Dairy products, foods and foodstuffs and paper and plastic supplies* used by drive-in restaurants and dairy stores, in containers in vehicles equipped with mechanical refrigeration, from Granite City, Ill., to points in Tennessee; (2) *margarine*, from Osceola, Ark., to Granite City, Ill.; (3) *empty milk cartons*, from Sikeston, Mo., to Granite City, Ill.; (4) *chocolate syrup*, from Humboldt, Tenn., to Granite City, Ill.; and (5) *cheese*, from Monett, Mo., to Granite City, Ill.; (1) through (5) above are for the account of and under a continuing contract, or contracts, with P.F.D. Supply Corporation.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at St. Louis, Mo.

No. MC 134534 (Sub-No. 10), filed August 2, 1976. Applicant: LUIS BASTERRECHEA, doing business as BASTERRECHEA DISTRIBUTING, 341 Colorado, Gooding, Idaho 83330. Applicant's representative: Jay L. Depew, P.O. Box 961, Twin Falls, Idaho 83301. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Fresh meats and packing house products*, from points in Gooding County, Idaho, to points in Cascade, and Silver Bow County, Mont.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at either Boise, Idaho, Salt Lake City, Utah or Denver, Colo.

No. MC 135007 (Sub-No. 54), filed June 23, 1976. Applicant: AMERICAN TRANSPORT, INC., 7850 "F" St., Omaha, Nebr. 68127. Applicant's representative: Frederick J. Coffman, 521 South 14th St., P.O. Box 81849, Lincoln, Nebr. 68501. Authority sought to operate as a *contract carrier*, by motor vehicle, over irregular routes, transporting: *Carpet lining and padding*, from Richmond, Va., to points in Arizona, Arkansas, California, Colorado, Idaho, Iowa, Kansas, Louisiana, Missouri, Montana, Nebraska, Nevada, New Mexico, Oklahoma, Oregon, South Dakota, Texas, Utah, Washington, and Wyoming, under a continuing contract, or contracts, with William Volker and Company.

NOTE.—Applicant holds common carrier authority in No. MC 135078 and subs thereunder, therefore dual operations may be involved. If a hearing is deemed necessary, the applicant requests it be held at either San Francisco, Calif. or Omaha, Nebr.

No. MC 135444 (Sub-No. 3), filed July 2, 1976. Applicant: SOUTHERN OHIO TRUCK LINES, INC., 3585 Hamilton-Trenton Road, Hamilton, Ohio 45011. Applicant's representative: Earl N. Merwin, 85 East Gay Street, Columbus, Ohio 43215. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Paper, and paper products;* and *materials and supplies* (except commodities in bulk), used or useful in the production, manufacture and distribution of paper and paper products, (1) between West Carrollton, Ohio, on the one hand, and, on the other, Binghampton and Sidney, N.Y.; and (2) between Oneonta, N.Y., on the one hand, and, on the other, Jeffersonville, Ind.; Louisville, Ky. and Aurora, Columbus, Cincinnati, Dayton, and Toledo, Ohio.

NOTE.—If a hearing is deemed necessary, the applicant requests that it be held at Columbus, Ohio.

No. MC 135895 (Sub-No. 11), filed August 2, 1976. Applicant: DON RAY BOYD AND JACKIE ROGERS, a partnership, doing business as B & R DRAYAGE COMPANY, P.O. Box 8534, Battlefield Station, Jackson, Miss. 39204. Applicant's representative: Christopher A. Shapley, P.O. Box 1295, Greenville, Miss. 38701. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: (1) *Pre-cast concrete products;* (2) *steel reinforcing bars, mesh and wire;* and (3) *articles* used in the manufacture, installation or construction of commodities described in (1) and (2) above, between the plantsites and warehouses of Con-Plex Corporation, a Division of U.S. Industries, Inc., located in Madison County, Miss. and points in Alabama, Arkansas, Louisiana, and Mississippi.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at either Jackson, Miss. or New Orleans, La.

No. MC 136008 (Sub-No. 75), filed Augut 2, 1976. Applicant: JOE BROWN COMPANY, INC., P.O. Box 1669, Ardmore, Okla. 73401. Applicant's representative: G. Timothy Armstrong, Suite 200, Timbergate Office Gardens, 6161 North May Avenue, Oklahoma City, Okla. 73112. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Sand, gravel, rock, caliche, ore, ready mix asphalt, aggregate, clinker, gypsum, clay and cement* mixed with aggregate in bulk, (1) between points in Colorado and Kansas (except points in Blue Rapids, Buffalo, and Chanute, Kans.; Baca, Bent, Crowley, Las Animas, and Prowers Counties, Colo.); (2) between points in Colorado and Oklahoma (except points in Baca, Bent, Crowley, Las Animas, and Prowers Counties, Colorado); (3) between points in Colorado and Texas (except points in Baca, Bent, Crowley, Las Animas, and Prowers Counties, Colo.); (4) between points in Kansas and Oklahoma (except points in Blue Rapids, Buffalo, and Chanute, Kans.; Craig and Ottawa Counties, Okla.; and Cherokee, Clark, Crawford, Finney, Ford, Grant, Gray, Hamilton, Haskell, Hodgeman, Kearney, Meade, Morton, Seward, Stanton, and Stevens Counties, Kans.; Marble City, Sallisaw, and Stroud, Okla.); (5) between points in Kansas and Texas (except points in Cherokee, Clark, Crawford, Finney, Ford, Grant, Gray, Hamilton, Haskell, Hodgeman, Kearney, Meade, Morton, Seward, Stanton, and Stevens Counties, Kans.); (6) between points in Oklahoma and Texas (except points in Freestone, Liberty, Navarro, Polk, and

Walker Counties, Tex.; Marble City, Mill Creek, and Sallisaw, Okla.; Atoka, Beaver, Beckham, Bryan, Choctaw, Cimarron, Craig, Custer, Dewey, Ellis, Greer, Harmon, Harper, Jackson, Kiowa, McCurtain, Major, Ottawa, Pushmataha, Roger Mills, Texas, Tillman, Washita, Woods, and Woodward Counties, Okla.; and (7) between points in Oklahoma, restricted in (1), (2) and (3) above against the transportation of gravel from Pueblo County, Colo.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at Oklahoma City, Okla.

No. MC 136247 (Sub-No. 12) (correction), filed July 9, 1976, published in the FEDERAL REGISTER issue of August 12, 1976, and republished as corrected this issue. Applicant: WRIGHT TRUCKING, INC., 409 17th Street SW., Jamestown, N. Dak. 58401. Applicant's representative: Richard P. Anderson, 502 First National Bank Building, Fargo, N. Dak. 58102. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Glass beverage containers*, from Rosemont, Minn., to Jamestown, N. Dak., restricted to traffic originating at the plantsite and storage facilities of Brockway Glass Company, Inc., at Rosemont, Minn., and destined to the plantsite and storage facilities of Coca-Cola Bottling Co., at Jamestown, N. Dak.

NOTE.—The purpose of this amendment is to indicate the proper destination as Jamestown, N. Dak., in lieu of James, N. Dak. If a hearing is deemed necessary, applicant requests it be held at Fargo or Jamestown, N. Dak., or Minneapolis, Minn.

No. MC 136301 (Sub-No. 5), filed August 4, 1976. Applicant: MER-LOU TRANSPORTATION, INC., P.O. Box 333, Millsboro, Del. 19966. Applicant's representative: Jack R. Turney, Jr., 2001 Massachusetts, Ave., NW., Washington, D.C. 20036. Authority sought as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Malt beverages*, from South Volney, N.Y., to Salisbury, Cambridge, and Centerville, Md.; points in Delaware; and points in Accomac and Northampton Counties, Va.

NOTE.—Common control and dual operations may be involved. If a hearing is deemed necessary, applicant requests it be held at Wilmington, Del., or Washington, D.C.

No. MC 136310 (Sub-No. 5) (amendment), filed June 1, 1976, published in the FEDERAL REGISTER issue of July 15, 1976, and republished as amended this issue. Applicant: R. WALKER TRUCKING, INC., 1409 East 19th, The Dalles, Oreg. 97058. Applicant's representative: Douglas A. Wilson, 303 East D Street, Yakima, Wash. 98901. Authority sought to operate as a *contract carrier*, by motor vehicle, over irregular routes, transporting: (1) *Flour, cereals, and seeds and grains*, in packages, from Seattle, Wash., to Portland, Oreg.; Phoenix, Ariz., and points in California; and (2) *bakery goods*, in packages, from Montebello, Calif., to Portland, Oreg.; Seattle, Wash; and Phoenix, Ari., for the account of, and under a continuing contract, or contracts, with Oroweat Foods Co., Grocery Products Div., located at Seattle, Wash. and Oroweat Baking Company, located at Montebello, Calif.

NOTE.—The purpose of this republication is to amend applicant's requested authority. If a hearing is deemed necessary, the applicant requests it be held at either Portland, Oreg. or Seattle, Wash.

No. MC 136315 (Sub-No. 9), filed August 4, 1976. Applicant: OLEN BURRAGE TRUCKING, INC., Route No. 9, Box 22-A, Philadelphia, Miss. 39350. Applicant's representative: Fred W. Johnson, Jr., 1500 Deposit Guaranty Plaza, P.O. Box 22628, Jackson, Miss. 39205. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: (1) *Lumber and lumber products*, from the plantsite of Crown Zellerbach Corporation, located at Joyce, La., to points in Alabama, Arkansas, Florida, Illinois, Indiana, Kentucky, Mississippi, Missouri, Ohio, Oklahoma, Tennessee, and Texas; and (2) *posts, poles and piling*, from the plantsite of Crown Zellerbach Corporation, located at Urania, La., to points in Alabama, Arkansas, Colorado, Iowa, Kansas, Minnesota, Nebraska, Illinois, Indiana, Oklahoma, Texas, and Wisconsin.

NOTE.—Applicant holds contract carrier authority in MC 123905 and subs thereunder, therefore dual operations may be involved. If a hearing is deemed necessary, the applicant requests it be held at Jackson, Miss.

No. MC 136489 (Sub-No. 2), filed August 2, 1976. Applicant: RALPH L. NORTON, Route 15, P.O. Box 27, Jericho, Vt. 05465. Applicant's representative: W. Norman Charles, 80 Bay Street, Glens Falls, N.Y. 12801. Authority sought to operate as a *contract carrier*, by motor vehicle, over irregular routes, transporting: (1) *Malt beverages*, from Secaucus, N.J., and Fogelsville, Pa., to Burlington, Vt.; (2) *empty malt beverage containers*, from Burlington, Vt., to Secaucus, N.J., and Fogelsville, Pa.; (3) *soda*, from Burlington, Vt., to Claremont, N.H., and Malone and Ogdensburg, N.Y.; (4) *empty glass bottles*, from New York, N.Y., and Glenshaw, Pa., to Burlington, Vt.; and (5) *wine*, from Newark, N.J., and Long Island City, N.Y., to Burlington, Vt.; (1) through (5) above are under a continuing contract, or contracts, with Vermont Fruit & Grocery Company, Inc.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at either Burlington or Montpelier, Vt.

No. MC 138144 (Sub-No. 11), filed August 5, 1976. Applicant: FRED OLSON CO., INC., 6022 W. State Street, Milwaukee, Wis. 53213. Applicant's representative: Daniel C. Sullivan, 327 South La Salle Street, Chicago, Ill. 60604. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: (1) *Iron and steel articles;* and (2) *materials and supplies* used in the manufacture and distribution of electric motors and generators, from Earlville, Ill., to Wausau, Wis.

NOTE.—Common control may be involved. If a hearing is deemed necessary, the applicant requests it be held at either Milwaukee, Wis., or Chicago, Ill.

No. MC 138256 (Sub-No. 5), filed August 2, 1976. Applicant: INTERIOR TRANSPORT, INC., P.O. Box 3347, 2124 Waterworks Way, Spokane, Wash. 99220. Applicant's representative: George H. Hart, 1100 IBM Bldg., Seattle, Wash. 98101. Authority sought to operate as a *contract carrier*, by motor vehicle, over irregular routes, transporting: (1) *Metal building materials*, from Minneapolis, Minn., to points in Arizona, California, Colorado, Idaho, Illinois, Iowa, Kansas, Missouri, Montana, Nebraska, Nevada, New Mexico, North Dakota, Oklahoma, Oregon, South Dakota, Texas, Utah, Washington, Wisconsin, and Wyoming, under a continuing contract, or contracts,, with Gifford-Hill Company, Inc.; and (2) *steel coil*, from points in California, Oregon, Utah, and Washington, to Minneapolis, Minn., under a continuing contract, or contracts, with Gifford-Hill Company, Inc.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at either Seattle or Spokane, Wash.

No. MC 138741 (Sub-No. 24), filed August 4, 1976. Applicant: E. K. MOTOR SERVICE, INC., 2005 North Broadway, Joliet, Ill. 60435. Applicant's representative: Tom B. Kretsinger, 910 Brookfield Bldg., 101 West 11th St., Kansas City, Mo. 64105. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Building materials* (except commodities in bulk), from the plantsite, shipping and warehouse facilities of GAF Corporation, in Posey and Vanderburgh Counties, Ind., to points in Arkansas, Iowa, Kansas, Nebraska, Oklahoma, and Wisconsin.

NOTE.—Common control may be involved. If a hearing is deemed necessary, applicant requests it be held at Chicago, Ill., or Washington, D.C.

No. MC 139495 (Sub-No. 156), filed August 3, 1976. Applicant: NATIONAL CARRIERS, INC., 1501 East 8th Street, P.O. Box 1358, Liberal, Kans. 67901. Applicant's representative: Herbert Alan Dubin, 1819 H St. NW., Suite 1030, Washington, D.C. 20006. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Personal care products*, from the facilities of the Warner-Lambert Company, located at or near Milford and Orange, Conn., to the facilities of Warner-Lambert Company, located at or near Lititz, Pa.; Elk Grove Village, Ill.; Grand Prairie, Tex.; Anaheim, Calif.; and Milwaukee, Oreg., restricted to shipments originating at and destined to the facilities of the Warner-Lambert Company.

NOTE.—Applicant holds contract carrier authority in MC 133106 and subs thereunder, therefore, dual operations may be involved. If a hearing is deemed necessary, applicant requests it be held at Washington, D.C.

No. MC 134592 (Sub-No. 9), filed August 2, 1976. Applicant: HERB MOORE

AND HAZEL MOORE, doing business as H & H TRUCKING CO., 10360 North Vancouver Way, Portland, Oreg. 97217. Applicant's representative: Robert G. Simpson, 1200 Standard Plaza, Portland, Oreg. 97204. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Wine, champagne, brandy, and malt beverages*, between points in California, on the one hand, and, on the other, points in Idaho, Oregon, and Washington.

NOTE.—Common control may be involved. If a hearing is deemed necessary, the applicant requests it be held at either Portland, Oreg., San Francisco, Calif., or Seattle, Wash.

No. MC 139858 (Sub-No. 8), filed July 22, 1976. Applicant: AMSTAN TRUCKING INC., 1255 Corwin Avenue, Hamilton, Ohio 45015. Applicant's representative: Chandler L. Van Orman, 704 Southern Building, Washington, D.C. 20005. Authority sought to operate as a *contract carrier*, by motor vehicle, over irregular routes, transporting: *General commodities* (except commodities in bulk, those of unusual value, Classes A and B explosives, household goods as defined by the Commission, and those which require the use of special equipment), from the warehouse and distribution facilities of American Standard, located at Hamilton, Ohio, to points in and west of Colorado, Montana, New Mexico, and Wyoming, under a continuing contract, or contracts, with American Standard, Inc.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at either Cincinnati, Ohio, or Washington, D.C.

No. MC 140693 (Sub-No. 8), filed August 3, 1976. Applicant: BEER TRANSPORTATION COMPANY, a corporation, 1120 Germantown Ave., Philadelphia, Pa. 19123. Applicant's representative: Edward J. Kiley, 1730 M St. NW., Suite 501, Washington, D.C. 20036. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Malt, beverages*, in containers, and *related advertising materials*, from Baltimore, Md., to points in Connecticut, Maine, Massachusetts, New Hampshire, New Jersey, New York, Rhode Island, and Vermont.

NOTE.—If a hearing is deemed necessary, applicant requests it be held at Philadelphia, Pa., or Washington, D.C.

No. MC 141076 (Sub-No. 7), filed August 2, 1976. Applicant: ROGERS MOTOR LINES, INC., R.D. No. 2, P.O. Box 388 D2, Hackettstown, N.J. 07840. Applicant's representative: Morton E. Kiel, Suite 6193, 5 World Trade Center, New York, N.Y. 10048. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Foodstuffs* (except in bulk), in vehicles equipped with mechanical refrigeration, from Newburgh, N.Y., to the District of Columbia.

NOTE.—Applicant holds contract carrier authority in No. MC 140781, therefore, dual operations may be involved. If a hearing is deemed necessary, the applicant requests it be held at New York, N.Y.

No. MC 141114 (Sub-No. 1), filed July 21, 1976. Applicant: RETAILERS DELIVERY FACILITY CO., INC., 901 Washington Street, Wilmington, Del. 19899. Authority sought to operate as a *contract carrier*, by motor vehicle, over irregular routes, transporting: *Garden supplies, lawn ornaments, lawn tools, assembled garden trellises, patio blocks, curbstone, paving and construction materials, flower boxes, pots, and containers*, from points in the United States on and west of a line beginning at the mouth of the Hudson River where it joins the Atlantic Ocean, thence northerly along the east bank of the Hudson River, over U.S. Highway 9, to the International Boundary line between the United States and Canada, to points in the United States in and east of Arkansas, Iowa, Minnesota, Missouri, and Texas, under a continuing contract, or contracts, with Lawn & Garden Shops Co., Inc.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at Washington, D.C.

No. MC 141141 (Sub-No. 4) (Amendment), filed July 2, 1976, published in the FEDERAL REGISTER issue of August 5, 1976, and republished as amended this issue. Applicant: NAVAJO LINE, INC., Route No. 1, Moncure, N.C. 27559. Applicant's representative: Wilmer B. Hill, 805 McLachlen Bank Bldg., 666 Eleventh St., N.W., Washington, D.C. 20001. Authority sought to operate as a *contract carrier*, by motor vehicle, over irregular routes, transporting: *Clay products* (except commodities in bulk), on special I-beam flatbed trailers with hydraulic unloaders, (1) from points in Chatham and Wake Counties, N.C., to points in Ohio and West Virginia; (2) from Nitro, W. Va., Coal Grove, Ohio and Minerva, Ohio, to points in North Carolina, South Carolina, and Virginia, and (3) from points in York County, S.C., to points in North Carolina, South Carolina, Virginia, and West Virginia, under a continuing contract, or contracts, with Cherokee Brick Company of North Carolina.

NOTE.—The purpose of this republication is (A) to indicate the correct name of the Applicant as "Navajo Line, Inc." in lieu of "Navajo Lines, Inc." as was previously published; and (B) to indicate in part (2) of the territorial description the origin point of Coal Grove, Ohio in lieu of Ironton, Ohio. If a hearing is deemed necessary, the applicant requests it be held at either Raleigh, N.C. or Washington, D.C.

No. MC 141759 (Sub-No. 4), filed August 2, 1976. Applicant: OHIO PACIFIC EXPRESS, INC., 6914 Conservation Drive, Springfield, Va. 22153. Applicant's representative: Thomas F. Kilroy, P.O. Box 624, Springfield, Va. 22150. Authority sought to operate as a *contract carrier*, by motor vehicle, over irregular routes, transporting: *Plastic materials, plastic articles and chemical compounds* (except in bulk, in tank or hopper vehicles), between Ottowa, Ill. and Morgantown, Parkersburg, and Washington, W. Va., on the one hand, and, on the other, points in Alabama, Arkansas, California, Connecticut, Delaware, Georgia, Indiana, Iowa, Kentucky, Louisiana, Maryland, Massachusetts, Michigan, Mississippi, Missouri, New Jersey, New York, North Carolina, Ohio, Pennsylvania, South Carolina, Tennessee, Texas, Virginia, and West Virginia, under a continuing contract, or contracts, with Borg-Warner Chemicals.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at Columbus, Ohio.

No. MC 141918 (Sub-No. 5), filed August 2, 1976. Applicant: AURELIA TRUCKING CO., a Corporation, 2136 Pine Grove Avenue, Port Huron, Mich. 48060. Applicant's representative: Robert D. Schuler, 100 West Long Lake Road, Suite 102, Bloomfield Hills, Mich. 48013. Authority sought to operate as a *contract carrier*, by motor vehicle, over irregular routes, transporting: *Foodstuffs* (except in bulk), from Duluth, Minn., to points in Illinois, Indiana, and Michigan, restricted to a transportation service to be performed under a continued contract or contracts with Jeno's Inc., of Duluth, Minn.

NOTE.—Applicant holds common carrier authority in MC 117820 and subs thereunder, therefore dual operations may be involved. If a hearing is deemed necessary, the applicant requests it be held at either Minneapolis, Minn., Chicago, Illinois or Washington, D.C.

No. MC 142071 (Sub-No. 1), filed July 28, 1976. Applicant: AMERICAN TERMINALS, INC., 1187 N. Kraemer, Anaheim, Calif. 92806. Applicant's representative: Stanley Gustafson, Suite 909, World Trade Center 333 S. Flower St., Los Angeles, Calif. 90071. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Swimming pool and flooring glazed and quarried tile products and related bonding materials*, (1) between the plantsites of Quality Marble and Tile Company, located in Atlanta, Ga., Baltimore, Md., Dallas, Tex., Englewood, Colo., Lenexa, Kans., Phoenix, Ariz., and Anaheim, North Hollywood, Sacramento, San Diego, and San Leandro, Calif.; (2) from the plantsites of U.S. Ceramics located in Houston, Miss., and Canton, Ohio, to the plantsites of Quality Marble and Tile Company as listed in paragraph (1) above; (3) from the plantsites of Chicago Mastics located in Hamilton, Ohio, to the plantsites of Quality Marble and Tile Company as listed in paragraph (1) above; and (4) from Miami, Fla., Mobile, Ala., and Long Beach, Los Angeles, Oakland, San Francisco and San Pedro, Calif., to the plantsites of Quality Marble and Tile Company as listed in paragraph (1) above, restricted against transportation between points in California.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at either Washington, D.C. or San Francisco, Calif.

No. MC 142186 (Sub-No. 3), filed August 4, 1976. Applicant: WHEELS WEST, INC., 612 159th Place SE., Bellevue, Wash. 98008. Applicant's representative: Henry C. Winters, 100 IBM Building,

Seattle, Wash. 98101. Authority sought to operate as a *contract carrier*, by motor vehicle, over irregular routes, transporting: *Tire shop equipment and supplies, and parts and accessories*, for automobiles, trucks, utility trailers, mobile homes, and for off-road pneumatic-tired machinery, from points in California, Illinois, Indiana, Iowa, Kentucky, Michigan, Missouri, Ohio, Pennsylvania, and Wisconsin, to points in Idaho, Montana, Oregon, Utah, and Washington, restricted to a transportation service to be performed under a continuing contract or contracts, with Six Robblees' Inc., at Seattle, Wash., and Six Robblees', Inc., at Portland, Oreg.

NOTE.—If a hearing is deemed necessary, applicant requests it be held at Seattle, Wash.

No. MC 142196 (Sub-No. 2), filed July 27, 1976. Applicant: THREE-B'S TRANSPORTATION, INC., 230 South 30th Street, Philadelphia, Pa. 19104. Applicant's representative: J. Michael Farrell, 1725 K Street, N.W., Suite 814, Washington, D.C. 20006. Authority sought to operate as a *contract carrier*, by motor vehicle, over irregular routes, transporting: *Such foods, commodities and equipment* as are used in connection with the operation of hotels, restaurants, and others engage in food operations, from the facilities of Buff-Hanley Paper Company, located at Baltimore and Columbia, Md.; Wood Ridge, N.J.; and Philadelphia, Pa., to points in Connecticut, Delaware, Maryland, Massachusetts, New Jersey, New York, North Carolina, Pennsylvania, Rhode Island, and Virginia, under a continuing contract, or contracts, with Buff-Hanley Paper Company.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at either Washington, D.C. or Philadelphia, Pa.

No. MC 142207 (Sub-No. 1), filed July 29, 1976. Applicant: GULF COAST TRUCK SERVICES, INC., P.O. Box 29486, New Orleans, La. 70189. Applicant's representative: Bruce E. Mitchell, 3379 Peachtree Rd., NE., Suite 375, Atlanta, Ga. 30326. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Lumber, lumber and wood products*, from the facilities of Crown Zellerbach, located at or near Joyce, La., to points in Alabama, Arkansas, Florida, Georgia, Illinois, Indiana, Kansas, Kentucky, Louisiana, Mississippi, Missouri, Ohio, Oklahoma, Tennessee, and Texas.

NOTE.—Common control may be involved. If a hearing is deemed necessary, applicant requests it be held at New Orleans, La.

No. MC 142308, filed July 23, 1976. Applicant: BOB FORMAN ASSOCIATES, INC., 3221 Commerce Street, Dallas, Tex. 75226. Applicant's representative: Jack L. Coke, Jr., 4555 First National Bank Building, Dallas, Tex. 75202. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *New furniture*, in cartons, or in paper, polyurethane and/or sisal wrap, from Dallas, Houston and Lubbock, Tex., to points in Texas, restricted to traffic having a prior movement by rail.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at either Greensboro or Charlotte, N.C. or Dallas, Tex.

No. MC 142314, filed July 21, 1976. Applicant: EVANS TRUCKING, INC., 52 Harrison Ave., Branford, Conn. 06405. Applicant's representative: William J. Meuser, 86 Cherry St., P.O. Box 507, Milford, Conn. 06460. Authority sought to operate as a *contract carrier*, by motor vehicle, over irregular routes, transporting: *Powdered shale* (aggregate), between Cohoes and Saugerties, N.Y., on the one hand, and, on the other, Westbrook, Conn., under a continuing contract, or contracts, with Westbrook Concrete Block Co., Inc.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at either Hartford, Conn. or New York, N.Y.

PASSENGER APPLICATIONS

No. MC 59717 (Sub-No. 8), filed August 4, 1976. Applicant: JACKSONVILLE BUS LINE CO., a Corporation, 2106 East Cornell Street, Springfield, Ill. 62703. Applicant's representative: Melvin Routman, 300 Reish Building, Springfield, Ill. 62702. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: *Passengers, and their baggage* in the same vehicle with passengers, in charter and special operations, in all expense sightseeing and pleasure tours, between points in Hancock, McDonough, Fulton, Peoria, Tazewell, Mason, Menard, Sangamon, Cass, Brown, Schuyler, Adams, Morgan, Calhoun, Pike, Scott, Macoupin, Greene, Jersey, Montgomery, Madison, St. Clair, Logan, McLean and Dewitt Counties, Ill., Marion, Lewis and St. Louis Counties, Mo., including the St. Louis-East St. Louis, Mo.-Kans. Commercial Zone and Lee County, Iowa, on the one hand, and, on the other, points in the United States, including Alaska but excluding Hawaii.

NOTE.—If a hearing is deemed necessary, applicant requests it be held at Springfield, Ill. The application is filed with applicant's initial verified statements.

No. MC 84697 (Sub-No. 1), filed June 25, 1976. Applicant: LEIPHART BUS COMPANY, INC., R.D. No. 12, Hellam Branch, York, Pa. 17406. Applicant's representative: Penny Bonadonna, 141 E. Market Street, P.O. Box 709, York, Pa. 17405. Authority sought to operate as a *common carrier*, by motor vehicle over irregular routes, transporting: *Passengers and their baggage*, in groups, in charter operations, between York, Pa., and points within 15 miles thereof, and points in New York, North Carolina, Ohio, Virginia and West Virginia.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at either York, Harrisburg or Philadelphia, Pa.

BROKER APPLICATION

No. MC 130198 (Sub-No. 1), filed August 2, 1976. Applicant: ROBERT GAVIN & ASSOCIATES, INC., 2258 South Kinnickinnic Avenue, Milwaukee, Wis. 53207. Applicant's representative: F. Thomas Olson, 211 West Wisconsin Avenue, Milwaukee, Wis. 53203. Authority sought to engage in operation, in interstate or foreign commerce, as a *broker* at Milwaukee, Wis., to sell or offer to sell the transportation by motor, rail, water or air carreirs, of *Individual passengers and groups of passengers, and their baggage*, in special and charter operations, in round-trip, all-expense tours, beginning and ending at points in Adams, Brown, Calumet, Columbia, Dane, Dodge, Fond du Lac, Green Lake, Jefferson, Langlade, Lincoln, Manitowoc, Marathon, Marquette, Oneida, Outagamie, Ozaukee, Portage, Walworth, Waupaca, Waushara, Winnebago and Wood Counties, Wis., and extending to points in the United States, including Alaska and Hawaii.

NOTE.—If a hearing is deemed necessary, the applicant requests it be held at Milwaukee, Madison or Green Bay, Wis.

FINANCE APPLICATIONS

The following applications seek approval to consolidate, purchase, merge, lease operating rights and properties, or acquire control through ownership of stock, of rail carriers or motor carriers pursuant to Sections 5(2) or 210a(b) of the Interstate Commerce Act.

An original and two copies of protests to the granting of the requested authority must be filed with the Commission on or before October 12, 1976. Such protest shall comply with Special Rules 240(c) or 240(d) of the Commission's *General Rules of Practice* (49 CFR § 1100.240) and shall include a concise statement of protestant's interest in the proceeding. A copy of the protest shall be served concurrently upon applicant's representative, or applicant if no representative is named.

No. MC-F-12913. Authority sought for purchase by RYDER TRUCK LINES, INC., 2050 Kings Road, Jacksonville, FL., 32203, of a portion of the operating rights of ASSOCIATED TRANSPORT, INC., THOMAS J. CAHILL, TRUSTEE IN BANKRUPTCY, c/o Arthur S. Olick, 39th Floor, 630 Fifth Avenue, New York, N.Y., 10020, and for acquisition by IU TRANSPORTATION SERVICES, INC., 1105 N. Market St., Wilmington, Del., 19801, The Wilmington Tower, which is in turn controlled by IU INTERNATIONAL CORPORATION, The Wilmington Tower, 1105 N. Market St., Wilmington, Del., 19801, of control of such rights through the purchase. Applicants' attorneys: H. Beatty Chadwick, 1500 Walnut Street, Philadelphia, PA., 19102, Roland Rice, Suite 501, Perpetual Bldg., Washington, D.C., 20004, and Fritz R. Kahn, 1660 L Street, NW., Washington, D.C. 20036. Operating rights sought to be transferred: *General commodities*, with exceptions as a *common carrier* over irregular routes between points in Suffolk and Middlesex Counties, Mass., on the one hand, and, on the other, points in New Hampshire; between points in Rhode Island, on the one hand, and, on the other, points in New Hampshire, moving through Boston, Mass., and

points within 10 miles of Boston, in Suffolk and Middlesex Counties; between points in that part of Maine, on and south of a line beginning at the New Hampshire-Maine State line, and extending along Maine Highway 16 to junction unnumbered highway (formerly portion Maine Highway 16) near Milo, thence along unnumbered highway to junction Maine Highway 6 (formerly portion Maine Highway 16) near Howland, thence along Maine Highway 6 to the United States-Canada Boundary line, at New Brunswick, on the one hand, and, on the other, points in that part of Massachusetts beginning at a point on and east of a line and extending in a general northerly direction along Massachusetts Highway 32 to junction Massachusetts Highway 2, thence along Massachusetts Highway 2 to junction Massachusetts Highway 78, and thence along Massachusetts Highway 78 to the Massachusetts-New Hampshire State line, except points in Hampden County, and those on Cape Cod east and south of Cape Cod Canal; between points in Massachusetts, on the one hand, and, on the other, points in New Hampshire, moving through Suffolk and Middlesex Counties, Mass., any duplication of authority granted herein or to the extent that such authority duplicates any heretofore granted to or now held by carrier shall not be construed as conferring more than one operating right. Vendee is authorized to operate as a *common carrier* in all the States in the United States (except Alaska and Hawaii). Application has been filed for temporary authority under section 210a(b).

NOTE.—Applicant does not intend to tack its irregular route authority with those of the vendor.

No. MC–F–12923. Authority sought for purchase by JACK B. KELLEY, INC., Route 1, Box 400, Amarillo, TX 79106, of a portion of the operating rights of FAIRWAY TRANSIT, INC., N. 10 W. 24730 Highway TJ, Pewaukee, WI 53072, and for acquisition by JACK B. KELLEY, of Amarillo, TX 79106, of control of such rights through the purchase. Applicants' attorney: Austin L. Hatchell, 1102 Perry Brooks Bldg., Austin, TX 78701. Operating rights sought to be transferred: *Liquid Oxygen, Liquid Nitrogen and Liquid Argon*, in tank vehicles, as a *common carrier* over irregular routes from Waukesha, Wisconsin, to points in Michigan, Indiana, Ohio, Illinois, Minnesota and Iowa, with no transportation for compensation on return except as otherwise authorized, with restriction. Vendee is authorized to operate as a *common carrier* in all the States in the United States including District of Columbia, but excluding Alaska and Hawaii. Application has been filed for temporary authority under section 210a(b).

NOTE.—No. MC–123392 (Sub-No. 69) is a directly related matter.

No. MC–F–12946. Authority sought for purchase by BILKWAYS EXPRESS, CO., 830 Old Corlies Avenue, Neptune, N.J., 07753, of the operating rights of BENTON'S HARTFORD EXPRESS, INC., 1 Cooper Lane, Stafford Springs, CT., 06076, and for acquisition by WILLIAM J. KORTENHAUS, 510 Bowne Rd., Wayside, N.J., 07712, and ROBERT A. KORTENHAUS, 18 Pitney Ave., Spring Lake, N.J., 07762, of control of such rights through the purchase. Applicants' attorneys: Thomas W. Murrett, 342 North Main Street, West Hartford, CT., 06117, and John L. Alfano and Edward M. Alfano, 550 Mamaroneck Avenue, Harrison, N.Y., 10528. Operating rights sought to be transferred: Under a certificate of registration in Docket No. MC–57346 (Sub No. 1) covering the transportation of general commodities, as a common carrier, in interstate commerce, within the State of Connecticut. Vendee is authorized to operate as a *common carrier* in Connecticut, New York, and New Jersey. Application has been filed for temporary authority under section 210a (b).

NOTE.—No. MC–73616 (Sub-No. 3) is a directly related matter.

No. MC–F–12947. Authority sought for control and merger by McLEAN TRUCKING CO., 617 Waughtown Street, P.O. Box 213, Winston-Salem, NC 27102, of the operating rights and property of CRESCENT MOTOR LINE, 7105 Lone Oak Road, Spartanburg, SC 29302, of control of such rights and property through the transaction. Applicants' attorneys: David G. Macdonald, Esq., Macdonald, & McInerny, 1000 16th Street, NW., Washington, D.C., 20036 and Horace L. Bomar, Esq., Suite 305, Montgomery Building, Spartanburg, S.C., 29301. Operating rights sought to be controlled and merged: *Commodities generally*, except those of unusual value, and except dangerous explosives (other than small-arms ammunition), livestock household goods as defined in Practices of Motor Common Carriers of Household Goods, 17 M.C.C. 467, loose-bulk commodities, and those requiring special equipment, as a *common carrier* over irregular routes from Charleston, S.C., Savannah and Port Wentworth, Ga., to points and places in Spartanburg and Greenville, Cys., S.C., and return with no transportation for compensation, except as otherwise authorized; *Textile Products, Bagging, Bags and Cotton-Baling Ties*, from points and places in Anderson, Greenville, Spartanburg, and Union Cy., S.C., and Savannah and Port Wentworth, Ga., and return with no transportation for compensation, except as otherwise authorized; *General commodities*, except those of unusual value, classes A and B explosives, livestock, household goods as defined by the Commission, commodities in bulk, and those requiring special equipment, between Spartanburg and Lyman, S.C., on the one hand, and, on the other, points in Georgia, North Carolina, and South Carolina within 100 miles of Spartanburg; *Calcium carbide*, in containers, limited to shipments weighing not less than 20,000 pounds each from any one consignor, from Ivanhoe, Va., and points within 2 miles of Ivanhoe, to points in North Carolina and South Carolina; and *Empty calcium carbide containers*, from the above specified destination points to Ivanhoe, Va., and points within 2 miles of Ivanhoe; *Canned goods*, limited to shipments weighing not less than 20,000 pounds each from any one consignor, from points in Spartanburg County, S.C., except Spartanburg and Lyman, to points in North Carolina within 100 miles of Spartanburg, with no transportation for compensation on return except as otherwise authorized; *Calcium carbide*, over irregular routes, from Ivanhoe, Va., to points in Alabama and Georgia;

Empty containers used in transportation of calcium carbide, from points in Alabama and Georgia to Ivanhoe, Va.; *General commodities*, with exceptions, from Charleston, S.C., and Savannah and Port Wentworth, Ga., to points in South Carolina within 100 miles of Spartanburg, S.C., points in that part of Georgia on and north of a line extending from the Alabama-Georgia State line near Columbus, Ga., over U.S. Highway 80 to Macon, Ga., thence along Georgia Highway 49 to Milledgeville, Ga., thence along Georgia Highway 22 to Sparta, Ga., thence along Georgia Highway 16 to Warrenton, Ga., and thence along U.S. Highway 278 to the Georgia-South Carolina State line, and points in North Carolina on and north of a line extending from the North Carolina-South Carolina State line near Rockingham, N.C., over U.S. Highway 1 to the North Carolina-Virginia State line; and *Textile Products, Bagging, Bags, and Cotton-Bailing Ties*, from points in South Carolina within 100 miles of Spartanburg, S.C., from points in that part of Georgia on and north of a line extending from the Alabama-Georgia State line near Columbus, Ga., along U.S. Highway 80 to Macon, Ga., thence along Georgia Highway 49 to Milledgeville, Ga., thence along Georgia Highway 22 to Sparta, Ga., thence along Georgia Highway 16 to Warrenton, Ga., thence along U.S. Highway 278 to the Georgia-South Carolina State line, and from points in North Carolina on and north of a line extending from the North Carolina-South Carolina State line near Rockingham, N.C., over U.S. Highway 1 to the North Carolina-Virginia State line, to Charleston, S.C., and Savannah and Port Wentworth, Ga. Vendee is authorized to operate as a common carrier in Alabama, Arkansas, Connecticut, Delaware, District of Columbia, Florida, Georgia, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Nebraska, New Hampshire, New Jersey, New York, North Carolina, Ohio, Pennsylvania, Rhode Island, South Carolina, Tennessee, Texas, Vermont, Virginia, West Virginia, and Wisconsin. Application has not been filed for temporary authority under Section 210a(b).

NOTE.—No. MC–31389 is a directly related matter.

No. MC–F–12949. Application under Section 5(1) of the Interstate Commerce

Act for approval of an agreement between common carriers for the pooling of traffic. Applicants: CONSOLIDATED FREIGHTWAYS CORPORATION OF DELAWARE, 175 Linfield Drive, Menlo Park, CA., 94025 (MC-42487), (A) BEST-WAY MOTOR FREIGHT, INC., 1765 6th Avenue, South Seattle, WA., 98134 (MC 9269), SUMAS-EVERSON AUTO FREIGHT, 308 Baker, Everson, WA., MC-69626), (C) WALLACE-COLVILLE MOTOR FREIGHT, INC., N. 400 Sycamore, Spokane, WA., 99202, (MC 1924), (D) OAK HARBOR FREIGHT LINES, 6400 South 143rd, Seattle, WA., 98168, (MC 139763), (E) EVERGREEN FREIGHT LINES, INC., 5205 E. Union Avenue, Spokane, WA., 99206, (MC 125624), (F) HASLETT COMPANY, 324 Union Street, Oakland, CA., 94607, (MC 73826), (G) SYSTEM 99, 8201 Edgewater Drive, Oakland, CA., 94621, (MC 98327), and (H) VICTORVILLE-BARSTOW TRUCK LINE, 4366 E 26th Street, Los Angeles, CA., 90023, (MC 97863), seeks to enter into an agreement for the pooling of traffic consisting of (A) general commodities moving in interstate commerce between interchange on all traffic at Spokane, Washington. From Spokane over interstate 90 to Moses Lake serving no intermediate points and the off route points in Grant and Franklin Counties as follows: Othello, Warden, Moses Lake, Soap Lake, Ephrata, Quincy, Grant Orchards, Grant County Airport, Wheeler, Westlake, and Bruce. (B) Between Acme, Deming Everson, Nooksack, and Sumas, Washington. (C) Between (Part I) points located on U.S. Highway 10 (Interstate Highway 90) between Post Falls, Idaho and the Idaho-Montana State line, including Post Falls. (Part II) points located on U.S. Highway 95 between Dalton Gardens, Idaho and Bonners Ferry, Idaho including Dalton Gardens and Bonners Ferry. (Part III) Moyie Springs Idaho, Troy, Montana, Libby, Montana, points of interchange, Spokane, Washington—(1) All traffic destined to points in Part I above. (2) All traffic destined to points in Part II above located on U.S. Highway 95 between Dalton Gardens, Idaho and Sandpoint, Idaho, excluding Sandpoint. (3) All traffic destined to points in Parts I, II and III originating west of the western boundaries of the States of Montana, Wyoming, Colorado and New Mexico, Kalispell, Montana—(1) All traffic destined to points in Part III above which originates east of the western boundaries of the States of Montana, Wyoming, Colorado and New Mexico. (2) All traffic destined to points in Part II above located on U.S. Highway 95 between Sanpoint and Bonners Ferry, Idaho, including Sanpoint and Bonners Ferry, which originates east of the western boundaries of the States of Montana, Wyoming, Colorado and New Mexico. Representative points; Post Falls, ID., Kingston, ID., and Coeur D'Alene, ID., Kellogg, ID., Eagle, ID., Smelterville, ID., Osburn, ID., Wallace, ID., Mullan, ID., Sandpoint, ID., Bonners Ferry, ID., Moyie Springs, ID., Troy, MT., Libby, MT.; (D) Allen, Big Lake, Birch Bay, Blaine, Bow, Chuckanut, Conway, Custer, Edison, Lynden, Monteborne, and Samish, WA.;

(E) Reardan, Deep Creek, Davenport, Harrington, Odessa, Wilson Creek, Marlin, Stratford, Coulee City, Hartline, Almira, Wilbur, Creston, Lincoln (City), Electric City, Grand Coulee, Coulee City, Ritzville, and Sprague, WA; (F) all intermediate points between the junction of Interstate 5 and California Highway 104 to and including Ione, California, Herald Clay and Ione, CA; (G) Part I—Traffic to following points to be interchanged at Portland, Oregon: Beaver Marsh, Bend, Burns, Chemult, Chiloquin, OR, Crescent, Culver, Fort Klamath, Gilchrist, Hines, LaPine, Lakeview, Madras, Metolius, Paisley, Prineville, Prineville S.E., Redmond, Sisters, Terrebonne, Warm Springs, Harney, Buchanan, Drewsey, Juntura, Harper. Part II—Traffic to following points to be interchanged at Eugene, Oregon: Blue River, OR, Couger Dam, McKenzie Bride, Part III—Traffic to following points to be interchanged at Reno, Nevada: Garderville, NV, Minden, NV, Part IV—Traffic to following points to be interchanged at Los Angeles, California: West Yuma, AZ, (H) Victorville, Barstow, Daggett, George Air Force Base, Marine Corps Supply Center, Newberry Springs, Oro Grande, Hodge, Lenwood, and Helendale, CA, applicants' representative: G. T. West, Vice President—Traffic, 175 Linfield Drive, Menlo Park, CA, and Robert M. Bowden, Commerce Supervisor, P.O. Box 3062, Portland, OR 97028. CONSOLIDATED FREIGHTWAYS CORPORATION OF DELAWARE, is authorized to operate as a common carrier in all the States in the United States (except Hawaii).

No. MC-F-12951. Authority sought for purchase by B AND P MOTOR LINES, INC., 710 Oakland Road, P.O. Box 741, Forest City, NC 28043, of the operating rights of (B) FOREST DALE MOTORS, INC., Route 4, Box 374, Forest City, NC 28043, and for control and merger of (BB) SHELBY MOTOR LINES, INC., Box 1787 E., Dixon Boulevard, Shelby, NC 28150, and for acquisition by R. D. WORKMAN, COY LAMBERT, and ALMA MOOREE WORKMAN, all of the Forest City, NC 28043, address of control of such rights through the purchase and transaction. Applicants' attorney: Clyde W. Carver, Suite 212, 5299 Roswell Road NE., Atlanta, GA 30342. Operating rights sought to be transferred: (B) *New furniture*, crated and uncrated, and *furniture parts*, as a *common carrier* over irregular routes from points in McDowell County, N.C., to points in Rutherford County, N.C., with no transportation for compensation on return except as otherwise authorized; from Forest City, Rutherford County, N.C., to points in that part of North Carolina west of U.S. Highway 220, with no transportation for compensation on return except as otherwise authorized; Operating rights sought to be controlled and merged: (BB) *General commodities* (with usual exceptions) as a common carrier over irregular routes between Shelby, N.C., and points in North Carolina within 25 miles thereof; between Shelby, NC, and points in North Carolina within 25 miles thereof, on the one hand, and, on the other, points in North Carolina on and east of U.S. Highway 221 and on and west of U.S. Highway 220. Vendee is authorized to operate as a *common carrier* in all the United States including District of Columbia but excluding Alaska and Hawaii. Application has been filed for temporary authority under Section 210a(b).

NOTE.—No. MC 106074 (Sub-Nos. 26 and 27) is a directly related matter.

No. MC-F-12952. Authority sought for control and merger by NAVAJO FREIGHT LINES, INC., 1205 South Platte River Drive, Denver, CO 80223, of EXLEY EXPRESS, INC., 2610 SE. 8th Avenue, Portland, OR 97202, and for acquisition by UNITED TRANSPORTATION INVESTMENT COMPANY and DAVID H. RATNER, 310 South Michigan Avenue, Chicago, IL 60604, of control of such rights through the transaction. Applicants' attorneys: Leonard R. Kofkin, 39 S. La Salle St., Chicago, IL 60603, Edward K. Wheeler, 15th and H Streets NW., Washington, D.C. 20005, and James T. Johnson, 1610 IBM Building, Seattle, WA 98101. Operating rights sought to be controlled and merged: *Commodities* requiring refrigeration, as a common carrier over regular routes between Seattle, Wash., and Los Angeles, Calif., serving the intermediate points of Tacoma, Kalama, and Chehalis, Wash., Portland and Medford, Oreg., and Sacramento, San Francisco, Stockton, Fresno, and Bakersfield, Calif., with restrictions; *commodities* requiring refrigeration, over alternate routes for operating convenience only, between Tacoma, Wash., and Teniono, Wash., serving no intermediate points or the termini except as otherwise authorized, between Goshen, Oreg., and Weed, Calif., serving no intermediate points or the termini except as otherwise authorized, between San Francisco, Calif., and Los Angeles, Calif., serving no intermediate points or the termini except as otherwise authorized, between Gilroy, Calif., and junction California Highway 152 and U.S. Highway 99 serving no intermediate points or the termini except as otherwise authorized; *fish and seafoods*, as a *common carrier* over irregular routes from Westport and Ilwaco, Wash., to points in that part of California south of a line drawn east and west through Chico, Calif., with no transportation for compensation on return except as otherwise authorized; *fish*, fresh, frozen, smoked, and salted, *fish livers, processed seafoods, poultry, agricultural and horticultural products, frozen and processed fruits, berries, and vegetables*, from points in King and Pierce Counties, Wash., and Marion, Multnomah, and Washington Counties, Oreg., to points in that part of California south of a line drawn east and west through Chico, Calif.; *agricultural and horticultural products*, from points

in that part of California south of a line drawn east and west through Chico, Calif., to points in that part of Oregon and Washington west of the Cascade Mountains; *fish livers,* from Eureka, California and Pacific Coast points in that part of California south of a line drawn east and west through Chico, Calif. to Seattle, Wash.

Lumber, from points in Curry County, Oreg., and points in Oregon within five miles of Curry County, and from Bandon, Oreg., to points in California; *frozen fruits, frozen vegetables,* and *frozen berries,* between points in California, Oregon, and Washington, from points in Oregon and Washington, to Phoenix, Tucson, and Safford, Ariz., and Las Vegas and Reno, Nev., from Nampa and Lewiston, Idaho, to points in Oregon and California; *bananas, fresh fruits,* and *fresh vegetables,* in mixed loads, from Los Angeles, Calif., to Portland, Oreg.; *fish,* in mixed loads with frozen fruits, frozen vegetables, and frozen berries, from Hillsboro, Oreg., to Phoenix and Tucson, Ariz.; *frozen foods* (except frozen fruits, frozen vegetables, and frozen berries), between points in Yamhill, Umatilla, Multnomah, Marion, and Washington Counties, Oreg., on the one hand, and, on the other, Phoenix and Tucson, Ariz., between Walla Walla, Wash., and Phoenix, Ariz.; *bananas* and *fresh fruits, fresh vegetables,* and *fresh berries* when moving in the same vehicle with bananas, from points in California, to Pendleton, Oreg., Lewiston, Idaho, and points in Washington east of the Cascade Mountains; *frozen foods* and *potato products,* not frozen, from points in Oregon and Washington to points in California and Phoenix, Safford, and Tucson, Ariz.; *frozen foods,* except frozen fruits, vegetables and berries, from Ventura, Corona, Modesto, and Ontario, Calif., to Seattle, Wash., and Portland, Oreg.; *canned goods,* between Sherwood, Oreg., on the one hand, and, on the other, Vancouver, Wash., and points in Multnomah, Polk, Lane, Benton, and Umatilla Counties, Oreg.; *bananas* and *fresh fruits, fresh vegetables,* and *fresh berries,* when moving in the same vehicle with bananas, from points in California, to Bend and Klamath Falls, Oreg.; *canned fruits, berries, and vegetables,* from points in Polk, Lane, Benton, and Umatilla Counties, Oreg., and Vancouver, Wash., to points in that part of California south of a line drawn east and west through Chico. Calif.; *frozen foods,* from points in California, to Spokane, Wash.

Frozen prepared vegetables, from points in California, to Seattle, Wash., and points in Yamhill, Multnomah, Marion, and Washington Counties, Oreg., from points in Oregon to points in California, from points in Yamhill, Umatilla, Multnomah, Marion, and Washington Counties, Oreg., to Seattle, Wash., and Phoenix and Tucson, Ariz., from points in Washington, to points in California, and points in Marion, Multnomah, Washington, Umatilla, and Yamhill Counties, Oreg., from Walla Walla, Wash., to Phoenix, Ariz, from Nampa, Idaho, to Hillsboro, Woodburn, and Portland, Oreg., and San Francisco, Calif., from points in Oregon and Washington, to Phoenix, Safford, and Tucson, Ariz., and points in California; *foodstuffs* (except in bulk) from Kennewick, Wash., to points in Nevada; *foodstuffs* (except in bulk, in tank vehicles), from the plantsites of the Welch Grape Juice Company, Inc., at or near Kennewick and Grandview, Wash., to points in California; *foodstuffs,* from Anaheim and Santa Fe Springs, Calif., to Lewiston, Idaho, and to points in Oregon and Washington, from Vacaville, Calif., to points in Oregon and Washington, with restrictions; *foodstuffs and matches,* from Fullerton, Hayward, Oakdale, and Davis, Calif., to Lewiston, Idaho, and to points in Oregon and Washington, with restrictions; frozen foods, fresh and cured meats, and commodities the transportation of which is partially exempt pursuant to the provisions of section 203(b)(6) of the Interstate Commerce Act, when moving in the same vehicle and at the same time with frozen foods, and fresh and cured meats, from points in California, to points in Oregon, Washington, and Lewiston, Idaho; *canned goods,* from points in California, to points in Oregon and Washington; *pickles, sauerkraut,* and *relish,* from the plantsites of Steinfield's Products Company at Scappose and Portland, Ore., to Redding, Calif.; *candy,* in vehicles equipped with mechanical refrigeration from San Jose, Calif., to Bellevue and Spokane, Wash., and Clackamas, Oreg.; *foodstuffs,* from Kennewick, Wash., to points in Arizona, with restrictions; *canned goods and frozen foods,* from Prosser, Wash., to points in Arizona, California, Nevada, and Oregon; *canned goods, frozen foods,* and *processed fruits, berries,* and *vegetables,* from Grandview, Wash., to points in Arizona, Nevada, and Oregon, from Kennewick, Wash., to points in Oregon.

Containers, from Portland, Oreg., to the plantsite of Welch Foods, Inc., at or near Grandview and Kennewick, Wash.; *bananas,* from Seattle, Wash., to Portland, Oregon; foodstuffs, not frozen (except commodities in bulk), canned goods, and meats, in vehicles equipped with mechanical refrigeration, from Los Angeles, Calif., to Aberdeen, Everett, Spokane, Yakima, Grandview, Kennewick, and Walla Walla, Wash., and Albany, Astoria, Bend, Coos Bay, Cornelius, Corvallis, Grants Pass, Hood River, Klamath, Falls, Salem, and Springfield, Oreg.; *canned goods,* from Gresham, Portland, Salem, Stayton, Silverton, Springbrook, and Weston, Oreg., to points in Arizona; *pickles, sauerkraut,* and *relish,* from Scappose, Oreg., to points in California (except Redding and points in its commercial zone as defined by the Commission), and to points in Arizona and Nevada; *bananas,* from Seattle, Wash. to ports of entry on the United States-Canada boundary line located at or near Blaine and Sumas, Wash.; cheese, cheese products, and whey powder, from Tillamook, Oreg., to points in California; *canned goods* in mixed loads with frozen foods, and (2) *frozen foods* in mixed loads with canned goods, from Gresham, Portland, Salem, Stayton, Silverton, Springbrook, and Weston, Oreg., to points in Nevada; meat, meat products, and meat by-products, as described in section A of Appendix I to the report in *Descriptions in Motor Carrier Certificates,* 61 M.C.C. 209 and 766, from Wallula and Toppenish, Wash., to points in California, from Seattle, Wash., to points in Oregon and Arizona, from Ellensburg, Wash., to points in California and Oregon, from Albany, Oreg., to points in California and Washington, canned goods, from Walla Walla, Wash., to points in California from Vancouver, Wash., and points in Benton, Lane, Polk, Marion, Multnomah, Umatilla, and Washington Counties, Oreg., to points in that part of California north of a line drawn east and west through Chico, Calif.; *bananas,* from Seattle, Wash., to points in Oregon, Idaho, Washington, and Montana, from points in California, to La Grande, Oreg.; *frozen foods,* from the plantsite and storage facilities utilized by Lamb-Weston, Inc., division of Amfac, Inc., at points in Umatilla County, Oreg., and Benton, Franklin, Grant, and Walla Walla Counties, Wash., to points in Oregon and Washington, and those in Washoe County, Nev.; *wine,* (except in bulk, in tank vehicles), from Prosser, Wash., to points in Oregon, California, Arizona and Nevada.; *pet food,* in containers, from Long Beach, Terminal Island, and Vernon, Calif., to points in Oregon and Washington.

Canned seafoods and pet foods, from Bellingham, Wash., and Astoria, Oreg., to points in Arizona and California; meat, meat products, and meat by-products, and articles distributed by meat packinghouses, as described in Sections A and C of Appendix I to the report in *Descriptions in Motor Carrier Certificates,* 61 M.C.C. 209 and 766 (except hides and commodities in bulk), from Spokane, Wash., to points in Oregon and California; *containers,* in mixed loads with foodstuffs, not frozen (except commodities in bulk, canned goods, and meats), from the plants of Wilsey Foods, Inc., at Los Angeles, Calif., to the plant of Wilsey Foods at Salem, Oreg.; *milk cartons,* from Turlock, Calif., to Tillamook, Oreg.; *margarine, mayonnaise, salad and cooking oils, and salad dressings,* from Sunnyvale and Oakland, Calif., to points in Oregon and Washington; *such merchandise as is dealt in by wholesale and retail grocers,* from Fullerton, Hayward, Davis, and Oakdale, Calif., to Lewiston, Idaho, and points in Oregon and Washington, with restrictions; *meat products, and smoked salmon,* from Tillamook, Oreg., to points in California; there are pending before the Commission pending applications for authority under irregular routes (MC 114290 Sub-No. 74) *Margarine, mayonnaise, salad and cooking oils,* and salad dressings, from points in Alameda, San Francisco, Santa Clara, and San Mateo Counties, California, to points in Oregon, (MC 114290 Sub-78) *canned vegetables,* from

La Conner, Wash., to Salem, Oregon, and (MC 114290 Sub-80) *pet food*, in containers from San Diego, Calif., to points in Oregon and Washington. NAVAJO FREIGHT LINES, INC., is authorized to operate as a *common carrier* in Illinois, Indiana, Iowa, Kansas, Colorado, Oklahoma, New Mexico, Arizona, California, Wyoming, Utah, Nebraska, Missouri, Texas, Nevada, Louisiana, Virginia, Maryland, Arkansas, Florida, New York, Tennessee, Kentucky, Ohio, and Michigan. Application has not been filed for temporary authority under section.

No. MC–F–12957. Authority sought for control by ROY A. LEIPHART TRUCKING, INC., 1298 Toronita Street, York, Pa., 17402, of York Transportation Company, Inc., 2301 Mt. Rose Avenue, P.O. Box 707, York, Pa., 17402, and for acquisition by Clair E. Forry, and Robert M. Ewell, both of 1298 Toronita Street, York, Pa., 17402, of control of York Transportation Company, through the acquisition by Clair E. Forry and Robert M. Ewell. Applicants' attorneys: Charles E. Creager, 1329 Pennsylvania Avenue, Hagerstown, Md., 21740 and Maxwell A. Howell, 1100 Investment Bldg., 1511 K Street, NW., Washington, D.C. 20005. Operating rights sought to be controlled: *General commodities*, with exceptions as a common carrier over regular routes between York, Pa., and New York, N.Y., serving the intermediate points between and including Trenton, N.J., and New York, N.Y., restricted to eastbound movement, and those between and including Lancaster and York, Pa., restricted to westbound movement, and the off-route points of Mineola and White Plains, N.Y., and those in New York, in the New York, N.Y., Commercial Zone, as defined by the Commission, those in New Jersey within 20 miles of New York, N.Y., and those within 30 miles of York, Pa., between Paoli, Pa., and junction Pennsylvania Highway 43 and U.S. Highway 1, serving no intermediate points, as an alternate route for operating convenience only; *Iron and steel chains and parts, hardware, and mechanics' tools*, as a common carrier over regular and irregular routes between York, Pa., and Bridgeport, Conn., serving no intermediate points. Vendee is authorized to operate as a *common carrier* in Connecticut, Delaware, the District of Columbia, Illinois, Indiana, Maryland, Massachusetts, New Jersey, New York, Ohio, Pennsylvania, Rhode Island, Virginia, and West Virginia. Application has been filed for temporary authority under section 210a(b).

OPERATING RIGHTS APPLICATIONS DIRECTLY RELATED TO FINANCE PROCEEDINGS

The following operating rights applications are filed in connection with pending finance applications under Section 5(2) of the Interstate Commerce Act, or seek tacking and/or gateway elimination in connection with pending transfer applications under Section 212(b) of the Interstate Commerce Act.

An original and two copies of protests to the granting of the authorities must be filed with the Commission on or before October 12, 1976. Such protests shall comply with Special Rule 247(d) of the Commission's *General Rules of Practice* (49 CFR § 1100.247) and include a concise statement of protestant's interest in the proceeding and copies of its conflicting authorities. Verified statements in opposition should not be tendered at this time. A copy of the protest shall be served concurrently upon applicant's representative, or applicant if no representative is named.

Each applicant states that there will be no significant effect on the quality of the human environment resulting from approval of its applications.

No. MC 114273 (Sub-No. 253), filed August 10, 1976. Applicant: CRST, INC., P.O. Box 68, Cedar Rapids, Iowa. Applicant's representative: Robert E. Konchar, Suite 315 Commerce Exchange Building, 2720 First Avenue NE., P.O. Box 1943, Cedar Rapids, Iowa 52406. Authority sought to operate as a *common carrier*, by motor vehicle, over irregular routes, transporting: (1) *Meats, meat products, and meat by products, and articles distributed by meat packinghouses*, as described in Sections A and C of Appendix I to the report in *Descriptions in Motor Carrier Certificates*, 61 M.C.C. 209 and 766, (except commodities in bulk, in tank vehicles, and hides), (a) from the plantsite of Swift and Company, located at or near Grand Island, Nebr., to points in Indiana and Louisville, Ky.; (b) from Sioux City, Iowa, and Omaha, Nebr., to Louisville, Ky., and points in Indiana; (2) *canned goods* from Grundy Center, Iowa to Louisville, Ky., and points in Indiana; (3) *canned goods, canning factory machinery and supplies* between points in Indiana and Louisville, Ky., and points in Iowa within 100 air miles of Cedar Rapids, Iowa, and Sac City, Storm Lake, LaPorte City and Garrison, Iowa, points in Minnesota, points in Missouri on and north of U.S. Highway 50 and on and west of U.S. Highway 63 and Aurora, Bolivar, Carthage, Clinton, Joplin, Neosho, St. Louis, Springfield, and Webb City, Mo., and points in Kansas on and west of U.S. Highway 81; (4) *iron and steel articles* from Louisville, Ky., and points in Indiana, to Dubuque, Iowa and points in Iowa within 100 miles of Cedar Rapids, Iowa. (5) *iron and steel articles* from Louisville, Ky., and points in Indiana, to points in Minnesota. (6) *iron and steel articles and non-ferrous metal articles* when moving in the same vehicle and at the same time with iron and steel articles, from Louisville, Ky., and points in Indiana, to points in Colorado on and east of the Continental Divide.

(7) *General commodities*, (except commodities in bulk, Classes A and B explosives, household goods as defined by the Commission, and those requiring special equipment), between that part of Michigan on and west of a line beginning at Battle Creek, Mich., and extending along Michigan Highway 66 to the Michigan-Indiana State line, on the one hand, and, on the other, that part of Indiana on and west of U.S. Highway 31; (8) *General commodities*, (except commodities in bulk, Classes A and B explosives, household goods as defined by the Commission, and those requiring special equipment), between that part of Michigan on, east, and south of a line beginning at Bay City, Mich.; thence along Michigan Highway 47 to Saginaw, thence along Michigan Highway 46 to St. Louis, thence along U.S. Highway 27 to Marshall, thence along Interstate Highway 94 to the junction of Michigan Highway 66, thence along Michigan Highway 66 to the Indiana-Michigan State line, located at Midland, Mich., and Toledo, Ohio, on the one hand, and, on the other, that part of Indiana on, west and north of a line beginning at the Indiana-Michigan State line along Indiana Highway 15 to the junction of Indiana Highway 25, to the junction of Indiana Highway 28, thence along Indiana Highway 28 to the junction of U.S. Highway 41, thence along U.S. Highway 41 to the Indiana-Kentucky State line; (9) *General commodities* (except commodities in bulk, Classes A and B explosives household goods as defined by the Commission, and those requiring special equipment), between that part of Pennsylvania on and west of U.S. Highway 119 and on and south of U.S. Highway 422, and Dayton Cincinnati and Hamilton, Ohio on the one hand, and on the other, that part of Indiana on, west and south of a line beginning at the Indiana-Michigan State line extending along Indiana Highway 39 to the junction of Indiana Highway 10, thence along Indiana Highway 10 to the Illinois-Indiana State line.

(10) *Frozen Foods, food products, meats, meat products, and meat by products articles distributed by meat packinghouses*, as described in Sections A and C of Appendix I to report in *Descriptions in Motor Carrier Certificates*, 61 M.C.C. 209 and 766, (except commodities in bulk, in tank vehicles, and hides), between points in Indiana and Louisville, Ky., on the one hand, and on the other, points in Minnesota, those in Missouri on and north of U.S. Highway 50 and on and west of U.S. Highway 63, points in Kansas on and east of U.S. Highway 81; (11) *Paper, paper products, craft wrapping paper, and wood pulpboard in rolls*, from Franklin, Va. to Chicago, Ill.; and points in Indiana. (12) *General commodities*, (except commodities in bulk, in tank vehicles, and hides), between that part of Indiana on, west and south of a line beginning at the Indiana-Michigan State line extending along Indiana Highway 39 to the junction of Indiana Highway 10, thence along Indiana Highway 10 to the Illinois-Indiana State line, on the one hand, and on the other, points in that part of Ohio on and south of U.S. Highway 40 (except Dayton, Cincinnati and Hamilton), restricted in (1) above to traffic originating at the plantsite of Swift & Company.

NOTE.—The purpose of this filing is to eliminate (A) the gateway of Chicago, Ill. in (1), (2), (3), (4), (6), (7), (8), and (9) above; (B) the gateways of the facilities of Central Steel & Wire; A. M. Castle & Co., and Joseph T. Ryerson & Son, Inc., located at

Chicago, Ill. in (5) above; (C) the gateways of Chicago and Chicago Heights, Ill. in (10) above; (D) the gateways of Pittsburgh, Pa., and Hammond, Ind. in (11) above; and (E) the gateways of Dayton, Ohio and Chicago, Ill. in (12) above. This matter is directly related to a Section 5(2) finance proceeding in MC-F-12929, published in the Federal Register issue of August 26, 1976. If a hearing is deemed necessary, the applicant requests it be held at Washington, D.C.

MOTOR CARRIER ALTERNATE ROUTE DEVIATIONS

The following letter-notices to operate over deviation routes for operating convenience only have been filed with the Commission under the Commission's Deviation Rules—Motor Carriers of Property (49 CFR § 1042.4(c)(11)).

Protests against the use of any proposed deviation route herein described may be filed with the Commission in the manner and form provided in such rules (49 CFR § 1042.4(c)(12)) at any time, but will not operate to stay commencement of the proposed operations unless filed on or before October 12, 1976.

Each applicant states that there will be no significant effect on the quality of the human environment resulting from approval of its request.

MOTOR CARRIERS OF PROPERTY

No. MC 85850 (Sub-No. 7) (Deviation No. 3), (Correction) NEYLON FREIGHT LINES, INC., c/o Jones Truck Lines, Inc., 610 E. Emma Ave., Springdale, Ark. 72764, filed August 6, 1976. Carrier's representative: Kim D. Mann, Suite 1010, 7101 Wisconsin Ave., Washington, D.C. 20014. Carrier proposes to operate as a *common carrier*, by motor vehicle, of *general commodities*, with certain exceptions, over a deviation route as follows: From Kansas City, Mo., over Interstate Highway 29 to junction Iowa Highway 2, thence over Iowa Highway 2 to Nebraska City, Nebr., thence over Nebraska Highway 2 to Lincoln, Nebr., and return over the same routes for operating convenience only. The notice indicates that the carrier is presently authorized to transport the same commodities, over a pertinent service route as follows: From Kansas City, Mo., over U.S. Highway 73 to Hiawatha, Kans., thence over U.S. Highway 36 to junction Kansas Highway 15E, thence east over U.S. Highway 36 to Marysville, Kans., thence over U.S. Highway 77 to Lincoln, Nebr., and return over the same route.

NOTE.—The purpose of this republication is to add a Nebraska Highway to the proposed deviation route which was inadvertently omitted.

MOTOR CARRIER ALTERNATE ROUTE DEVIATIONS

The following letter-notices to operate over deviation routes for operating convenience only have been filed with the Commission under the Commission's Deviation Rules—Motor Carriers of Passengers (49 CFR § 1042.2(c)(9)).

Protests against the use of any proposed deviation route herein described may be filed with the Commission in the manner and form provided in such rules (49 CFR § 1042.2(c)(9)) at any time, but will not operate to stay commencement of the proposed operations unless filed on or before October 12, 1976.

Each applicant states that there will be no significant effect on the quality of the human environment resulting from approval of its request.

MOTOR CARRIERS OF PASSENGERS

No. MC 1515 (Deviation No. 712) (Cancels Deviation No. 677), GREYHOUND LINES, INC., Greyhound Tower, Phoenix, Ariz. 85077, filed August 18, 1976. Carrier proposes to operate as a *common carrier*, by motor vehicle, of *passengers and their baggage*, and *express* and *newspapers* in the same vehicle with passengers, over deviation routes as follows: From Chicago, Ill., over Interstate Highway 90 to junction Illinois Highway 5, thence over Illinois Highway 5 to junction Interstate Highway 80 and Illinois Highway 92, with the following access routes: (1) From junction Illinois Highway 5 and De Kalb East Road, over De Kalb East Road to junction Illinois Highway 38, thence over Illinois Highway 38 to De Kalb, Ill., (2) From junction Illinois Highway 5 and Anne Glidden Road, over Anne Glidden Road to junction Illinois Highway 38, thence over Illinois Highway 38 to De Kalb, Ill., and (3) From junction Illinois Highway 78 and Illinois Highway 5 over Illinois Highway 78 to junction Illinois Highway 2, and return over the same routes for operating convenience only. The notice indicates that the carrier is presently authorized to transport passengers and the same property over a pertinent service route as follows: From junction Illinois Highway 2 and Illinois Highway 92 over Illinois Highway 2 to junction Illinois Highway 38, thence over Illinois Highway 38 to Geneva, Ill., thence over Illinois Highway 31 to St. Charles, Ill., thence over Illinois Highway 64 to Chicago, Ill., and return over the same route.

MOTOR CARRIER INTRASTATE APPLICATIONS

The following application for motor common carrier authority to operate in intrastate commerce seek concurrent motor carrier authorization in interstate or foreign commerce within the limits of the intrastate authority sought, pursuant to Section 206(a)(6) of the Interstate Commerce Act. These applications are governed by Special Rule 245 of the Commission's *General Rules of Practice* (49 CFR § 1100.245), which provides, among other things, that protests and requests for information concerning the time and place of State Commission hearings or other proceedings, any subsequent changes therein, and any other related matters shall be directed to the State Commission with which the application is filed and shall not be addressed to or filed with the Interstate Commerce Commission.

Texas Docket No. 002892 A1A, filed August 18, 1976. Applicant: HENSLEY FREIGHT LINES, INC., P.O. Box 276, Marion, Tex. 78124. Applicant's representative: Mike Cotton, P.O. Box 1148, Austin, Tex. 78767. Certificate of Public Convenience and Necessity sought to operate a freight service as follows: Transportation of *General commodities*, over the following routes (1) Between Marion, Tex., and Seguin, Tex., serving all intermediate points; From Marion over FM-78 to Seguin and return over the same route. (2) Between Seguin, Tex. and Luling, Tex., serving all intermediate points; From Seguin over U.S. Highway 90 to Luling and return over the same route. (3) Between Luling, Tex. and Gonzales, Tex., serving all intermediate points and serving the junction of U.S. Highway 183 and U.S. Highway 90-A for purposes of joinder: From Luling over U.S. Highway 183 to Gonzales and return over the same route. (4) Between junction U.S. Highway 183 and U.S. Highway 90-A and Seguin, Tex., serving all intermediate points: From junction U.S. Highway 183 and U.S. Highway 90-A over U.S. Highway 90-A to Seguin, Tex. and return, and joining, tacking and coordinating the authority described above with authority presently contained in Common Carrier Certificate No. 2892. Intrastate, interstate and foreign commerce authority sought.

HEARING.—Date, time and place will be assigned for a hearing approximately 30 days after publication in the FEDERAL REGISTER. Requests for procedural information should be addressed to the Transportation Division, Railroad Commission of Texas, P.O. Drawer 12967, Austin, Tex. 78711 and should not be directed to the Interstate Commerce Commission.

By the Commission.

H. G. HOMME, Jr.,
Acting Secretary.

[FR Doc.76-26389 Filed 9-8-76;8:45 am]

[Ex Parte MC 103]

PETITION OF HERMAN BROS., INC., FOR THE INSTITUTION OF RULEMAKING PROCEEDINGS

SEPTEMBER 2, 1976.

Notice to all parties: At the request of Fritz R. Kahn, representative for Herman Bros., Inc., the time for filing comments in the above-entitled proceeding has been extended from September 22, 1976, to November 22, 1976. No further extensions.

H. GORDON HOMME, Jr.,
Acting Secretary.

[FR Doc.76-26397 Filed 9-8-76;8:45 am]

federal register

THURSDAY, SEPTEMBER 9, 1976



PART II:

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

■

OVER-THE-COUNTER DRUGS

Establishment of a Monograph for OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 341]

[Docket No. 76N-0052]

OVER-THE-COUNTER DRUGS

Establishment of a Monograph for OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products

The Food and Drug Administration (FDA) proposes to establish conditions under which over-the-counter (OTC) cold, cough, allergy, bronchodilator and antiasthmatic drugs are generally recognized as safe and effective and not misbranded, based on the recommendations of the Advisory Review Panel on Over-the-Counter (OTC) Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products; comments by December 8, 1976.

Pursuant to Part 330 (21 CFR Part 330), the Commissioner of Food and Drugs received on March 3, 1976, the report of the Advisory Review Panel on Over-The-Counter (OTC) Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products. In accordance with § 330.10(a)(6) (21 CFR 330.10(a)(6)), the Commissioner is issuing (1) a proposed regulation containing the monograph recommended by the Panel establishing conditions under which OTC cold, cough, allergy, bronchodilator and antiasthmatic drugs are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph on the basis of a determination by the Panel that they would result in the drugs not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph on the basis of a determination by the Panel that the available data are insufficient to classify such conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel to the Commissioner. The summary minutes of the Panel meetings are on public display in the office of the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20852.

The purpose of issuing the unaltered conclusions and recommendations of the Panel is to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The Commissioner has not yet fully evaluated the report, but has concluded that it should first be issued as a formal proposal to obtain full public comment before any decision is made on the recommendations of the Panel. The report of the Panel represents the best scientific judgment of the members. The report has been prepared independently of FDA and does not necessarily reflect the agency position on any particular matter contained therein. After a careful review of all comments submitted in response to this proposal, the Commissioner will issue a tentative final regulation in the FEDERAL REGISTER to establish a monograph for OTC cold, cough, allergy, bronchodilator and antiasthmatic drug products.

In accordance with § 330.10(a)(2) (21 CFR 330.10(a)(2)), all data and information concerning OTC cold, cough, allergy, bronchodilator and antiasthmatic drug products submitted for consideration by the Advisory Review Panel have been handled as confidential by the Panel and FDA. All such data and information shall be put on public display at the office of the Hearing Clerk, Food and Drug Administration, on or before October 12, 1976, except to the extent that the person submitting it demonstrates that it still falls within the confideniality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality shall be submitted to FDA, Bureau of Drugs, Division of OTC Drug Products Evaluation (HFD-510), 5600 Fishers Lane, Rockville, MD 20852.

Based upon the conclusions and recommendations of the Panel, the Commissioner proposes, upon publication of the final regulation:

1. That the conditions included in the monograph on the basis of the Panel's determination that they are generally recognized as safe and effective and are not misbranded (Category I) be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

2. That the conditions excluded from the monograph on the basis of the Panel's determination that they would result in the drug not being generally recognized as safe and effective or would result in misbranding (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER, regardless whether further testing is undertaken to justify their future use.

3. That the conditions excluded from the monograph on the basis of the Panel's determination that the available data are insufficient (Category III) to classify such conditions either as Category I—generally recognized as safe and effective and not misbranded, or as Category II—not being generally recognized as safe and effective or would result in misbranding, be permitted to remain in use for not longer than 2 to 5 years (for the specific conditions specified in this document) after the date of publication of the final monograph in the FEDERAL REGISTER, if the manufacturer or distributor of any such drug utilizing such conditions in the interim conducts tests and studies adequate and appropriate to satisfy the questions raised with respect to the particular condition by the Panel. The period of time within which studies must be completed will be carefully reviewed by the Commissioner after receipt of comments on this document and will probably be revised downward.

This proposal sets forth the conclusion of the Advisory Review Panel on Over-the-Counter (OTC) Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products that several ingredients are safe and effective for OTC use which heretofore have been limited to prescription use or classified for OTC use at a dosage level lower than that recommended by the Panel. The Commissioner is aware that a number of questions have been presented to the agency regarding the OTC marketing status of ingredients or amounts of ingredients previously limited to prescription use prior to finalization of an applicable monograph for the ingredients. The reclassification of ingredients from prescription to OTC status presents important issues that need careful and special consideration.

Accordingly, the Commissioner proposed, in the FEDERAL REGISTER of December 4, 1975 (40 FR 56675), a policy to clarify the marketing status of (1) all ingredients currently restricted to prescription use which an OTC advisory panel recommends as Category I (safe and effective), Category II (not safe and effective), or Category III (the available data are insufficient to classify the drug); and (2) the use of active ingredients at dosage levels higher than that available in any OTC drug product.

The Commissioner also advised in the preamble to the proposal in the December 4, 1975 FEDERAL REGISTER that he may indicate his disagreement with the panel's recommendation(s) regarding specific ingredients proposed for Category I, e.g., ingredients having manufacturing or formulation problems or unresolved questions concerning a potential for abuse or misuse; and he may make a tentative determination that an approved new drug application (NDA) is required for marketing an OTC product containing such ingredients. The Commissioner acted on this proposal by final regulation published in the FEDERAL REGISTER of August 4, 1976 (41 FR 32580).

The Commissioner has reviewed those ingredients included in the Panel's recommendations that are currently limited to prescription use or classified for OTC use at a dosage level lower than that recommended by the Panel. He has made an initial determination that an approved NDA is required for OTC marketing of promethazine for any indication, for OTC marketing of doxylamine succinate as an antihistamine at a dosage level in excess of 7.5 milligrams (mg), and for OTC marketing of diphenhydramine as an antihistamine. The Commissioner is deferring his decision on the Panel's recommendation that diphenhydramine be considered generally recognized as safe and effective for OTC use as an antitussive until the agency has had an opportunity to rule on a supplemental NDA now pending for OTC use of an antitussive product containing diphenhydramine. The Commissioner has made an initial determination to accept the Panel's recommendations on OTC use of a number of ingredients among which are chlorpheniramine, pseudoephedrine, theophylline, and methoxyphenamine. However, the Commissioner wishes to raise several pertinent points regarding these drugs, and they are fully explained below.

Promethazine. The Panel recommended classification of the ingredient promethazine as a Category I OTC antihistaminic drug. This ingredient is presently a component of drug products that are the subject of approved NDA's for prescription use as antihistamines, as

sedatives, as antiemetics, as adjuncts with narcotics for preoperative sedation, and in the postoperative management of pain. Promethazine is the only antihistaminic drug reviewed by the Panel that is chemically identified as a phenothiazine derivative; no ingredients in this class are currently available for OTC use. Promethazine, like other phenothiazines, is known to produce certain serious adverse effects, including agranulocytosis, thrombocytopenia, hypoplastic anemia, extrapyramidal symptoms, and hypotension (*AMA Drug Evaluations*, 2d Ed., p. 497), although it may produce these less frequently than do other phenothiazines. Although these adverse effects are of considerable concern, the major consideration relates to the effects of promethazine on the central nervous system (CNS). Promethazine is known to have a hypnotic effect more conspicuous than that of the other antihistaminics (see Krantz and Carr, *The Pharmacologic Principles of Medical Practice*, 8th Ed., p. 818), a problem sufficient to cause the Panel to recommend a warning, "may cause marked drowsiness," a warning not required for OTC antihistamines in general. Overdosage is thus potentially a problem with promethazine, especially for children. Children also seem particularly liable to develop such CNS adverse reactions as disturbances of the psyche, changes in sensorium, evidence of extrapyramidal disturbances, convulsions, and, rarely, coma and death. The Commissioner notes that other OTC antihistamines are available that are as effective as promethazine and less hazardous. Thus the risk of adverse effects from OTC availability of this ingredient is not justified in the absence of an offsetting benefit in the form of therapeutic superiority in comparison with antihistamine ingredients already marketed OTC.

Doxylamine succinate. The Panel recommended classification of the ingredient doxylamine succinate as a Category I OTC antihistaminic drug at the 7.5 to 12.5 mg dosage level. This ingredient is presently the subject of an approved NDA for prescription use, and for OTC use at the 7.5 mg dosage level, for several indications, including the management of perennial and seasonal rhinitis and vasomotor rhinitis pursuant to the requirements of § 310.201(a)(13) (21 CFR 310.201(a)(13)). The Commissioner concludes that doxylamine succinate should continue to be classified as a new drug and a prescription drug at dosage levels in excess of 7.5 mg. The Commissioner makes this determination because other OTC antihistaminic agents are available that are safer than doxylamine succinate at that dosage level.

Doxylamine succinate is a member of the ethanolamine class of antihistamines. As noted in the *AMA Drug Evaluations*, 2d Ed., p. 493, this class of drugs exhibits a high incidence of drowsiness compared with the other classes of antihistamines (ethylenediamines and alkylamines). As noted in the proposal regarding OTC sleep-aid drug products, published in the FEDERAL REGISTER of December 8, 1975 (40 FR 57292), about 50 percent of those persons receiving conventional antihistamine treatment doses of drugs in the ethanolamine class experienced drowsiness. In addition to the pronounced tendency to induce sedation, drugs in this group also possess significant atropine-like activity. Therefore, the Commissioner concludes that doxylamine succinate should remain a prescription new drug ingredient at the dosage levels greater than 7.5 mg.

Diphenhydramine hydrochloride. Diphenhydramine hydrochloride is the active ingredient in several products with approved NDA's. All such products are limited to prescription use. The Panel recommended that diphenhydramine hydrochloride be classified in Category I for antihistaminic use at 25 to 50 mg, which is the usual prescription dosage level. Diphenhydramine hydrochloride, like doxylamine succinate, is a member of the ethanolamine class of antihistamines. It, too, has a pronounced tendency to produce sedation in a high proportion of those persons who take it (*AMA Drug Evaluations*, 2d Ed., p. 493). For this reason, the Commissioner concludes that diphenhydramine hydrochloride should remain a prescription new drug ingredient and not be available for use as an OTC antihistamine. No diphenhydramine hydrochloride product is currently marketed OTC as an antihistamine at any dosage level.

The Panel also recommended that diphenhydramine hydrochloride be classified in Category I for OTC use as an antitussive. Diphenhydramine hydrochloride is the active ingredient in a cough syrup product now being marketed OTC. The currently effective NDA for this product limits it to prescription use and labels it as an expectorant only. The holder of the NDA has submitted a supplemental NDA that contains data in support of a claim that the product is safe and effective for use as an antitussive. The supplemental NDA also requests that the product be approved for OTC use. The Commissioner has concluded that the marketing status of diphenhydramine hydrochloride as an antitussive should be resolved by first considering the approvability of this supplemental NDA. After that, he will address the Panel's recommendation that diphenhydramine hydrochloride be considered generally recognized as safe and effective for OTC use as an antitussive.

The agency will rule on the pending supplemental NDA in the near future. The Commissioner advises that if the supplemental NDA is denied because diphenhydramine hydrochloride in the amount present in that product is not considered safe and effective for OTC use as an antitussive, he will at that time issue a notice in the FEDERAL REGISTER stating his disagreement with the Panel's recommendation that diphenhydramine hydrochloride be classified in Category I for OTC antitussive use. In that event, any such product marketed OTC would thereupon be subject to immediate regulatory action, in accordance with the enforcement policy announced in the FEDERAL REGISTER of August 4, 1976 (41 FR 32580). If the supplemental NDA is approved, the Commissioner may nevertheless conclude that the safety and/or effectiveness of antitussive products containing diphenhydramine hydrochloride has not achieved general recognition in the scientific community, and he may state such conclusion by notice in the FEDERAL REGISTER when the supplemental NDA is approved or at a later time, e.g., in the preamble to the tentative final monograph.

The Commissioner notes that the marketing status of diphenhydramine hydrochloride as an antihistamine raises different issues from those surrounding its OTC use as an antitussive. The indications, dosage levels, and number of available effective alternatives are different depending on the condition for which diphenhydramine hydrochloride is to be used. Also, the effectiveness of the ingredient is established in relation to antihistaminic use, but has not yet been ruled on in the context of the pending supplemental NDA for OTC use of a cough syrup product. Accordingly, the Commissioner's initial decision not to accept the Panel's recommendation for Category I classification of diphenhydramine hydrochloride for use as an antihistamine is independent of his decision on its status as an antitussive, although, obviously, some of the underlying factual considerations are common to each.

Chlorpheniramine, pseudoephedrine, theophylline, and methoxyphenamine. The Panel recommended that chlorpheniramine as an OTC antihistamine and pseudoephedrine as an OTC oral nasal decongestant be available at dosage levels twice those currently permitted for OTC use. Although he does not disagree with these recommendations at this time, the Commissioner is concerned that consumers accustomed to purchasing a particular product may not be aware of the increased amount of active ingredient per dosage unit. The Commissioner concludes that consumers should be fully informed about the increased dosage. He has determined, therefore, that all manufacturers who elect to reformulate their marketed products shall clearly indicate any increased dosage level on the principal display panel of each product. He further suggests that, in the case of tablet formulations, scored tablets be available to assist the consumer in achieving a lower dosage, if one is desired.

The Panel further recommended that theophylline and methoxyphenamine be made available OTC as single ingredients. The Commissioner does not contest the judgment of the Panel regarding the safety of these ingredients. However, he points out that he believes there is a scientific issue whether the recommended dosage levels are therapeutically effective for a significant identifiable population of asthmatics. Therefore, these two ingredients are currently undergoing extensive review within the agency. Consequently, the decision of the Panel may be subject to modification in the tentative final monograph.

The Commissioner invites full public comment on all of the conclusions and

recommendations of the Panel, and on his own specific conclusions regarding promethazine, doxylamine succinate, diphenhydramine, chlorpheniramine, pseudoephedrine, theophylline, and methoxyphenamine.

The Commissioner has reviewed the potential environmental impact of the recommendations and proposed monograph of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products and has concluded that the Panel's recommendations and proposed monograph will not significantly affect the quality of the human environment and that an environmental impact statement is not required. The Commissioner has also considered the inflation impact of the Panel's recommendations and proposed monograph, and no major inflation impact has been found, as defined in Executive Order 11821, OMB Circular A-107, and the Guidelines issued by the Department of Health, Education, and Welfare. Copies of the environmental and inflation impact assessments are on file with the office of the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20852.

The conclusions and recommendations in the report of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products follow:

In the FEDERAL REGISTER of January 5, 1972 (37 FR 85), the Commissioner of Food and Drugs announced a proposed review of the safety, effectiveness and labeling of all OTC drugs by independent advisory review panels. On May 8, 1972, the Commissioner signed the final regulations providing for the OTC drug review under § 330.10 published in the FEDERAL REGISTER of May 11, 1972 (37 FR 9464), which were made effective immediately. Pursuant to these regulations the Commissioner issued a request for data and information on all cold, cough, allergy, bronchodilator and antiasthmatic (CCABA) active ingredients in drug products, in the FEDERAL REGISTER of August 9, 1972 (37 FR 16029).

The Commissioner appointed the following Panel to review the data and information submitted and to prepare a report on the safety, effectiveness, and labeling of OTC cold, cough, allergy, bronchodilator and antiasthmatic ingredients pursuant to § 330.10(a)(1):

Francis C. Lowell, M.D., Chairman
Hylan A. Bickerman, M.D.
Halla Brown, M.D.
Robert K. Chalmers, Ph.D.
Mary Jo Reilly, M.S.
James R. Tureman, M.D.
Colin R. Woolf, M.D.

The Panel was first convened on November 6, 1972, in an organizational meeting. Working meetings were held on December 11 and 12, 1972; January 23 and 24, February 28 and March 1, April 5 and 6, May 10 and 11, June 19 and 20, September 25 and 26, October 31 and November 1, December 6 and 7, 1973; January 8 and 9, March 19 and 20, June 12 and 13, September 11 and 12, October 31, November 1, December 3 and 4, 1974; January 30 and 31, April 3, 4 and 5, May 15 and 16, July 17 and 18, September 24 and 25, November 19, 20 and 21, and December 17, 18 and 19, 1975; February 2, and March 2 and 3, 1976.

Two nonvoting liaison representatives served on the Panel. Mrs. Anita Ohlhausen, nominated by an ad hoc group of consumer organizations, served as the consumer liaison and Joseph L. Kanig, Ph. D., nominated by the Proprietary Association, served as the industry liaison. The following employees of the Food and Drug Administration served: Anna L. Standard, M.D., Executive Secretary until March 26, 1974 followed by Joel Aronson, R. Ph.; Thomas D. DeCillis, R. Ph., Panel Administrator; Recie Bomar, R. Ph., Drug Information Analyst until February, 1973 followed by Lloyd G. Scott, R. Ph. until May, 1974 followed by Gary P. Trosclair, R. Ph.

In addition to the Panel members and liaison representatives, the following individuals were given an opportunity to appear before the Panel to express their views either at their own or at the Panel's request:

Paul Bass, Ph. D.
C. Warren Bearman, M.D.
John Behrman, M.D.
Richard C. Brogle, Ph. D.
C. Edward Buckley III, M.D.
A. Lee Caldwell, Jr., Ph. D.
Robert B. Choate
Sanford Chodosh, M.D.
John T. Connell, M.D.
Joseph Dresner
Constantine Falliers, M.D.
Arthur D. Flanagan, M.D.
Spencer Free, Ph. D.
Arthur Grollman, M.D.
Robert M. Hodges
George F. Hoffnagle, Sc. D.
Clarence Imboden, M.D.
Charles Janeway, M.D.
Anita Johnson, Esq.
Stuart J. Land, Esq.
Ben Marr Lanman, M.D.
Vincent D. Larkin, M.D.
Louie G. Linarelli, M.D.
Jennifer Loggie, M.D.
S. J. London, M.D.
Leslie M. Lueck, M.D.
Guillermo Martinez
John McLean, M.D.
Fletcher B. Owen, M.D.
Elias W. Packman, Sc. D.
Joseph Page, Esq.
Joseph J. Pittelli, M.D.
William R. Pool
Thomas W. Richards, M.D.
Norman Salik, M.D.
Robert T. Scanlon, M.D.
Daniel L. Shaw, Jr., M.D.
Alex Silverglade, M.D.
Joseph Smith, M.D.
Alfred E. Sutherland, Esq.
Garret W. Swenson, Esq.
M. L. Thomson, M.D.
Sumner Yaffee, M.D.

No person who so requested was denied an opportunity to appear before the Panel.

The Panel has thoroughly reviewed the literature, and the various data submissions, has listened to additional testimony from interested parties and has considered all pertinent data and information submitted through March 3, 1976 in arriving at its conclusions and recommendations.

In accordance with the OTC drug review regulations (21 CFR 330.10), the Panel's findings with respect to these classes of drugs are set out in three categories:

Category I. Conditions under which cold, cough, allergy, bronchodilator and antiasthmatic products are generally recognized as safe and effective and are not misbranded.

Category II. Conditions under which cold, cough, allergy, bronchodilator and antiasthmatic products are not generally recognized as safe and effective or are misbranded.

Category III. Conditions for which the available data are insufficient to permit final classification at this time.

The Panel recommends the following for each group of drugs:

1. That the conditions included in the monograph on the basis of the Panel's determination that they are generally recognized as safe and effective and are not misbranded (Category I) be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

2. That the conditions excluded from the monograph on the basis of the Panel's determination that they would result in the drug not being generally recognized as safe and effective or would result in misbranding (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER, regardless of whether further testing is undertaken to justify their future use.

3. That the conditions excluded from the monograph on the basis of the Panel's determination that the available data are insufficient (Category III) to classify such conditions either as Category I—generally recognized as safe and effective and not misbranded; or as Category II not being generally recognized as safe and effective or would result in misbranding, be permitted to remain in use for a period of time justified in the report of 2, 3, 4 or 5 years for the specific conditions after the date of publication of the final monograph in the FEDERAL REGISTER, if the manufacturer or distributor of any such drug utilizing such conditions in the interim conducts tests and studies adequate and appropriate to satisfy the questions raised with respect to the particular condition by the Panel.

I. SUBMISSION OF DATA AND INFORMATION

Pursuant to the notice published in the FEDERAL REGISTER of August 9, 1972 (37 FR 16029) requesting the submission of data and information on cold, cough, allergy, bronchodilator and antiasthmatic (CCABA) drugs, the following firms made submissions relating to the indicated products:

A. SUBMISSIONS BY FIRMS

Firm	*Marketed products*
Abbott Laboratories, North Chicago, Ill. 60064.	Calcidrine Syrup, Quelidrine Cough Syrup.
Block Drug Co., Inc., Jersey City, N.J. 07302	BC All Clear.
Boericke & Tafel, Inc., Philadelphia, Pa. 19107.	B & R Dictan Cough Syrup, B & R Tablets No. 241.
Breon Laboratories, Inc., New York, N.Y. 10016.	Bronkotabs, Bronkotabs-HAFS, Broncholixir.
Calgon Consumer Prod., Co., Inc., Pittsburgh, Pa. 15230.	Sucrets Cold Decongestant Formula, Sucrets Cough Control Formula, Sucrets Sore Throat Lozenges.
Chesebrough-Pond's, Inc., Trumbull, Conn. 06611.	Cold-Team-24 Daytime Tablets, Cold-Team-Nighttime Liquid, Pertussin 8-Hour Cough Formula, Pertussin Medicated Vaporizer, Pertussin Plus Night-Time Cold Medicine, Pertussin Wild Berry Cough Syrup.
Ciba-Geigy Corp., Summit, N.J. 07901	Otrivin Nasal Solution, Otrivin Nasal Spray, Otrivin Pediatric Nasal Solution, Otrivin Pediatric Nasal Spray, Privine Nasal Solution, Privine Nasal Spray.
Colgate-Palmolive Co., Piscataway, N.J. 08854.	Congestaid Aerosol.
Creomulsion Co., Atlanta, Ga. 30301	Cough Chek, Colchek, Creomulsion Cough Medicine, Creomulsion Cough Medicine for Children, Creozets Cough and Throat Lozenges.
Dorsey Laboratories, Lincoln, Nebr. 68501	Chexit Tablets, Dor-C Tablets, Dorcol Pediatric Cough Syrup, Triaminic Expectorant, Triaminic Syrup, Triaminicin Nasal Spray, Triaminicin Tablets, Triaminicol Cough Syrup, Tussagesic Suspension, Tussagesic Tablets, and Ursinus Tablets.
The Dow Chemical Co., Zionsville, Ind. 46077	Novahistine DH, Novahistine Elixir, Novahistine Expectorant, Novahistine Fortis Capsules, Novahistine Melet Tablets, 2/G, and 2G/DM.
Drew Laboratories, New York, N.Y. 10016	Bronkaid Mist, Bronkaid Tablets.
F & F Laboratories, Inc., Chicago, Ill. 60632	F. & F. Original Formula Cough Lozenges.
Father John's Medicine Co., Inc., Lowell, Mass. 01853.	Father John's Medicine for Cough and Colds.
G. E. Laboratories, Inc., Shamokin, Pa. 17872	Troutman's Cough Syrup.
Glenbrook Laboratories, New York, N.Y. 10016.	Breacol Decongestant Cough Medication with Neo-Synephrine.
Hall Brothers, Radcliffe, Manchester England.	Hall's Honey-Lemon Cough Drops.
Hall Brothers, Whitefield, Manchester England.	Hall's Cherry Cough Drops.
Hoffman-LaRoche, Inc., Nutley, N.J. 07110	Theporin, Phenindamine.
The Holford Co., Minneapolis, Minn. 55403	Holford's Famous Inhaler, Indian Chief Inhaler.
Ives Laboratories, Inc., New York, N.Y. 10017	Cerose, Cerose Compound Cerose-DM, Cetro-Cerose.
Johnson & Johnson, New Brunswick, N.J. 08903.	Sine-Aid.
Key Pharmaceuticals, Inc., Miami, Fla. 33169	Key Tusscapine.
Knoll Pharmaceutical Co., Whippany, N.J. 07981.	Verequad Suspension, Verequad Tablets.
LaMay's Asthma Eze, Inc., Kalaska, Mich. 49646.	Asthma Eze.
Luden's, Inc., Reading, Pa. 19601	Luden's Honey Lemon Cough Drops, Luden's Honey Licorice Cough Drops, Luden's Menthol Cough Drops, Luden's Menthol Eucalyptus Cough Drops, Luden's Wild Cherry Cough Drops.
Menley & James Laboratories, Philadelphia, Pa. 19101.	Contac.
The Metholatum Co., Inc., Buffalo, N.Y. 14213.	Mentholatum Ointment.
Merck and Co., Inc., Rahway, N.J. 07065	Nectadon.
Merck Sharp & Dohme, West Point, Pa. 19486	Propadrine Capsules 25 mg, Propadrine Capsules 50 mg, Propadrine Elixir.
Miles Laboratories, Inc., Elkhart, Ind. 46514	Alka-Seltzer Plus Cold Tablets.
Monsanto Co., St. Louis, Mo. 63166	Methapyrilene Fumarate, Methapyrilene Hydrochloride.
McNeil Laboratories, Inc., Fort Washington, Pa. 19034.	Co-Tylenol Cold Formula.

Mitchum-Thayer, Inc., New York, N.Y. 10020	Arrestin Extra Strength Cough Medicine with D-Methorphan, Asthma-Nefrin Solution "A" Inhalant, AsthmaNefrin Automatic Aerosol Mist, AsthmaNefrin Capsules, Liquiprin Nighttime Cold Medicine for Children.
Norwich Products, Norwich, N.Y. 13815	Norwich Baby Cough Syrup, Norwich Terpin Hydrate and Dextromethorphan Hydrobromide Elixir N.F., Quadrin Decongestive Tablets.
Parke-Davis & Co., Detroit, Mich. 48232	Benylin Cough Syrup, Benadryl.
S. B. Penick & Co., New York, N.Y. 10007	Glyceryl Guaiacolate.
Pfipharmecs Pfizer Pharmaceuticals, New York, N.Y. 10017.	Toclase Cough Syrup, Toclase Cough Tablets.
Pharmacraft, Rochester, N.Y. 14603	Allerest Allergy Tablets, Allerest Nasal Spray, Allerest Time Capsules, Children's Allerest Allergy Tablets, Sinarest.
Plough, Inc., Memphis, Tenn. 38101	St. Joseph Cough Syrup for Children.
Reid-Provident Laboratories, Inc., Atlanta, Ga. 30308.	Coton Syrup, Histalet-DM, Reidacol, Tusstrol, Tusstrol-DM.
A. H. Robins Co., Richmond, Va. 23220	Dimetane Elixir, Dimetane Tablets, Robitussets Troches, Robitussin, Robitussin-DM Cough Calmers, Robitussin-DM, Robitussin-PE Decongestant Expectorant.
Roerig, New York, N.Y. 10017	Coryban-D Cold Capsules, Coryban-D Cough Syrup, Coryban-D Nasal Spray.
Sandoz Pharmaceuticals, E. Hanover, N.J. 07936.	Flogesic.
Sauter Labs., Inc., Nutley, N.J. 07110	Children's Romilar Cough Syrup, Romilar CF Capsules, Romilar CF Syrup, Romilar CF 8-Hour Cough Formula, Romilar Chewable Cough Tablets for Children, Romilar Cough and Cold Capsules, Romilar Cough Discs, Romilar Expectorant, Romilar Hydrobromide Tablets, Romilar Syrup, Romilar III Cough Syrup with Expellin.
G. D. Searle & Co., Chicago, Ill. 60680	Amodrine.
Schering Corp., Bloomfield, N.J. 07003	Afrin Decongestant Nasal Spray, Afrin Decongestant Nose Drops, Chlor-Trimeton Antihistamine Syrup, Chlor-Trimeton Antihistamine Tablets, Coricidin "D" Tablets, Children's Coricidin Demilets Tablets, Children's Coricidin Medilets, Coricidin.
R. Schiffmann Co., Los Angeles, Calif. 90031	Asthmador.
Smith, Kline, & French Laboratories, Philadelphia, Pa. 19101.	Benzedrex Inhaler, Ornacol Cough and Cold Capsules, Ornacol Cough and Cold Liquid, Ornex, Toryn Syrup, Toryn Tablets.
E. R. Squibb & Sons, Inc., New Brunswick, N.J. 08903.	Spec-T Anesthetic Lozenges, Spec-T Sore Throat Decongestant Lozenges, Spec-T Sore Throat Spray, Spec-T Sore Throat Cough Suppressant Lozenges.
Sterling Products International, New York, N.Y. 10016.	Breacol with Prylon.
Templetons, Inc., Buffalo, N.Y. 14223	Raz-Mah Greys Capsules.
Henry Thayer Co., Cambridge, Mass. 02138	Thayers Slippery Elm Throat Lozenges, Thayers Slippery Elm Throat Lozenges (Wild Cherry).
Thayer Labs, Inc., Cambridge, Mass. 02138	AsthmaNefrin Syrup.
The Upjohn Co., Kalamazoo, Mich. 49001	Cheracol Cough Syrup, Cheracol D Cough Syrup, Cidicol Syrup, Elixir Terpin Hydrate and Codeine N.F., Elixir Terpin Hydrate and Codeine Sulfate, Emeracol Cough Syrup, Hydriodic Acid Cough Syrup, Aromatic Iodized Lime Expectorant Tablets, Orthoxicol Cough Syrup, Pyrroxate Capsules, Pyrroxate Tablets, Special Formula No. 2 Analgesic Antipyretic Tablets.
Vick Chemical Co., New York, N.Y. 10017	Vicks NyQuil Nighttime Colds Medicine, Vicks Cough Silencers, Vicks Cough Syrup, Vicks Formula 44 Cough Discs, Vicks Formula 44 Cough Mixture, Vicks Formula 44-D Cough Mixture, Vicks Inhaler, Vicks Medicated Cough Drops (Blue Mint), Vicks Medicated Cough Drops (Menthol-Eucalyptus), Vicks Medicated Cough Drops (Regular), Vicks Medicated Cough Drops (True Lemon), Vicks Medicated Cough Drops (Wild Cherry), Vicks Sinex Decongestant Nasal Spray, Vicks Vaporub, Victors Menthol-Eucalyptus Dual Action Cough Drops and Victors Menthol-Eucalyptus Dual Action Cough Drops (Cherry), Vicks Vaporub, Vicks Vaposteam, Oil of Turpentine, Doxylamine Succinate.

Warner-Chilcott Laboratories, Morris Plains, N.J. 07950.	Tedral Tablets, Tedral Anti-H Tablets, Tedral Pediatric Suspension.
Warner-Lambert Co., Morris Plains, N.J. 07950.	Listerine Big 4 Cough Formula, Hall's Mentho-Lyptus Cough Tablets, Listerine Antiseptic, Listerine Antiseptic Throat Lozenges (lemon-mint), Listerine Antiseptic Throat Lozenges (orange), Listerine Antiseptic Throat Lozenges (regular), Listerine Cold Tablet, Listerine Cough Control Lozenges, Smith Brothers Medicated Cough Drops (black licorice), Smith Brothers Medicated Cough Drops with Benzocaine (minted menthol), Smith Brothers Medicated Cough Drops (Wild Cherry), Super Anahist Decongestant Tablets, Super Anahist Decongestant Nasal Spray.
Whitehall Laboratories, Inc., New York, N.Y. 10017.	Bronitin Tablets, Bronitin Mist, Clear & Dry Sinus Clearant Tablets, Dondril Anticough Tablets, Dristan Decongestant Tablets, Dristan Capsules, Dristan Nasal Mist, Dristan Decongestant Vapor Nasal Spray, Primatene M Formula Tablets, Primatene Mist, Primatene P Formula Tablets, Dristan Decongestant Cough Formula.
Winthrop Laboratories, New York, N.Y. 10016.	Neo-Synephrine Compound Decongestant Cold Tablets, Neo-Synephrine HCl Decongestant Elixir, Neo-Synephrine HCl Jelly, Neo-Synephrine Nasal Spray ¼ percent, Neo-Synephrine Nasal Spray ½ percent, Neo-Synephrine Decongestant Nose Drops ⅛ percent, Neo-Synephrine Decongestant Nose Drops ¼ percent, Neo-Synephrine Decongestant Nose Drops ½ percent, Neo-Synephrine Decongestant Nose Drops 1 percent, NTZ Nasal Spray, NTZ Decongestant Nose Drops, Synephricol Antihistaminic Cough Syrup.
Winthrop Products, Inc., New York, N.Y. 10016.	NRT Antihistaminic Decongestant, NRT Nasal Spray, Asafen Tablets, Deka Expectorant Cough Syrup, NTR Decongestant Antihistaminic, NTR Nasal Spray, Recindal, Synephricol Cold Tablets, Neosynephrine Intranasal Drops ¼ percent, Neosynephrine Intranasal Drops 1 percent.
Wyeth Laboratories, Philadelphia, Pa. 19101.	Phenergan.

In addition, the following firms or groups made related submissions:

Firm	*Submissions*
Bristol-Myers Products, New York, N.Y. 10022.	Phenylephrine hydrochloride, Phenylpropanolamine.
Chattem Drug & Chemical Co., Chattanooga, Tenn. 37409.	Theophylline sodium glycinate.
Lilly Research Laboratories, Indianapolis, Ind. 46206.	Methapyrilene hydrochloride.
Miles Laboratories, Inc., Elkhart, Ind. 46514.	Phenylpropanolamine salts.
Parke Davis & Co., Detroit, Mich. 48232.	Diphenhydramine and pseudoephedrine.
A. H. Robins, Richmond, Va. 23220.	Glyceryl guaiacolate.
Smith, Kline & French Laboratories, Philadelphia, Pa. 19101.	Chlorpheniramine, Brompheniramine maleate, Phenylpropanolamine, propylhexedrine, caramiphen edisylate.
Linda Taliaferro, Austin, Tex. 78712.	Stramonium-belladonna.
Vick Chemical Co., New York, N.Y. 10017.	Topical ephedrine, doxylamine succinate, xylometazoline hydrochloride.
Vick Division Research, Mount Vernon, N.Y. 10553.	Alcohol.
Whitehall Laboratories, Inc., New York, N.Y. 10017.	Oral phenylephrine, and oral phenindamine.
Wyeth Laboratories, Inc., Philadelphia, Pa. 19101.	Promethazine hydrochloride.

B. LABELED INGREDIENTS CONTAINED IN MARKETED PRODUCTS SUBMITTED TO THE PANEL

Acetaminophen (*N*-acetyl-*p*-aminophenol)
Acetic acid
N-acetyl-*p*-aminophenol (acetaminophen)
Alcohol
Alkyl dimethyl benzylammonium chloride (benzalkonium chloride)
Aloin
Aluminum hydroxide-magnesium carbonate co-dried gel
Aminophylline
Ammonium chloride
Anethole
Anise
Antimony potassium tartrate
Ascorbic acid (vitamin C)
Aspirin
Atropine sulfate
Banana arome
Beechwood creosote
Belladonna
Belladonna alkaloids
Benzalkonium chloride (alkyl dimethyl benzylammonium chloride)
Benzocaine
Benzyl alcohol
Benzaldehyde
Blood root
Boric acid
Bornyl acetate
Brompheniramine maleate
Bryonia tincture
Caffeine
Calcium carbaspirin
Calcium iodide anhydrous (iodides)
Camphor
Capsicum
Caramel
Caramiphen edisylate (caramiphen ethanedisulfonate)
Caramiphen ethanedisulfonate (caramiphen edisylate)
Carbetapentane citrate
Cascara
Cedar leaf oil
Cedar, natural
Cetalkonium chloride
Cetylpyridinium chloride
Cherry flavoring
Cherry nut flavoring
Chlorobutanol
Chloroform
Chlorpheniramine maleate
Citric acid
Citric acid (hydrate)
Cocillana
Cod liver oil
Codeine
Codeine alkaloid
Codeine phosphate
Codeine sulfate
Compound white pine syrup
1-Desoxyephedrine
Dextromethorphan
Dextromethorphan hydrobromide
Dextrose
Dioctyl sodium sulfosuccinate
Diphenhydramine hydrochloride
Dipropylene glycol
Disodium edetate
Doxylamine succinate
Drosera tincture
Elm bark
Ephedrine
Ephedrine hydrochloride
Ephedrine sulfate
Epinephrine
Epinephrine bitartrate
Epinephrine hydrochloride (racemic)
Eriodictyon fluid extract (yerba santa)
Ethylmorphine hydrochloride
Eucalyptol
Eucalyptus oil
Euphorbia pilulifera
Exract white pine compound
F. E. Horehound
Fluidextract ipecac (ipecac fluidextract)
Glycerin
Glyceryl guaiacolate
Glycyrrhiza (licorice)
Grape flavoring
Grindelia
Gum arabic
Hexylresorcinol
Honey
Hydriodic acid (iodides)
Hydrocodone bitartrate
Hyoscyamine sulfate
Iodides (calcium iodide anhydrous, hydriodic acid syrup, iodized lime, potassium iodide)
Iodized lime (iodides)
Ipecac
Ipecac fluidextract (fluidextract ipecac)
Lemon oil
Licorice (glycyrrhiza)
Lobelia
Lobelium
Menthol/peppermint oil
Methapyrilene fumarate
Methapyrilene hydrochloride
Methoxyphenamine hydrochloride
Methylcellulose
Methylparaben

Methyl salicylate
Monocalcium phosphate
Mustard oil
Myristica oil
Naphazoline hydrochloride
Noscapine
Noscapine hydrochloride
Oil of pine
Oleyl alcohol
Oxymetazoline hydrochloride
Peppermint oil/menthol
Petrolatum base
Phenacetin
Phenindamine tartrate
Pheniramine maleate
Phenobarbital
Phenylephrine bitartrate
Phenylephrine hydrochloride
Phenylmercuric acetate
Phenylpropanolamine hydrochloride
Phenylpropanolamine bitartrate
Phenylpropanolamine maleate
Phenyltoloxamine citrate
Pineapple flavoring
Pine tar
Podophyllum resin
Potassium guaiacolsulfonate
Potassium nitrate
Promethazine hydrochloride
Propylhexedrine
Propylparaben
Pseudoephedrine sulfate
Pyrilamine maleate
Quinine sulfate
Racemic epinephrine hydrochloride
Racephedrine hydrochloride
Rumex
Salicylamide
Saline phosphate buffer solution
Scopolamine hydrobromide
Sodium bicarbonate
Sodium bisulfite
Sodium citrate
Spirits of turpentine (turpentine oil)
Squill extract
Sticta pulmonaria
Stramonium
Sucrose
Sugar
Sugar base
Syrup base
Terpin hydrate
Thenyldiamine hydrochloride
Theophylline
Theophylline anhydrous
Theophylline calcium salicylate
Thimerosal
Thonzonium bromide
Thonzylamine hydrochloride
Thymol
Tincture of benzoin
Tolu
Tolu balsam
Tolu balsam tincture
Triethylene glycol
Vegetable stearate
Vitamin C (ascorbic acid)
White pine
Wild cherry
Wild cherry fluid extract
Yerba santa (eriodictyon fluid extract)
Xylometazoline hydrochloride

Ingredients reviewed by the Panel in addition to the submitted data:

Ipecac syrup
Potassium iodide (iodides)
Theophylline sodium glycinate

C. CLASSIFICATION OF INGREDIENTS

1. Active ingredients. The Panel has classified the following ingredients submitted to the Panel into groups identified below:

ANTITUSSIVES

Beachwood creosote
Camphor
Caramiphen edisylate (caramiphen ethanedisulfonate)
Caramiphen ethanedisulfonate (caramiphen edisylate)
Carbetapentane citrate
Cod liver oil
Codeine
Codeine alkaloid
Codeine phosphate
Codeine sulfate
Dextromethorphan
Dextromethorphan hydrobromide
Diphenhydramine hydrochloride
Elm bark
Ethylmorphine hydrochloride
Eucalyptol/eucalyptus oil
Horehound
Horehound (horehound fluid extract)
Hydrocodone bitartrate (dihydrocodeinone)
Menthol/peppermint oil
Noscapine
Noscapine hydrochloride
Thymol
Turpentine oil (spirits of turpentine)

EXPECTORANTS

Ammonium chloride
Antimony potassium tartrate
Beechwood creosote
Camphor
Chloroform
Compound benzoin tincture
Compound white pine syrup
Eucalyptol/eucalyptus oil
Extract white pine compound
Glyceryl guaiacolate
Iodides (calcium iodide anhydrous, hydriodic acid syrup, iodized lime, potassium iodide)
Ipecac fluidextract
Ipecac syrup
Menthol/peppermint oil
Pine tar
Potassium guaiacolsulfonate
Sodium citrate
Squill
Squill extract
Syrup of pine tar
Terpin hydrate
Terpin hydrate elixir
Tincture of benzoin
Tolu
Tolu balsam
Tolu balsam tincture
Turpentine oil (spirits of turpentine)
White pine

BRONCHODILATORS

SYMPATHOMIMETIC AMINES

Belladonna alkaloids
Ephedrine
Ephedrine hydrochloride
Ephedrine sulfate
Epinephrine
Epinephrine bitartrate
Epinephrine hydrochloride (racemic)
Methoxyphenamine hydrochloride
Pseudoephedrine hydrochloride
Pseudoephedrine sulfate
Racephedrine hydrochloride

THEOPHYLLINES

Aminophylline
Theophylline anhydrous
Theophylline calcium salicylate
Theophylline sodium glycinate

MISCELLANEOUS

Euphorbia pilulifera

ANTICHOLINERGICS

Atropine sulfate
Belladonna
Belladonna alkaloids
Hyoscyamine sulfate
Scopolamine hydrobromide
Stramonium

ANTIHISTAMINES

Brompheniramine maleate
Chlorpheniramine maleate
Diphenhydramine hydrochloride
Doxylamine succinate
Methapyrilene fumarate
Methapyrilene hydrochloride
Phenindamine tartrate
Pheniramine maleate
Phenyltoloxamine citrate
Promethazine hydrochloride
Pyrilamine maleate
Thenyldiamine hydrochloride
Thonzylamine hydrochloride

NASAL DECONGESTANTS

Beechwood creosote
Bornyl acetate
Camphor
Cedar leaf oil
1-Desoxyephedrine
Ephedrine
Ephedrine hydrochloride
Ephedrine sulfate
Eucalyptol/eucalyptus oil
Menthol/peppermint oil
Mustard oil (allylisothiocyanate)
Naphazoline hydrochloride
Oxymetazoline hydrochloride
Phenylephrine hydrochloride
Phenylpropanolamine hydrochloride
Phenylpropanolamine bitartrate
Phenylpropanolamine maleate
Propylhexedrine
Pseudoephedrine hydrochloride
Pseudoephedrine sulfate
Racephedrine hydrochloride
Thenyldiamine hydrochloride
Thymol
Turpentine oil (spirits of turpentine)
Xylometazoline hydrochloride

2. Miscellaneous labeled ingredients:

Antihistamines with sleep-aid claims
Ascorbic acid (vitamin C)
Caffeine
Phenobarbital
Vitamins

3. Ingredients submitted to the Panel and classified as inactive and/or pharmaceutical necessary ingredients:

Acetic acid
Alcohol
Alkyl dimethyl benzylammonium chloride (benzalkonium chloride)
Aluminum hydroxide—magnesium carbonate (co-dried gel)
Anethole
Anise
Banana arome
Benzaldehyde
Benzalkonium chloride (alkyl dimethyl benzylammonium chloride)
Blood root
Bryonia tincture
Caramel
Cedar, natural
Cetalkonium chloride
Cetylpyridinium chloride
Cherry flavoring
Cherry nut flavoring
Chlorobutanol
Chloroform (0.4% maximum)
Citric acid
Citric acid (hydrate)
Cocillana
Dextrose
Dipropylene glycol
Disodium edetate
Drosera tincture
Eriodictyon fluidextract (yerba santa)
Glycerin
Glycyrrhiza (licorice)
Grape flavoring
Grindelia
Gum arabic

Honey
Lemon oil
Licorice (glycyrrhiza)
Lobelia
Lobelium
Methyl cellulose
Methylparaben
Monocalcium phosphate
Myristica oil
Oleyl alcohol
Petrolatum base
Phenylmercuric acetate
Pineapple flavoring
Potassium nitrate
Propylparaben
Rumex
Saline phosphate buffer solution
Sodium bisulfite
Sticta pulmonaria
Sucrose
Sugar
Sugar base
Syrup base
Thimerosol
Thonzonium bromide
Triethylene glycol
Vegetable stearate
Wild cherry
Wild cherry fluidextract
Yerba santa (eriodictyon fluidextract)

4. Ingredients submitted to the Panel and deferred to other OTC advisory review panels.

a. Ingredients deferred to the Advisory Review Panel on OTC internal analgesic including antirheumatic drug products:

(1) Acetaminophen (*N*-acetyl-*p*-aminophenol)
(2) *N*-acetyl-*p*-aminophenol (acetaminophen)
(3) Aspirin
(4) Calcium carbaspirin
(5) Phenacetin
(6) Quinine sulfate
(7) Salicylamide

b. Ingredients deferred to the Advisory Review Panel on OTC laxative, antidiarrheal, emetic and antiemetic drug products:

(1) Aloin
(2) Cascara
(3) Dioctyl sodium sulfosuccinate
(4) Podophyllum resin

c. Ingredients deferred to the Advisory Review Panel on OTC topical analgesic, antirheumatic, otic, burn, and sunburn treatment and prevention drug products:

(1) Benzocaine
(2) Benzyl alcohol
(3) Boric acid
(4) Capsicum
(5) Methyl salicylate

d. Ingredients deferred to the Advisory Review Panel on OTC oral cavity drug products:

(1) Hexylresorcinol
(2) Methyl salicylate

e. Ingredient deferred to the Advisory Review Panel on antacid drug products:

(1) Sodium bicarbonate

II. General Statements and Recommendations

A. General Comment

The OTC cold, cough, allergy, bronchodilator and antiasthematic Panel was charged with the review and the evaluation of safety and effectiveness data on cold, cough, allergy, bronchodilator, and antiasthmatic ingredients and combinations thereof, the adequacy of their labeling, and to advise the Commissioner of Food and Drugs on the promulgation of monographs establishing conditions under which these over-the-counter (OTC) drug products are generally recognized as safe and effective and not misbranded. The Panel also served as a forum for the exchange of views regarding the prescription or nonprescription status of these various active ingredients and combinations thereof. Panel members were expected to call upon their own expert knowledge and experience in carrying out each element of this charge. Specifically the Panel was charged with the following:

1. Review and evaluation of all data made available to the panel members concerning the safety and effectiveness of cold, cough, allergy, bronchodilator and antiasthmatic treatment and prevention agents, and combinations thereof, utilized in these OTC drug products.

2. Advising the Food and Drug Administration as to the adequacy of the labeling of such cold, cough, allergy, bronchodilator and antiasthmatic treatment and prevention drug products and to make recommendations as to the contents of future labeling of such products.

3. Making recommendations to the Food and Drug Administration regarding those ingredients, their amounts, and combinations thereof, which, based upon the available data, could be considered safe and effective for the above stated uses. These recommendations must be in keeping with agency stated definitions of the terms "safe" and "effective" and in keeping with the agency OTC drug combination policy (21 CFR 330.10(a)(4)(iv)).

4. Making recommendations to the Food and Drug Administration regarding those ingredients, their amounts, and combinations thereof, which based upon the available data, are not considered as safe and effective for the above stated uses. The same criteria must apply as in the determinations of those ingredients which are found to be safe and effective.

5. Advising the Food and Drug Administration regarding those ingredients which in their judgment are likely to be safe and effective, but for which more data are needed. In such cases the Panel was requested to give some guidance as to what type of studies and the maximum time period they feel would be adequate to produce such information for future consideration by the Food and Drug Administration.

6. Advising the Food and Drug Administration on the promulgation of a monograph or monographs establishing conditions under which these OTC drug products are generally recognized as safe and effective and not misbranded. This information is submitted in the form of a written report by the Panel containing the following basic recommendations:

a. Listing of the acceptable active ingredients, singly or combinations thereof.

b. Acceptable dosage ranges of these active ingredients and their combinations.

c. A statement of the acceptable indications for use.

d. Recommended labeling guidelines—warnings, precautions, contraindications, directions for use.

B. Diseases and Related Symptoms Relieved by OTC Cold, Cough, Bronchodilator and Antiasthmatic Products

The Panel makes the following statements and recommendations concerning the symptoms related to the use of antitussives, expectorants, bronchodilators, anticholinergics, antihistamines and nasal decongestants. The symptoms which these drugs may be expected to relieve are those occurring in certain allergic states such as hay fever, asthma, and symptoms in the nose, eyes, sinuses and throat caused by the common cold and other mild respiratory infections. It must be kept in mind that the ingredients and combinations reviewed are not intended to cure but are OTC drugs to provide symptomatic relief.

The Panel has prepared the following table which lists symptoms and the acceptable corresponding pharmacologic groups of drugs for the treatment of these symptoms:

Symptom	*Pharmacologic group*
1. Bronchospasm or asthma	Bronchodilators (sympathomimetic amines, theophyllines)—with the Category I labeling indications recommended by the Panel. (See pt. V. par. B.1. below—Labeling.)
2. Cough	Antitussives—with the Category I labeling indications recommended by the Panel. (See pt. III. par. B.1. below—Labeling.) Expectorants—with the Category I labeling indications recommended by the Panel. (See pt. IV. par. B.1. below—Labeling.).
3. Runny nose	Anticholinergics—with the Category I labeling indications recommended by the Panel. (See pt. VI. par. B.1. below—Labeling.)
4. Nasal congestion	Nasal decongestants—with the Category I labeling indications recommended by the Panel. (See pt. VIII. par. B.1. below—Labeling.)
5. Sinus congestion	Do. Analgesics—with the Category I labeling indications recommended by the OTC Internal Analgesic Panel.
6. Sneezing, watery eyes, and itchy eyes	Antihistamines—with the Category I labeling indications recommended by the Panel. (See pt. VII. par. B.1. below—Labeling.)
7. Sore throat	Analgesics—with the Category I labeling indications recommended by the OTC Internal Analgesic Panel. Local anesthetics—with the Category I labeling indications recommended by the OTC Oral Cavity Panel.
8. Generalized aching	Analgesics—with the Category I labeling indications recommended by the OTC Internal Analgesic Panel.
9. Fever	Antipyretics—with the Category I labeling indications recommended by the OTC Internal Analgesic Panel.

1. *Allergy.* Allergy is a complex of symptoms which arises under circumstances when a person who has acquired a hypersensitivity to a substance encounters that substance. Although one may be born with a tendency to become allergic, one must be exposed to a substance for weeks, months or years before one actually becomes allergic to it. Probably about 15 percent or more of the population becomes significantly allergic. Substances to which people ordinarily become allergic are pollens, mold spores, animal dander and certain dusts and sprays in the home and in industry. These are airborne and are inhaled. One may also become allergic to certain foods and drugs and to substances coming in contact with the skin such as drugs and poison ivy (poison oak). Substances to which people become allergic are called allergens. In our highly industrial and technological society we are increasingly exposed to allergens never encountered by our forebears; for this reason, the number of persons with allergies is rising and may continue to rise.

The allergic symptoms with which the Panel is concerned are nasal (sneezing, watery or mucous discharge, itching and obstruction), and bronchial (cough, bronchospasm and expectoration). Another manifestation of allergy is itchy and watery eyes. Allergy of this type belongs to a subgroup of the so-called "immune" class of disease termed "atopy." In this class of disease an antibody mediates the reaction. The antibody belongs to the IgE class of immunoglobulins which has the peculiarity of attaching itself to a certain type of cell (mast cells in the tissues and basophils in the blood). With the arrival of the allergen, union between the allergen and the antibody attached to these cells occurs and leads to the release of substances which in turn cause the symptoms we call "allergic." One of the substances released, and perhaps the principal one, is histamine. The antihistaminic drugs block the action of histamine.

Identification and elimination of the offending substance (allergen) are the measures of choice. However, these are often impossible to achieve. The proper use of OTC products containing antihistamines, sympathomimetics, or theophyllines may provide relief of allergy symptoms. Although OTC drugs are often adequate for relief, the allergic reaction may be so intense that OTC drugs are not adequate and other measures, such as epinephrine by injection, and corticosteroids, requiring the supervision of a physician are needed. In the case of allergy to pollens and some other inhaled allergens, symptoms can be lessened or eliminated under medical supervision by a course of injections of suitably prepared allergenic extract.

REFERENCES

(1) Sheldon, J. M., R. G. Lovell and K. P. Mathews, "A Manual of Clinical Allergy," 2d Ed., W. B. Saunders Co., Philadelphia, 1967.

(2) Patterson, R., "Allergic Diseases: Diagnosis and Management," The J. B. Lippincott Co., Philadelphia, 1972.

2. *Asthma and other respiratory diseases and the use of bronchodilators.* Asthma is a disease in which there is widespread narrowing of the airways due to airway wall muscle spasm which occurs in response to various stimuli. Among the stimuli which may lead to asthma is the inhalation of substances such as pollens and animal danders in people who are allergic to these substances. This reaction causes partial obstruction to air flow and shortness of breath. The spasm causing narrowing of the air tubes may subside either spontaneously or as a result of therapy. Airway narrowing occurs also where there is widespread bronchial infection such as in acute or chronic bronchitis, in pulmonary emphysema where there is destruction of the lung tissue, and in pulmonary congestion from failure of the left side of the heart. Asthma is a difficult disease condition for the layman to diagnose and even physicians have difficulty in distinguishing asthma from the above other conditions which cause airway narrowing. Therefore, it is very important that the diagnosis of asthma first be established by a physician before the use of OTC bronchodilator preparations.

Medications which relax the airway muscle spasm and relieve the shortness of breath of asthma are called bronchodilators. Usually these drugs are given by mouth as a tablet or liquid, or they may be inhaled as a spray from a suitable dispenser. The response of mild or even moderate asthma to these drugs is often quick and there is effective relief from shortness of breath. The Panel believes that, when taken as directed, the drugs are safe for OTC use, but undesirable effects can occur. These adverse effects are mainly exhibited as increased rate and force of the heart beat, rise in blood pressure, nervousness and sleeplessness, and nausea or vomiting.

Asthma is a very common disease and it is reasonable to have bronchodilators available on a nonprescription basis so that in mild cases relief may be obtained quickly without the possible delays of obtaining a physician's prescription. However, it is very important that the diagnosis of asthma first be established by a physician as some of the other conditions which resemble asthma, such as pulmonary congestion from failure of the left side of the heart, should not be treated by certain types of bronchodilators. Even the patient with true asthma should be warned that if a bronchodilator does not cause excellent and rapid relief, he should call his physician. The reason he should call his physician is that in a severe and worsening attack of asthma, slight relief may be given by these bronchodilators and this may give a false sense of security. The patient may then postpone seeking medical help or going to a hospital until his disease has reached life-threatening severity. Therefore, labeling of these preparations should be very precise in that the patient should be instructed to seek medical assistance immediately if relief of his symptoms does not occur within a short time of us-

ing the bronchodilator preparation. In the use of epinephrine aerosol, relief should occur within 20 minutes; in the use of ephedrine, methoxyphenamine tablets and tablets of theophylline and its salts, relief should occur within 1 hour.

REFERENCES

(1) Harris, H. W. et al., "Chronic Bronchitis, Asthma and Pulmonary Emphysema. A statement by the Committee on Diagnostic Standards for Nontuberculous Respiratory Disease, American Thoracic Society," *American Review of Respiratory Diseases*, 85:762–768, 1962.

3. *The "common cold" (cold).* The "common cold" (cold) is a self-limited respiratory infection caused by one or more viruses. A cold is rarely serious and is readily transmitted. Throughout this document, the Panel has used the term "common cold" which the Panel considers synonymous with the term "cold."

A "common cold" often begins quite abruptly with soreness or discomfort in the pharynx, sneezing, watery nasal discharge, followed by nasal congestion. The discharge may subsequently become mucoid or purulent. After the first day or two the eyes may become suffused and the voice husky. The nasal congestion intensifies and the sense of smell and taste is often suppressed or absent. Extension into the sinuses may occur as described in the rhinitis statement. Lethargy, some aches and pains and slight fever may be present. The course is variable and may extend for 7 to 14 days. Cough may occur, especially in the later stages.

Early in its course, the cold is indistinguishable from the early stages of measles, rubella, chickenpox, pertussis, cerebrospinal fever, influenza and atypical pneumonia. The cold also closely simulates allergic rhinitis. The physician's main role in the cold is to exclude more serious illness.

There is no generally accepted treatment that can prevent, cure or shorten the course of the "common cold." Treatments which are available only relieve symptoms. Immunity is apparently of short duration since many individuals have one to three colds each year.

4. *Cough.* A cough is the rapid expulsion of air at high velocity from the respiratory airway producing a noise of varying pitch and intensity. Impulses that initiate the cough reflex may arise from many areas within and outside the respiratory tract.

Normally, coughing is produced by stimulation of the sensory endings of the glossopharyngeal and vagus nerves within the mucous membranes of the respiratory tract. This stimulation can be initiated by infection, chemical irritation, the presence of retained secretions, or foreign material blocking the breathing passages. Localized narrowing of the air tubes may play an important role in stimulation of the cough reflex. Cough can also occur from stimulation outside the respiratory tract. For example, if the external ear is tickled, a cough is produced. Cough can be under considerable voluntary control and therefore can be self-suppressed to a degree. Likewise, an individual can initiate a cough at will. Cough occurs in healthy individuals as a mechanism for clearing the airway of any obstructing mucus or inhaled foreign material.

Medications which suppress the act of coughing by reducing the number of coughs and/or the intensity of coughing are known as antitussive drugs. These preparations are administered by mouth in the form of tablets, syrups, elixirs and lozenges, and by inhalation in the form of rubs and vaporizer additives, and when used as directed provide relief from annoying cough. These drugs are generally safe at the dosages recommended for OTC use. However, antitussives derived from narcotics, such as codeine and hydrocodone, commonly cause constipation as a side effect.

The cough is a protective, physiologic reflex occurring in healthy as well as diseased individuals. It is frequently the presenting symptom in a wide variety of pathologic states, ranging from a mild, self-limiting illness to a serious and even fatal disease. In certain disease states such as asthma, chronic bronchitis and cystic fibrosis, the cough reflex is essential in maintaining an open airway by clearing the respiratory passages of excessive secretions. Because of its importance in preserving the function of the lung, by maintaining an open airway, the cough reflex should not be suppressed indiscriminately.

The irritative cough associated with a self-limiting respiratory tract infection is usually viral in nature or follows the inhalation of irritant gases or dusts, and can readily be recognized and serves no useful function. These conditions are usually associated with a dry, hacking, nonproductive cough in which no sputum is expectorated and lends itself to rational self-medication with OTC preparations. On the other hand, the loose, productive type of cough frequently associated with asthma and bronchitis indicates the presence of retained bronchial secretions which could lead to increasing disability if suppressed; and therefore, should not be treated with an antitussive drug. Any cough which persists for longer than 1 week should be investigated by a physician to exclude the presence of an underlying, potentially serious, respiratory disease.

5. *Symptoms of sinus congestion.* Paranasal sinuses are mucous membrane-lined air cavities in the bony structure of the skull which are continuous with the nasal cavity. Impaired sinus drainage due to nasal congestion, e.g., rhinitis of upper respiratory infection or nasal allergy, may result in sinus inflammation (sinusitis) with associated headache and facial pain or tenderness in the region of the affected sinus(es).

Self-medication with an oral or topical nasal decongestant may aid in resolving the problem by diminishing the nasal obstruction which impairs sinus drainage. An orally administered analgesic, e.g., aspirin, acetaminophen, should provide symptomatic relief from headache and pain associated with the sinus congestion. If symptoms persist, intensify and/or are accompanied by fever, a physician should be consulted.

6. *Rhinitis (allergic rhinitis, vasomotor rhinitis).* a. *Allergic rhinitis.* Allergic rhinitis is caused by allergy to airborne allergens including pollens, animal danders, molds and house dust as described elsewhere in this document. (See part II. paragraph B.1. above—Allergy).

The symptoms of allergic rhinitis are sneezing, watery discharge from the nose, nasal stuffiness and obstruction and nasal itching. The eyes may also be involved in which case there is itching, tearing or redness. There may also be puffiness of the eyelids. Less frequently there is headache, itching of the throat and ears and there may be cough. A few patients feel listless or very tired and some describe themselves as feeling generally ill. Hay fever is the familiar example of allergic rhinitis which occurs in persons allergic to pollens.

In addition to rhinitis the paranasal sinuses are frequently involved. This may cause headache usually frontal in distribution or pain or discomfort in the area of the frontal, ethmoid, maxillary or antral sinuses in the front of the face surrounding the nose.

Sneezing may occur irregularly or in paroxysms, more commonly on awaking in the morning, or may be caused by such nonspecific factors as exposure to abrupt changes in temperature or inhalation of particulate matter.

The nasal discharge may be watery in nature, mucoid or purulent. When purulent, bacterial infection is usually assumed to be present. However, this feature is determined by the number of white cells present and not necessarily by the presence of infectious organisms. The nasal discharge of some patients with rhinitis contains such a large number of eosinophils that the discharge acquires a purulent appearance without evidence of infection.

Rhinitis is classically an allergic response to an inhaled allergen, be it pollen, mold or animal dander. However, rhinitis also occurs as the characteristic feature of infections such as the "common cold."

The diagnosis of allergic rhinitis its based on a history of characteristic symptoms as described above and the demonstration by skin testing that the injection of an aqueous extract prepared from the appropriate pollen or allergen will cause within 10 to 20 minutes local redness, a wheal and itching similar to the reaction to the bite of a mosquito. Examination of the nose characteristically but not invariably shows swelling of the internal membranes which are often pearly gray or reddened instead of pink, their normal color.

b. *Vasomotor rhinitis.* There also occurs a form of rhinitis the symptoms of which are not caused by any recognized allergic exposure. This form of rhinitis tends to occur throughout the year with little or no seasonal variation. The condition is usually called vasomotor rhinitis suggesting an abnormal reactivity of the

blood vessels in the nasal lining but in fact the reason for symptoms is unknown. The symptoms of vasomotor rhinitis are the same as those in allergic rhinitis. Skin tests are not helpful in diagnosis.

c. *Treatment of rhinitis symptoms.* The antihistamines are most effective in the treatment of mild allergic rhinitis (such as hay fever). They are less effective in vasomotor rhinitis. These drugs are discussed more completely later in this document. (See part VII. below—Antihistamines.) Nasal decongestants and anticholinergics have also been used in the management of the symptoms of rhinitis. The use of these drugs will be discussed more completely later in this document. (See part VI. below—Anticholinergics and part VIII. below—Nasal Decongestants.)

C. PRINCIPLES APPLICABLE TO COMBINATION PRODUCTS

1. *General combination policy.* Most cold, cough, allergy, bronchodilator and antiasthmatic (CCABA) products currently in the marketplace containing ingredients which the Panel reviewed are promoted or sold to relieve a number of different symptoms. For example, OTC products commonly used for the treatment of the symptoms of the "common cold" include ingredients intended to provide relief of two or more concomitant symptoms such as nasal congestion, running nose, coughing, watery eyes, headache, fever and muscular aches. These products contain more than one active ingredient in order to cover a spectrum of symptoms. Some of these OTC preparations contain ingredients not reviewed by the Panel, e.g., aspirin, which has been deferred to the Advisory Review Panel on OTC internal analgesic including antirheumatic drug products for evaluation of analgesic and antipyretic claims.

In order to clarify the place of combinations in the marketplace, the Panel applied the OTC Drug Review Regulation (21 CFR 330.10(a)(4)(iv)) which states:

> An OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients and when the combination, when used under adequate direction for use, and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population.

The Panel concurs with the regulation and strongly believes that each active ingredient in a combination product must contribute to the claimed effects and that each active ingredient must be necessary for rational therapy of concurrent symptoms. It is the view of the Panel that it is irrational to use a combination product unless each of the contained active ingredients contributes to the effective treatment of at least one of the labeled symptoms for which the combination product is recommended.

The Panel is familiar with the arguments for combination products and at the same time recognizes the disadvantages of fixed-dosage combination products. One major disadvantage commonly expounded is the inability to permit individualized dosage of each active ingredient. The Panel agrees in principle with this argument. However, if the combination product contains only active ingredients at doses of demonstrated safety and effectiveness and all ingredients are necessary for treatment of symptoms, the Panel concludes that certain combinations may offer a convenient and rational approach for relief of concurrent symptoms.

The Panel refers to a recognized source of drug information which notes that cold remedy mixtures are widely used and enjoy a certain amount of acceptance by the medical profession and the laity (Ref. 1). It is the view of the Panel that certain combinations, as established by the Panel are acceptable and summarized below. (See part II. paragraph C.8.b. below—Criterion.) To support this view, the Panel refers to the conclusion in the above-referenced text (Ref. 1) which states "* * * a physician who chooses to prescribe a cold remedy must be certain that the mixture is composed of drugs with known effectiveness, that the ingredients are present in adequate therapeutic amounts, and that they are therapeutically rational for the type and severity of symptoms being treated."

The Panel has established specific criteria for the treatment of symptoms with combination products. Each Category I combination is currently limited to one active ingredient from any one pharmacologic group. The Panel has placed combinations of two active ingredients from the same pharmacologic group in Category III. Each active ingredient must be generally recognized as safe and effective when used alone for the labeled claim(s) and hence make a contribution to the claimed effect(s) of the combination. The acceptable pharmacologic groups included for treatment of symptoms as determined by the Panel differ sufficiently one from another to reduce the likelihood of a competitive or potentiating effect between agents. Therefore, the Panel has recommended only specific combinations be provided and limited to one active ingredient from any one pharmacologic group. The Panel concludes that products containing the combinations of ingredients provided for below are safe and effective. (See part II. paragraph C.8.b. below—Criterion.)

The Panel further concludes that such combinations of ingredients can provide rational concurrent therapy for a significant and existing target population that can benefit from such use. The Panel emphasizes that these combinations must contain adequate directions for use and include warnings against unsafe use. These combinations of ingredients must clearly indicate in their labeling that they are to be used only when the multiple symptoms are present concurrently. It would not be rational for a consumer having only one symptom to take a combination of ingredients intended for treatment of more than one symptom, or containing active ingredient(s) not required for relief of symptoms present in that individual.

2. *Limitation of ingredients in combination products.* The Panel concludes that, in general, the fewer the ingredients in an OTC product, the safer and more rational the therapy. The Panel has discussed the advantages of single ingredient products elsewhere in this document. (See part II. paragraph J. below—Advantages of Single Ingredient Products.) The Panel believes that the interests of the consumer are best served by exposing the user of OTC drugs to the smallest number of ingredients possible at the lowest possible dosage consistent with a satisfactory level of effectiveness. OTC drugs containing safe and effective single active ingredients are preferred to those having multiple active ingredients because with fewer ingredients there is a reduced risk of undesirable additive or synergistic effects.

Single ingredients are also preferred because the ratio in which components exist in a fixed combination may be unsuitable for some individuals. This is due in part to the great variability of reactions and side effects among these persons to the various drugs in the combination. It is also due in part to the inability of such persons to correlate certain side effects with the use of a particular drug when more than one drug is present in a combination. Both points are discussed more fully elsewhere in this document. (See part II. paragraph J. below—Advantages of Single Ingredient Products.)

The Panel believes that single active ingredient preparations should be available in the OTC market to allow the consumer the opportunity of selecting a single drug for a specific symptom or symptoms. As an example, a single active ingredient preparation containing only an antitussive should be available for treatment of cough. Likewise, a single active ingredient preparation containing only an antihistamine should be available for treatment of running nose, sneezing, and watery eyes. It is the Panel's opinion that presently the public has too little choice in selecting an appropriate drug treatment for such symptoms because of the current OTC market scarcity of single drug ingredient preparations.

In fact, of the 339 volumes received as submissions for review by the Panel, only 44 volumes contained data concerning 24 single active ingredients being marketed in 46 products. This represents 24 single active ingredients, out of a total of 152 active ingredients submitted by firms, as being present in marketed OTC CCABA products. The 46 products containing the single active ingredients represent a wide variety of dosage forms which include aerosols, liquids, tablets, syrups, drops, sprays, jellies and elixirs. The Panel has prepared the following table of the 24 single active ingredients marketed alone in CCABA products and submitted to the Panel for review:

MARKETED DRUG PRODUCTS CONTAINING A SINGLE ACTIVE INGREDIENT

Active ingredient	*Dosage form (number of products)*
Products for the relief of asthma:	
Epinephrine hydrochloride	Aerosols (5) and solutions (1).
Products for the relief of cough:	
Ammonium chloride	Drops (1).
Caramiphen ethanedisulfonate	Do.
Carbetapentane citrate	Syrups (1) and drops (1).
Cocillana	Drops (1).
Dextromethorphan	Syrups (2).
Menthol	Drops (2).
Noscapine	Syrups (2) and bulk chemicals—not a marketed drug product (1).
Products for relief of nasal congestion:	
Naphazoline hydrochloride	Drops (1) and sprays (1).
Oxymetazoline hydrochloride	Do.
Phenylephrine	Drops (1).
Phenylephrine hydrochloride	Sprays (2), jellies (1), and elixirs (1).
Phenylpropanolamine hydrochloride	Tablets (2) and liquids (1).
Xylometazoline hydrochloride	Drops (2) and sprays (2).
Products for use as antihistamines:	
Brompheniramine maleate	Tablets (1) and liquids (1).
Chlorpheniramine maleate	Tablets (1) and syrups (1).
Methapyrilene fumarate	Bulk chemicals—not a marketed drug product (1).
Methapyrilene hydrochloride	Bulk chemicals—not a marketed drug product (1).
Promethazine	Liquids (1).
Products for use as an expectorant:	
Glyceryl guaiacolate	Liquids (2).
Hydriodic acid	Liquids (1).
Iodized lime	Tablets (1).
Products for use in relief of sore throat:	
Benzocaine	Lozenges (1).
Hexylresorcinol	Lozenges (3).

The Panel concludes that in light of the numerous CCABA combination products on the market, there appears to be a shortage of single active ingredient products for the consumer to adequately and individually treat a specific symptom. This may or may not be representative of the marketplace but certainly indicates a paucity of single ingredient products. The Panel recommends that this situation be altered so that the public may make a more discriminating selection in the purchasing of OTC drugs. The Panel recognizes the consumer's prerogative for self-medication and believes that this can only be fully realized when single as well as combination products are more readily available.

The Panel is also aware of the inclusion of inactive, i.e., nontherapeutic, ingredients in CCABA preparations. These inactive ingredients are used for various purposes such as preservatives and flavors for specific product formulations. The Panel recognizes that some ingredients may be necessary for marketing purposes. However, the Panel recommends that the safety of inactive ingredients and the advisability of including them in drug products be reviewed by an appropriate body. The Panel further discusses inactive ingredients elsewhere in this document. (See part II. paragraph I. below—Inactive Ingredients.)

In summary, the Panel recommends that marketed products contain only those active and inactive ingredients that are essential to the product.

3. *Combining of active ingredients reviewed by the Panel from different pharmacologic groups.* The Panel is aware of the concept that it may be more convenient to include more than one active ingredient in the same product. Symptoms of the "common cold" or hay fever may include nasal congestion, running nose and coughing. The Panel has determined that if a combination product contains ingredients which are limited to one active ingredient from each representative pharmacologic group, e.g., nasal decongestant, antihistamine and antitussive, each of which is generally recognized as safe and effective when used alone for the specific symptom, e.g., antitussive for cough, the combination is rational and convenient for treatment of concurrent symptoms. The Panel concludes that the combinations of ingredients from pharmacologic groups identified below are safe and effective for a significant proportion of the target population having concurrent symptoms. (See part II. paragraph C.8.b. below—Criterion.)

The Panel clearly desires to avoid the so-called "shotgun approach" for the treatment of symptoms with a combination of ingredients in a single product. However, due to the unique nature of symptoms to be treated by CCABA preparations under consideration by this Panel, such combinations, with restrictions as established by the Panel, are justifiable.

The Panel is aware of a regulation (21 CFR 331.15(b)) providing for the combining of safe and effective (Category I) antacid and nonantacid active ingredients for the treatment of concurrent symptoms. The Panel emphasizes that the regulation provides for combining ingredients with different pharmacologic activities without additional clinical testing of the combination. This concept has been adopted by this Panel for certain combinations that the Panel has classified as Category I.

The Panel believes that these combinations of pharmacologic groups identified as Category I may offer a convenient and rational approach for relief of concurrent symptoms. The Panel has limited such combinations to three pharmacologic groups because it is unable to determine a significant target population which could benefit from a combination product containing greater than three pharmacologic groups. The Panel can find little scientific justification for including four or more pharmacologic groups in the same product since it is improbable that concurrent symptoms of sufficient duration and severity exist to warrant such combinations. As previously noted in the discussion pertaining to the "common cold," the course and symptoms of the disease are variable and may extend for 7 to 14 days. It would appear highly unlikely that at any one time, simultaneous symptoms would be present and of such severity in the course of the disease as to warrant the need for a product containing more than three pharmacologic groups. Therefore, the Panel has determined that combination products containing four or more different pharmacologic groups be classified as Category III. Before such products may be classified as Category I, a significant target population requiring such a combination for the treatment of concurrent symptoms of sufficient duration and severity must be identified.

4. *Combining of active ingredients reviewed by the Panel from the same pharmacologic group.* The Panel is concerned with the marketing of products containing drugs from the same pharmacologic group. Each Category I combination is currently limited to one active ingredient from any one pharmacologic group. The Panel can find little scientific justification for combining more than one active ingredient from the same pharmacologic group in the same product. The Panel is unaware of adequate supportive data which would establish sufficient argument for combining ingredients from the same pharmacologic group. For most products reviewed by the Panel, these ingredients from the same pharmacologic group are present in subtherapeutic doses. There is a lack of data on the effects of full therapeutic doses of ingredients from the same pharmacologic group in combination and therefore such combinations could not be evaluated by the Panel.

As an example, suppose two ingredients from the same pharmacologic group are combined in equal amounts in terms of pharmacologic activity (i.e., each at one-half the therapeutic dose) in the same product. The Panel doubts the justification in assuming that a dose of the product containing one-half the adult dose of each drug will produce an effect equal to one adult therapeutic dose of

either of the ingredients. The Panel is unable to find data to support the theory of the contribution of subtherapeutic doses of each ingredient in the same pharmacologic group in presently marketed combination products submitted for review to the Panel. The Panel is aware of certain combinations, such as "triple sulfas" to reduce the inherent toxicity of administering a single sulfa drug. However, this concept is difficult to relate to CCABA preparations since little evidence was submitted to the Panel demonstrating sufficient need for such combinations of ingredients from the same pharmacologic group.

It is the opinion of the Panel that to provide for combinations containing ingredients from the same pharmacologic group would contribute to the likelihood of undesirable additive or synergistic effects as noted above. (See part II. paragraph C.2. above—Limitation of ingredients in combination products.) It is accepted medical practice to give only those drugs necessary for the safe and effective treatment of the patient. The Panel believes that this concept should also apply to self-medication where a consumer treats symptoms without the advice of a physician.

In conclusion, to allow for the possibility, however unlikely, that there may be advantages to combining two drugs from the same pharmacologic group, the Panel has determined that such combination(s) be classified as Category III. Additional studies as described below in Principle No. 10 are needed for Category III combinations to determine their safety and effectiveness. (See part II. paragraph 10. below—Criteria and testing procedures for Category III combination products (for oral use unless otherwise specified).) The Panel has further determined that any combination product containing more than two active ingredients from the same pharmacologic group (e.g., three antihistamines) is irrational since there seems to be no reason to expect a possible benefit from the combination, and is therefore classified by this Panel as a Category II combination.

5. *Combining of active ingredients not reviewed by the Panel from the same or different pharmacologic group.* Many CCABA preparations contain active ingredients that have not been reviewed by this Panel because they are ingredients that have been or currently are being reviewed by other OTC panels. These ingredients include acetaminophen, aspirin, benzocaine, caffeine, quinine sulfate and salicylamide. Claims such as "temporarily relieves minor sore throat pain," or "For temporary relief of headache, aches, pains and fever due to colds" are examples of the labeling commonly found on CCABA preparations containing these ingredients. Such claims do not directly relate to the active ingredients reviewed by this Panel. The Panel has reviewed, for example, antitussives and the corresponding labeling claims for cough. However, the Panel has not reviewed analgesics and/or antipyretics for the labeling claims of pain and fever.

The Panel has evaluated the active ingredients in combination products submitted for review from the standpoint of their safe and effective use as cold, cough, allergy, bronchodilator and antiasthmatic products. Active ingredients included for concurrent symptoms, e.g., an analgesic for pain, have been reviewed only for their rational use in such combination products. The determination as to the safety and effectiveness of individual analgesics, for example, remains with the OTC Internal Analgesic Panel. The following are the Panel's conclusions as to the appropriateness of such combinations:

a. *Combination products containing vitamins.* The Panel is cognizant of the popular use of vitamin C (ascorbic acid) for the prevention or treatment of the "common cold." The Panel has reviewed the available data for the ingredient as a single entity and finds that the data are insufficient to permit final classification as safe and effective for OTC use in the prevention or treatment of the cold. The Panel has discussed the safety and effectiveness of vitamins including vitamin C as claimed active ingredients elsewhere in this document. (See part IX. paragraph B.1.b. below—Vitamins used alone or in combination CCABA products with labeling claims for the prevention or treatment of the "common cold.") and (See part IX. paragraph B.2.b. below—Ascorbic acid (vitamin C).) The Panel has also discussed the labeling of these claimed active ingredients elsewhere in this document. (See part IX. paragraph B.1.b. below—Vitamins used alone or in combination CCABA products with labeling claims for the prevention or treatment of the "common cold.") and (See part IX. paragraph B.2.b. below—Ascorbic acid (vitamin C).)

The Panel found no study which demonstrated that vitamin C is unequivocally effective for the prevention or treatment of the "common cold" although some data tended to favor effectiveness for treatment of cold symptoms. Since no conclusive data on the dose or dosage schedule are available on vitamin C used alone or in combination products with other ingredients for prevention or treatment of the cold, the Panel is unable to propose adequate labeling with a dosage regimen and has therefore classified such labeling as Category II. In summary, the Panel has reviewed vitamin C and has classified the "ingredient" as Category III and any "labeling" for the prevention or treatment of the cold as Category II.

With regard to combination products, the Panel further notes that the use of vitamins in CCABA combination products for the prevention of colds is irrational since the other ingredients in these products should only be used when the symptoms of the "common cold" are present. It is difficult for the Panel to rationalize the use of vitamin C or any other vitamin for the treatment of the "common cold" in combination products which are to be used only for a short duration while symptoms persist. It would be illogical for a consumer to take a cold combination product to prevent a cold. The Panel has therefore placed the labeling claims of combination products containing vitamins including vitamin C for prevention of the "common cold" in Category II.

b. *Combination products containing antihistamines with sleep-aid claims.* Antihistamines are primarily useful for relief of allergic disorders but secondarily act centrally to produce sedation or sleep. The Panel has discussed the safety and effectiveness of antihistamines elsewhere in this document. (See part VII. below—Antihistamines.) The Panel has established a safe and effective dosage range for certain antihistamines when used to treat symptoms of running nose, sneezing, itching nose or throat and watery eyes. The Panel has recommended that the labeling for these ingredients contain the warning, "May cause drowsiness".

The Panel notes that CCABA combination products are currently available for use at bedtime and promoted for such various claims as "for restful sleep". The Panel recognizes that if the symptoms of cough and cold are adequately treated, there is a greater likelihood of normal sleep. However, the duration of drug effects from "nighttime cold preparations" which are recommended to be taken once at bedtime is not fully documented.

The Panel is unable to make a final determination as to safe and effective use of an antihistamine or other agent when used as a sleep-aid in CCABA preparations. It is obvious an antihistamine may have several activities, e.g., antitussive, antihistamine, or sedative activity depending upon the dosage level used. The Panel has therefore placed sedation claims associated with CCABA combination products containing an antihistamine in Category III. The Panel further concludes that the combining of an additional antihistamine in a CCABA combination product for the exclusive purpose of sedation is irrational. Therefore, the Panel classifies such combinations as Category II.

c. *Combination products containing analgesics and antipyretics.* Many currently marketed combination products contain analgesics and antipyretics for treatment of concurrent symptoms of headaches, muscular aches, pains and fever which accompany colds. The Panel finds these claims to be acceptable and rational. Therefore, where not expressly prohibited, a generally recognized as safe and effective analgesic and/or antipyretic may be combined with the Category I ingredients reviewed by the Panel. Certain combinations that are contraindicated and placed in Category II are summarized below. (See part II. paragraph C.9. below—Criteria for Category II combination products (for oral use unless otherwise specified).)

d. *Combination products containing local anesthetics or other agents with*

claims for relief of sore throat. The symptoms of sore throat often accompany cough and the "common cold." It is usually a simple irritation aggravated by breathing through the mouth. The Panel has referred the evaluation of the safety and effectiveness of individual ingredients and labeling claims for sore throat to the OTC Oral Cavity Panel. The Panel believes that combination products containing safe and effective agents to relieve minor throat irritation are rational. The Panel has therefore placed combinations containing local anesthetics with other Category I CCABA agents in Category I. The Panel recommends that labeling contain adequate warnings against use when persistent or chronic sore throat is present and is accompanied by fever or other symptoms. (See part II. paragraph F. below—Deferral of "Sore Throat" Claim.)

The Panel recognizes that most sore throat remedies are applied topically while other symptoms of the cold are usually treated internally through oral ingestion. As an example, a throat lozenge containing a local anesthetic (benzocaine) and an antitussive (dextromethorphan) produces two pharmacologic activities. The lozenge releases benzocaine locally in the oral cavity whereas the dextromethorphan is ingested for a systemic action.

e. *Combination products containing correctives (stimulants and sedatives).* The Panel is aware that caffeine is included in some CCABA preparations with claims such as "for relief without drowsiness". Caffeine is also sometimes added to a combination product with no reference in the labeling as to its pharmacologic activity. The Panel presumes that the rationale for the inclusion of caffeine in such combinations is to reduce the sedating side effects of antihistamines.

While the Panel agrees with the rationale for caffeine serving as a "stimulant corrective," combinations containing it are placed in Category III until such "corrective" pharmacological action can be proven. This activity of caffeine should be identified on the label as "an ingredient added to counteract drowsiness caused by other drugs in this product." Where caffeine is added only as a corrective, labeling claims such as "for relief without drowsiness" are unjustified and are therefore misleading. The Panel has classified such labeling claims as Category II.

The Panel believes that combining Category I CCABA ingredients with a stimulant such as caffeine at a fully effective dose (not as a corrective) is irrational since the Panel is unaware of a significant target population having a need for CCABA ingredients and a stimulant. Accordingly, the Panel places combinations of CCABA ingredients combined with stimulants at effective dosage levels in Category II.

In addition, sympathomimetic drugs and theophyllines may cause central nervous system stimulation in some patients. To counteract this effect the Panel presumes that phenobarbital has been added to some combinations as a "sedative corrective" rather than as an active ingredient. While the Panel agrees with the rationale for phenobarbital serving as a "sedative corrective," combinations containing it are placed in Category III until such "corrective" pharmacologic action can be proven. (See part IX. paragraph B.2.d. below—Phenobarbital.) This activity of phenobarbital should be identified on the label as "an ingredient added to counteract nervousness caused by other drugs in this product." The Panel has included in this document a protocol designed to evaluate the effectiveness of phenobarbital under the above circumstances to show whether it has an additional beneficial or adverse effect on bronchospasm. (See part IX. paragraph B.2.d.(5) below—Evaluation.)

6. *Labeling of active ingredients.* As discussed above, the Panel has determined that each claimed active ingredient in a combination product must make a contribution to the claimed effect(s). (See part II. paragraph C.1. above—General combination policy.) Based upon this determination, the Panel concludes that combination products must be labeled to reflect all of the proven pharmacologic activities of each active ingredient in the combination. If a single ingredient has several activities, these should all be identified in the labeling consistent with the activities found at the recommended dosage for the product.

The Panel recommends that the labeling of a combination product containing active ingredients for treatment of concurrent symptoms emphasize the use of the product only when all such symptoms are present. The consumer should be adequately informed through the labeling of the therapeutic capabilities of the product. If, for example, only the symptom of running nose is present, a single ingredient rather than a combination product would be the rational therapy. Labeling should therefore fully reflect the activities of all active ingredients at the dosage recommended so that a consumer may select an appropriate product for relief of concurrent symptoms. If a product contains an active ingredient for which no labeling claim is made, it is clearly misleading to the consumer.

7. *Marketing experience for cold, cough, allergy, bronchodilator and antiasthmatic combination products.* The Panel recognizes the extensive marketing history of CCABA preparations. The drug industry presented data to the Panel summarizing consumer complaint information obtained from a survey of 32 pharmaceutical manufacturers (Ref. 2). A total of 117 combination CCABA products representing over 4 billion package units were included in the survey. The products were combinations of 83 ingredients representing 9 pharmacologic groups (nasal decongestants, antitussives, expectorants, antihistamines, anticholinergics, bronchodilators, analgesics, sedatives and stimulants). Inactive ingredients such as glycine and alcohol were also included in the data presented.

The drug industry reported to the Panel that the overall number of consumer complaints in the survey, in terms of either adverse reactions and/or ineffectiveness was less than one complaint per one million packages sold. However, from the survey data the Panel is unable to determine whether the information on adverse reactions was gathered during the entire period for which marketing data were reported for the products. The drug industry acknowledged that not every consumer complaint is well-founded or attributable to the drug product. In addition, not every consumer who fails to receive relief or experiences side effects registers complaints with the drug manufacturer.

The Panel has considered the marketing data submitted. The Panel finds that of the 83 ingredients included in the survey, only 11 ingredients have been classified by the Panel as Category I whereas 27 have been classified as Category III. Only one of the ingredients, belladonna alkaloids, has been classified as Category II when used by inhalation in the treatment of asthma. The remaining ingredients were not submitted for review to the Panel, pursuant to the call for data published in the FEDERAL REGISTER of August 9, 1972 (37 FR 16029), and therefore were not considered by the Panel. Several of these ingredients are currently available only by prescription while others are inactive ingredients. The actual quantities of active ingredients contained in the products and the amounts actually consumed by consumers were not included in the survey data and can only be estimated.

It would appear from the data that there is a low incidence of obvious adverse reactions which the consumer can attribute to the drug product. Since the quantities of drug administered in the surveyed products are not known, the Panel has reviewed the quantities of active ingredients contained in the marketed products submitted for review to the Panel. (See part I. paragraph A. above—Submissions by Firms.) The Panel presumes that the quantities of active ingredients contained in these products are generally representative of the products contained in the survey. The Panel concludes that while marketing data are limited and difficult to interpret they tend to support the safe use of combinations of active ingredients reviewed by the Panel.

The fact that over 4 billion packages of the 117 combination products have been sold would tend to indicate that consumers perceive a need for such drugs. It is obvious that consumers believe these products useful, to account for the many sales, but the extent to which this belief by the consumer is established by advertising rather than by a need perceived independently of advertising cannot be determined by the Panel. In addition, belief in the usefulness of a product may be related to a placebo response and also to the fact that a self-limiting illness is being treated.

Regarding effectiveness, the Panel has applied the OTC Drug Review Regulation (21 CFR 330.10(a)(4)(ii)) which provides, that as a source of corroboration for proof of effectiveness, the reports of significant human experience during

marketing are appropriate. The Panel finds the data helpful but not conclusive. The Panel believes that marketing experience, in and of itself, cannot be regarded as constituting adequate proof of effectiveness. Since the amounts of active ingredients included in the survey are not known, it is difficult for the Panel to determine the effectiveness of these combination products.

Data were contained in the survey of combinations by pharmacologic groups. For example, products with antitussives and nasal decongestants were compared to products containing antitussives, nasal decongestants and expectorants, etc. The data tend to indicate the addition of a drug from an additional pharmacologic group does not alter the complaint ratios. The Panel concludes that the data meet the criteria of the regulation (21 FR 330.10(a)(4)(ii)) and are limited but tend to support the effective use of certain combinations.

8. *Criteria for Category I combination products (for oral use unless otherwise specified).* Based upon an evaluation of the drug combinations submitted to the Panel for review, the following criteria have been established:

a. *Criterion.* Each claimed active ingredient and its labeling in a combination must be generally recognized as safe and effective (Category I) and each active ingredient must be combined within the established effective dosage range as set forth elsewhere in this document.

b. *Criterion.* Products containing one active ingredient from each pharmacologic group in the combinations identified below are classified as Category I combination products, provided the active ingredients and their labeling are generally recognized as safe and effective (Category I) and such ingredients are present in amounts within the effective dosage range.

(1) Combinations containing an analgesic-antipyretic and an antihistamine.

(2) Combinations containing an analgesic-antipyretic and a nasal decongestant.

(3) Combinations containing an analgesic-antipyretic, a nasal decongestant and an antihistamine.

(4) Combinations containing an antihistamine and an antitussive provided the product is labeled *"Caution:* May cause marked drowsiness." The labeling term "marked" relating to the warning statement may be removed if adequate data are supplied to the Food and Drug Administration to demonstrate that the combination product does not cause a significant increase in drowsiness as compared with each ingredient when tested alone.

(5) Combinations containing an antihistamine and a nasal decongestant.

(6) Combinations containing an antihistamine, an antitussive and a nasal decongestant.

(7) Combinations containing an antitussive and an expectorant provided the product is labeled only for nonproductive cough. Expectorants are expected to have their major usefulness in the irritative nonproductive cough as well as those coughs productive of scanty amounts of thick, sticky secretions. Antitussives suppress the act of coughing and may promote retention of some mucous secretions and thereby coat inflamed bronchial membrane linings.

(8) Combinations containing an antitussive and a nasal decongestant.

(9) Combinations containing an antitussive and a local anesthetic or local analgesic-antipyretic provided the product is available only as a lozenge.

(10) Combinations containing an antitussive, an expectorant and a nasal decongestant provided the antitussive and expectorant ingredients in the product are labeled only for nonproductive cough. Expectorants are expected to have their major usefulness in the irritative nonproductive cough as well as those coughs productive of scanty amounts of thick, sticky secretions. Antitussives suppress the act of coughing and may promote retention of some mucous secretions and thereby coat inflamed bronchial membrane linings.

(11) Combinations containing an oral bronchodilator and an expectorant provided the product is labeled only for cough associated with asthma.

(12) Combinations containing an oral bronchodilator (sympathomimetic) and an oral bronchodilator (theophylline).

(13) Combinations containing an expectorant and a nasal decongestant.

(14) Combinations containing a nasal decongestant and a local anesthetic or local analgesic-antipyretic provided the product is available only as a lozenge.

9. *Criteria for Category II combination products (for oral use unless otherwise specified).* Based upon an evaluation of the drug combinations submitted to the Panel for review, the following criteria have been established:

a. *Criterion.* A combination is Category II if a Category II ingredient or labeling is present in the combination product.

b. *Criterion.* A combination product containing Category I ingredients from different pharmacologic groups is classified as Category II if it includes any ingredient(s) at less than the minimum effective dosage established by the Panel unless the ingredient(s) are being used to treat the same symptom. (See Part II. paragraph C. 10.b.(1) below—Category III Combination.)

c. *Criterion.* If a product contains an active ingredient or labeling that has not been reviewed by this or other OTC Advisory Review Panels, such ingredient or labeling is classified by this Panel as Category II.

d. *Criterion.* A combination product is classified as Category II if it includes more than two active ingredients from the same pharmacologic group.

e. *Criterion.* Combinations of active ingredients and labeling which have been determined by the Panel to be unsafe or irrational and classified as Category II are as follows:

(1) Combinations containing an analgesic-antipyretic and a bronchodilator. This combination contains an analgesic for the symptomatic treatment of fever or muscular aches, etc., associated with the "common cold" and contains a bronchodilator with a claim for the treatment of symptoms of asthma. The Panel concludes that if an individual with a cold needs relief of asthma, he should take a bronchodilator separately since there may be a more frequent need of this drug than for the other ingredients contained in the preparation. In addition, the Panel further concludes that a bronchodilator should only be labeled for use in patients with asthma and that the addition of an analgesic is irrational. The Panel believes that for treatment of concurrent symptoms where an asthmatic requires an analgesic or antipyretic, he should take such drugs separately because the dosage and need for each of the ingredients varies with the likelihood that the bronchodilator is more frequently required.

(2) Combinations containing an anticholinergic and an expectorant. This combination is irrational because an expectorant promotes the production of secretions whereas the anticholinergic produces an opposite effect, i.e., antisecretory action.

(3) Combinations containing an antihistamine and an expectorant. This combination is irrational because an expectorant promotes the production of secretions whereas the anticholinergic activity of an antihistamine produces an opposite effect, i.e., anti-secretory action.

(4) Combinations containing a bronchodilator and an anticholinergic. This combination is irrational because the anti-secretory action of the anticholinergic may produce thickened bronchial secretions which may cause further obstruction of the airways in individuals with asthma.

(5) Combinations containing a bronchodilator and an antihistamine. This combination is irrational because the anticholinergic effect, i.e., anti-secretory action, of antihistamines may produce thickened bronchial secretions which may cause further obstruction of the airways in individuals with asthma.

(6) Combinations containing an oral bronchodilator and an antitussive when the product is labeled only for cough associated with asthma. This combination is irrational because the antitussive suppresses cough and the cough reflex is essential in asthma to maintain an open airway by clearing the respiratory passages of excessive secretions.

(7) Combinations containing an antitussive and an antihistamine if the antitussive is also generally recognized as safe and effective as an antihistamine. This combination is not safe because the antihistaminic side effects of the antitussive may combine with the side effects of the antihistamine.

(8) Combinations containing an antihistamine and an antitussive if the antihistamine is also generally recognized as safe and effective as an antitussive. This combination is not safe because the antitussive side effects of the antihistamine may combine with the side effects of the antitussive.

f. *Criterion.* Combination products containing any vitamins, e.g., vitamin C, with labeling claims which represent or

suggest the product for the prevention or treatment of the "common cold". (See part II. paragraph C.5.a. above—Combination products containing vitamins.)

g. *Criterion.* Combination products containing a stimulant, e.g., caffeine, at a fully effective level (not as a "corrective"). (See part II. paragraph C.5.e. above—Combination products containing correctives (stimulants and sedatives).)

h. *Criterion.* Combination products containing more than one antihistamine in which an additional antihistamine is added for the exclusive purpose of sedation and the product contains labeling which represents or suggests the additional antihistamine as a "sleep-aid." (See part II. paragraph C.5.b. above—Combination products containing antihistamines with sleep-aid claims.)

10. *Criteria and testing procedures for Category III combination products (for oral use unless otherwise specified).* Based upon an evaluation of the drug combinations submitted to the Panel for review the following criteria and corresponding testing procedures are recommended:

a. *Criterion.* (1) *Category III combination.* If a Category III ingredient or labeling is present in a combination product containing no Category II ingredient or labeling, the combination is classified as Category III.

(2) *Category III testing procedure.* The Category III ingredient (or ingredients) for the labeling claims (symptom(s)) must be tested in accordance with the evaluation protocol specified for that particular pharmacologic group. The appropriate protocol(s) under the heading "Data Required for Evaluation" are identified elsewhere in this document for each respective pharmacologic group. If when tested alone the Category III ingredient (or ingredients) can be shown to be safe and effective in accordance with the standards for evaluation established in the protocol(s), it then qualifies for Category I status. The combination will then contain only Category I ingredients and will be considered Category I without further testing provided the combination is identified above. (See part II. paragraph C.8.b. above—Criterion.)

b. *Criterion.* (1) *Category III combination.* If two or more ingredient(s) are being used to treat the same symptom (labeling claim), a combination product is classified as Category III even if it contains Category I ingredients from different pharmacologic groups when any ingredient(s) is present at less than the minimum effective dosage established by the Panel.

(2) *Category III testing procedure.* An acceptable test procedure will be one in which the combination, each of the individual ingredients in the minimum effective dosage, and each of the individual ingredients in the less than the minimum effective dosage used in the combination, and a placebo are evaluated, all in the same study, against the relevant symptom (labeling claim). In this way, comparisons of safety and effectiveness can be made directly between the combination, the individual ingredients and the placebo. The appropriate protocol(s) under the heading "Data Required for Evaluation" are identified elsewhere in this document for each respective pharmacologic group. Each individual ingredient which is in less than the minimum effective dosage should demonstrate a contribution, but not necessarily a significant effect, against the relevant symptom when compared to placebo. It is very difficult to develop a generally applicable definition of a "contribution." Each ingredient and the symptom that it should affect must be analyzed individually as to the effect on the patient population in which it is being used. For an ingredient to be judged as contributing to the alleviation of the relevant symptom, the Panel suggests that the drug effect should demonstrate a 10 percent or greater difference from placebo.

For a combination of Category I ingredients from different pharmacologic groups used to treat the same symptom and in which at least one of the ingredients is in less than the minimum effective dosage, to be classified as a Category I combination, the relative incidence of side effects and/or other untoward effects of the combination should not be significantly greater than those of any individual ingredient in that combination alone in the minimum effective dosage. In addition, the combination must exert a significant effect against the relevant symptom which is not less than any one of the ingredients when tested alone in the minimum effective dosage. The justification for these requirements is that such a combination should not compromise effectiveness nor should it pose a greater risk of side effects than is associated with an ingredient alone in its minimum effective dosage.

c. *Criterion.* (1) *Category III combination.* A combination product is classified as Category III if it includes two Category I ingredients from the same pharmacologic group.

(2) *Category III testing procedure.* An acceptable test procedure will be one in which the combination, each of the individual ingredients, at its minimum effective dosage, and a placebo are evaluated, all in the same study, against the relevant symptom (labeling claim). In this way, comparisons of safety and effectiveness can be made directly between the combination, the individual active ingredients from the same pharmacologic group at its minimum effective dosage and the placebo. The appropriate protocol(s) under the heading "Data Required for Evaluation" are identified elsewhere in this document for each respective pharmacologic group.

For a combination of two Category I ingredients from the same pharmacologic group to be classified as a Category I combination, the relative incidence of side effects and/or other untoward effects of the combination should not be significantly greater than those of either individual ingredient alone at its minimum effective dosage. In addition, the combination must exert a significant effect against the relevant symptom(s) which is not less than either one of the ingredients when tested alone at its minimum effective dosage. The justification for these requirements is that such a combination should not compromise effectiveness nor should it pose greater risk of side effects than is associated with an individual ingredient alone.

d. *Criterion.* (1) *Category III combination.* A combination product containing two Category I ingredients from the same pharmacologic group is classified as Category III if it includes either or both ingredient(s) at less than the minimum effective dosage established by the Panel.

(2) *Category III testing procedure.* An acceptable test procedure will be one in which the combination, each of the individual ingredients in the minimum effective dosage, and each of the individual ingredients in the less than the minimum effective dosage used in the combination, and a placebo are evaluated, all in the same study, against the relevant symptom. In this way, comparisons of safety and effectiveness can be made directly between the combination, the individual active ingredients from the same pharmacologic group and the placebo. The appropriate protocol(s) under the heading "Data Required for Evaluation" is identified elsewhere in this document for each respective pharmacologic group. Each individual ingredient which is in less than the minimum effective dosage should demonstrate a contribution, but not necessarily a significant effect, against the relevant symptom when compared to placebo. It is very difficult to develop a generally applicable definition of a "contribution." Each ingredient and the symptom that it should affect must be analyzed individually as to the effect on the patient population in which it is being used. For an ingredient to be judged as contributing to the alleviation of the relevant symptom, the Panel suggests that the drug effect should demonstrate a 10 percent or greater difference from placebo.

For a combination of two Category I ingredients from the same pharmacologic group to be classified as a Category I combination, the relative incidence of side effects and/or other untoward effects of the combination should not be significantly greater than those of either individual ingredient alone in the minimum effective dosage. In addition, the combination must exert a significant effect against the relevant symptom which is not less than either one of the ingredients when tested alone in the minimum effective dosage. The justification for these requirements is that such a combination should not compromise effectiveness nor should it pose greater risk of side effects than is associated with an individual ingredient alone in the minimum effective dosage.

e. *Criterion.* (1) *Category III combination.* Combinations of active ingredients for which the available safety data are insufficient for the Panel to make a final

determination and are classified as Category III: (i) Combinations containing atropine and an oral nasal decongestant. Additional studies are necessary to assess the potential additive central nervous system stimulant side effects.

(ii) Combinations containing an antihistamine and an anticholinergic. Additional studies are necessary to assess the nature and extent of additive anticholinergic side effects.

(2) *Category III testing procedure.* An acceptable test procedure will be one in which the combination and a placebo are evaluated in suitable subjects so that comparisons can be made of the particular side effect(s) of concern which are specified above. In addition, data on the relative incidence and intensity of those side effects must be available for the individual active ingredients in the same dosage as in the combination either evaluated in the same study as above, or evaluated in a separate study using a comparable test protocol. The appropriate protocol(s) under the heading "Data Required for Evaluation" are identified elsewhere in this document for each respective pharmacologic group.

If the relative incidence and intensity of the side effect(s) of the combination are increased to a degree which prevents its safe use as an OTC product, it will be classified as a Category II combination for those dosages. If the relative incidence and intensity of side effect(s) are significantly greater than with either ingredient administered alone but not to a degree to prevent its safe OTC use, a suitable warning regarding potential for that side effect should be specified in the labeling for the combination product. If the relative incidence and/or intensity of side effect(s) with the combination are not significantly greater than with either ingredient administered alone, no warnings other than the standard Category I warnings for those ingredients are needed on the label.

f. *Criterion.* (1) *Category III combination.* Combinations of active ingredients for which the available effectiveness data are insufficient for the Panel to make a final determination or for which there is no rationale for use and are classified as Category III are as follows: (i) Combinations containing a nasal decongestant and an antihistimine administered topically as a spray or drops. Additional studies are necessary to assess the contribution of the antihistamine administered by the topical route since there are inadequate studies demonstrating the effectiveness of the antihistamines topically in such combinations.

(ii) Combination products containing an antitussive and a bronchodilator used as an antitussive provided the product is labeled only for cough not associated with asthma. Additional studies are necessary to assess the antitussive effects of a bronchodilator in combination with an antitussive in reducing cough.

(iii) Combination products containing an expectorant and a bronchodilator used as an antitussive provided the product is labeled only for cough not associated with asthma. Additional studies are necessary to assess the antitussive effects of a bronchodilator in combination with an expectorant in reducing cough.

(iv) Combination products containing an antitussive and an expectorant provided the product is labeled only for productive cough. Additional studies are necessary to assess the combined effects of an antitussive and an expectorant in the presence of excessive or more fluid bronchial secretions.

(v) Combination products containing an antitussive, an expectorant and a nasal decongestant provided the antitussive and expectorant ingredients in the product are labeled only for productive cough. Additional studies are necessary to assess the combined effects of an antitussive and an expectorant in the presence of excessive or more fluid bronchial secretions.

(2) *Category III testing procedure.* An acceptable test procedure will be one in which the combination, each individual ingredient, and a placebo are evaluated against the relevant symptoms either in the same study or in separate studies using comparable test protocols. The appropriate protocol(s) under the heading "Data Required for Evaluation" is identified elsewhere in this document for each respective pharmacologic group. In this way, comparisons of effectiveness can be made between the combination, the individual active ingredients and the placebo by that route of administration. When tested alone by that route of administration, each individual ingredient should demonstrate a significant effect against the relevant symptom when compared to placebo.

For the combination of Category I ingredients from different pharmacologic groups to be a Category I combination by that route of administration, the combination must also exert a significant effect against each of the relevant symptoms when compared with the placebo.

g. *Criterion.* (1) *Category III combination.* Combination products containing an active ingredient specifically intended to counteract a side effect of other ingredients in the product, i.e., a "corrective", for which the available data are insufficient for the Panel to make a final determination, are classified as Category III.

(2) *Category III testing procedure.* An acceptable test procedure will be one in which the combination with and without the corrective is evaluated to assess the effectiveness of the corrective to significantly decrease the incidence and/or intensity of the undesirable side effect, and to assess the safety of this combination.

h. *Criterion.* (1) *Category III combination.* Combination products containing an antihistamine with a sleep-aid claim for which data are insufficient for the Panel to make a final determination and are classified as Category III.

(2) *Category III testing procedure.* If a sleep-aid effect is claimed for the antihistamine, the Panel recommends a testing protocol in conformance with requirements specified by the OTC sedative, tranquilizer and sleep-aid drug products Panel as published in the FEDERAL REGISTER of December 8, 1975 (40 FR 57292).

i. *Criterion.* (1) *Category III combination.* Combination products containing several claimed active ingredients which are mixtures of volatile substances with overlapping pharmacologic activities for which a minimum effective dosage cannot be established for one or more of the ingredients when tested alone are classified as Category III.

(2) *Category III testing procedure.* An acceptable test procedure will be one in which the combination, each of the individual ingredients in the dosage used in the combination, and a placebo must be evaluated against the relevant symptom (labeling claim), either in the same study, or in separate studies using comparable test protocols. The appropriate protocol(s) under the heading "Data Required for Evaluation" are identified elsewhere in this document for each respective pharmacologic group. When tested alone, each individual ingredient should demonstrate a contribution, but not necessarily a significant effect, against the relevant symptom when compared to placebo. It is very difficult to develop a generally applicable definition of a "contribution." Each ingredient and the symptom that it should affect must be analyzed individually as to the effect on the patient population in which it is being used. For an ingredient to be judged as contributing to the alleviation of the relevant symptom, the Panel suggests that the drug effect should demonstrate a 10 percent or greater difference from placebo.

For the combination of these ingredients to be classified as Category I, it must exert a significant effect against the relevant symptom when compared to placebo meeting the standards of evaluation set forth for that pharmacologic group. Furthermore, the combination product must be judged safe for OTC use as evaluated by the incidence and/or intensity of side effects and/or other untoward effects.

j. *Criterion.* (1) *Category III combination.* There is lack of data on a suitable target population with concurrent symptoms of sufficient duration to justify combination products containing four or more different pharmacologic groups. Therefore, the Panel classifies combination products containing four or more different pharmacologic groups as Category III. Examples of such combinations are as follows:

(i) Combinations containing an analgesic-antipyretic, an antitussive, an expectorant and a nasal decongestant.

(ii) Combinations containing an analgesic-antipyretic, an antitussive, an antihistamine and a nasal decongestant.

(2) *Category III testing procedure.* Before such combinations may be classified as Category I, a significant target population requiring such a combination for the treatment of concurrent symptoms of sufficient duration and severity must be identified by appropriate epidemiological studies. If a suitable target population is

found such combinations may be classified as Category I.

REFERENCES

(1) "AMA Drug Evaluations," 2d Ed., American Medical Association, Chicago, pp. 499–503, 1973.

(2) OTC Volume 040287.[1]

(3) Cohen, B. M., "Sympathomimetic/Xanthine Broncholysis in Obstructive Ventilatory Disorders," *International Journal of Clinical Pharmacology*, 9:6–15, 1974.

D. STATEMENT ON CATEGORY III TESTING PROCEDURES

1. *Comments on study design.* The Panel has agreed that the protocols recommended in this document for the studies required to bring a Category III drug into Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved technology in the future.

Experimental design should take into account the need to include a sufficient number of subjects or trials so as to provide meaningful conclusions which can be supported by appropriate statistical analysis. The selection of appropriate subjects or patients can be of major importance when the effect of a drug in a specific illness or symptom is under study.

A role for bias is assumed in all situations wherein the subject, the observer or both make a judgment as to the nature of magnitude of a response. Biological factors also contribute to variation in response between individuals in a given study sample. Although bias and biological variation cannot be eliminated, their effect on the outcome of an experiment can be avoided or minimized by adopting a "double-blind, placebo-controlled" or other suitably blinded design. In such a design, one group of subjects receives a placebo or dummy preparation so that the response unmodified by drug under test can be established. Neither the subjects nor the observer should be able to detect the identity of the preparations under test. This requires that the test and placebo preparations be indistinguishable in regard to taste, color and shape except in the case of preparations containing volatile substances where it will be impossible to make the active ingredients indistinguishable from the placebo.

It is often desirable to include a standard drug (a drug used as a positive control known to exert a significant effect against the relevant symptom(s) being tested) with which the unknown can be compared. Finally the inclusion of two or more dose levels of the drug under test may be desirable in order to provide an estimate of an effective therapeutic dose range free from undesirable side effects. If a crossover design is utilized, i.e., each subject serves as his own control, the sequence in which the placebo, standard and test drugs are administered should be randomized and a sufficient "washout period" between tests should be permitted.

Wherever possible, objective measurements should be made in perference to subjective judgments. However, such measurements should be relevant to the symptom or symptom complex for which the drug under test is to be used.

2. *Testing period provided for Category III conditions.* The Panel concludes that the conditions excluded from the monograph on the basis of the Panel's determination that the available data are insufficient (Category III) to classify such conditions either as Category I—generally recognized as safe and effective and not misbranded, or as Category II—not being generally recognized as safe and effective, or would result in misbranding be permitted to remain in use for the period of time specified below after the date of publication of the final monograph in the FEDERAL REGISTER, if the manufacturer or distributor of any such drug utilizing such conditions in the interim conducts tests and studies adequate and appropriate to satisfy the questions raised with respect to the particular condition by the Panel.

The Panel has established the following specific time limitations for testing based upon the applicable pharmacologic group:

Pharmacologic group:	*Time provided for testing (years)*
Anticholinergic	3
Antihistamine	3
Antitussive	4
Bronchodilator sympathomimetic	3
Bronchodilator theophylline	3
Expectorant	5
Nasal decongestant	3

The Panel believes that testing for bronchodilators, antihistamines, anticholinergics and nasal decongestants can be completed within 3 years. The techniques for testing are all well-established and are discussed in the relevant sections of the document below. The Panel feels that 1 year is necessary for the development of protocols with 2 years provided for the actual testing. Clinical testing should start within 6 months of publication of the final monograph.

The techniques for testing antitussives involve cough counting. At present, there are relatively few laboratories available to do this work, and the techniques are very time-consuming. Because of these factors, 4 years have been provided as the time limitation. Clinical testing should start within 1 year of the publication of the final monograph.

The Panel recognizes that the evaluation of expectorants is difficult and there is no completely accepted technique available for the assessment of this pharmacologic group of drugs. It seems likely that new techniques will have to be developed for effective testing of these substances. Because of the need for developmental technical work, the time limitation is placed at 5 years. Clinical testing should start within 18 months of the publication of the final monograph.

The Panel concludes that for Category III combination drug products containing more than one pharmacologic group, the time established for testing shall be determined by the pharmacologic group having the longest period provided for testing. (See part II. paragraph C.10 above—Criteria and testing procedures for Category III combination products (for oral use unless otherwise specified).)

In addition to establishing time limitations of testing for specific pharmacologic groups, the Panel has established the following periods for testing of other Category III conditions:

Category III condition:	*Time provided for testing (years)*
Antihistamines with sleep-aid claims	3
Caffeine (stimulant corrective)	2
Phenobarbital (sedative corrective)	2
Timed-release drug formulations	4
Vitamin C (ascorbic acid)	3

The Panel recognizes that CCABA combination products are available for use at bedtime and promoted for such various claims as "for restful sleep." The Panel has discussed sleep-aid claims elsewhere in this document (See part II. paragraph C.5.b. above—Combination products containing antihistamines with sleep-aid claims).

The Panel is unable to make a final determination as to safe and effective use of antihistamines or other agents as sleep-aids in CCABA preparations. The Panel has therefore placed sedation claims associated with CCABA combination products containing antihistamines in Category III and has provided 3 years for testing and documentation of such claims.

The Panel is aware that caffeine is included in some CCABA preparations with claims such as "for relief without drowsiness". Caffeine is also contained in combination products with no reference in the labeling as to its pharmacologic activity. The Panel presumes that the rationale for the inclusion of caffeine in such combinations is to reduce the sedating side effects of antihistamines. The Panel has discussed the use of "stimulant correctives" elsewhere in this document. (See part II. paragraph C.5.e. above—Combination products containing correctives (stimulants and sedatives).) The Panel agrees with the rationale for caffeine serving as a "stimulant corrective" but combinations containing it are placed in Category III until such "corrective" pharmacological action can be proven. The Panel has provided 2 years for testing and documentation of such claims.

Timed-release drug formulations have been reviewed elsewhere in this document. (See part II. paragraph E. below—Effect of Timed-Release Formulations on Effectiveness and Safety of OTC Drug

[1] Cited OTC Volumes refer to the submissions made by interested persons pursuant to the call for data notice published in the FEDERAL REGISTER of August 9, 1972 (37 FR 16029). The volumes are on file in the office of the Hearing Clerk, Food and Drug Administration, Room 4–65, 5600 Fishers Lane, Rockville, MD 20852.

Products.) The Panel has provided 4 years for the development of suitable tests for the standardization of all OTC timed-release CCABA products.

Vitamin C (ascorbic acid) has been reviewed elsewhere in this document. (See part IX. paragraph B.1.b. below—Vitamins used alone or in combination CCABA products with labeling claims for the prevention or treatment of the "common cold" and part IX. paragraph B.2.b. below—Ascorbic acid (vitamin C).)

The Panel concludes that the effectiveness of vitamin C in the prevention or treatment of the "cold" has not been established and has classified the ingredient as Category III with 3 years provided for testing. However, all labeling claims for the ingredient for the prevention or treatment of the "cold" are classified as Category II.

Phenobarbital has been reviewed elsewhere in this document. (See part II. paragraph C.5.e. above — Combination products containing correctives (stimulants and sedatives) and part IX. paragraph B.2.d. below—Phenobarbital.) Several products used in the treatment of the symptoms of asthma contain drugs which stimulate the central nervous system in some patients. The Panel presumes that phenobarbital is included to counteract these effects and is therefore a "sedative corrective" rather than an active ingredient. The Panel agrees with the rationale for phenobarbital serving as a "sedative corrective" but has classified such combinations as Category III until such "corrective" action is proven. The Panel has provided 2 years for testing and documentation of such claims.

E. EFFECT OF TIMED-RELEASE FORMULATIONS ON EFFECTIVENESS AND SAFETY OF OTC DRUG PRODUCTS

1. *Introduction.* The oral route is the most common method of administration for OTC cold, cough, allergy, bronchodilator and antiasthmatic products. Such products are swallowed and absorbed from the stomach and intestines. Drugs administered orally are dissolved in gastrointestinal fluids and are absorbed into the systemic circulation where they exert an action on "target" organs or receptors. Generally, this action occurs within an hour or so of ingestion of the drug and peaks, e.g., in an hour or two, but the drug action lasts for several hours, e.g., 3 to 6 hours. When the drug action begins to decline, e.g., at the end of 3 to 6 hours, it is necessary to take another dose so that the desired action will continue at a more or less constant level. Most drug studies showing safety and effectiveness have been carried out with oral dosage forms that act in this manner. There are, however, a number of OTC CCABA products that are formulated in another kind of oral dosage form called timed-release formulations. Theoretically, these products are formulated so as to dissolve in gastrointestinal fluids in a controlled manner so that small amounts will be absorbed over a longer period of time, e.g., over 3 to 6 hours rather than 1 hour, and the duration of drug action will be extended over a longer period, e.g., 8 to 12 hours rather than 3 to 6 hours.

Since the specific formulation of a product can affect its safety and effectiveness, the Panel has considered timed-release formulations of OTC products under its review. The Panel did not consider in detail each of these formulations nor evaluate the dissolution times of the specific formulation or the affect of formulation on safety and effectiveness of each individual ingredient under review when formulated in this unique manner. The Panel does recognize certain advantages and disadvantages of timed-released formulations. The Panel has reviewed the pertinent literature and selected articles regarding timed-release formulations and has set forth certain guidelines to be used in their evaluation (Refs. 1 through 9).

2. *General discussion.* To produce its characteristic effect, a drug must achieve adequate concentrations at its site of action. One important factor in determining the concentration attained is the extent and rate of drug absorption. Other factors include the amount of drug administered, its distribution within the body, binding or localization in tissues, inactivation or metabolism and excretion.

The latent period between administration of a drug and its onset of action is influenced by the route of administration, e.g., orally, topically, by inhalation, etc., and the rate of absorption and the penetration of the drug at the site of action. The duration of drug effects is determined largely by the rate of inactivation and excretion of the drug. The duration of action of the drug effect is determined by a balance between all of these factors.

The rate of absorption of oral dosage forms is dependent mainly on their dissolution rate in gastrointestinal fluids. Theoretically, slow release and sustained effects (up to 8 hours or longer) of drugs administered in oral dosage forms should be attained if such drugs are formulated so as to dissolve in gastrointestinal fluids in a controlled manner.

A number of the active ingredients reviewed by the Panel are presently formulated in repeat action or extended release dosage forms. These formulations are known by a variety of names such as sustained action, sustained release, prolonged release, controlled release, long-acting time release, etc. Repeat-action tablets periodically release complete doses of active drug to the gastrointestinal fluids. Extended-release tablets continuously release increments of the contained medication to the gastrointestinal fluids. These terms are often used interchangeably and, although technically different, are referred to in this document as timed-release formulations.

3. *Advantages.* The principle of controlled release of drugs from oral dosage units is generally accepted to provide several advantages over the conventional dosage forms that require a shorter time interval regimen of administration.

Among these advantages may be listed the principal ones of better patient compliance, increased patient convenience, and lower incidence and/or severity of side effects of the drugs due to elimination of the peaks in the level of drug concentration in the blood that often occur after repeated administration of traditional dosage forms.

4. *Disadvantages.* Among the disadvantages is the fact that uniformly effective preparations of time-released drugs have been difficult to achieve, in part because of technical problems associated with their manufacture, but also because the dissolution rate of these preparations in gastrointestinal fluids may be irregular and because variations in gastrointestinal acidity, gastric emptying, and intestinal motility and other physiological factors also influence drug absorption.

If reasonable uniformity of effectiveness is not achieved, for whatever reason, the dissolution rate, for example, may be so slow that no effect is achieved or, conversely, it may be so fast that the patient receives the effect of all the active drug within a short time period, resulting in an increased incidence and/or severity of side effects.

On theoretical grounds, there are a number of reasons why a given drug should not be formulated as a timed-release product. These reasons relate to the inherent nature of a specific drug. For example, a drug may have a very long half-life, i.e., it may be metabolized and eliminated from the body over a long period of time, and thus conventional dosing already provides sustained blood levels. A drug may require a very large dose before sustained action is possible and a timed-release product containing a dose sufficient for 8 or 12 hours would necessitate an inconvenient amount of drug being swallowed. Potent drugs, i.e., those having a very small difference between the effective and toxic doses, or those to which patient response is variable, necessitate individualization of dose or dosage interval, and timed-release products are designed to release the drug in a fixed pattern. Drugs that are poorly absorbed or poorly soluble are likely to be absorbed erratically, and thus the predictability of response following ingestion of a timed-released product is difficult. Since the amount of drug contained in a timed-release formulation is usually greater than in a conventional formulation, increased side effects or toxicity is possible. Variations in the patient's physiological response or a technical flaw in the formulation may result in the release of the entire amount of active drug from the formulation in a short period of time, thus producing adverse reactions.

Some drugs reviewed by the Panel are inappropriate for formulation in a timed-release product. Glyceryl guaiacolate is a drug that for effectiveness requires a relatively large dose at regular intervals. Thus, the dose of the drug required to obtain an effective action over an extended period of time, e.g., 8 to 12 hours, would be difficult to swallow. The theophyllines represent an example of a potent drug for which patient dosage should be individualized because of the drugs' variable rates of metabolism. Such

individualization of dosage is best obtained by ingestion of small doses of theophyllines at more frequent intervals than are possible with timed-release products.

All other drugs reviewed by the Panel would, on theoretical grounds, be suitable for incorporation into a timed-release product. For approval of any drug in a given type of timed-release formulation, evidence should be presented to demonstrate that blood levels or clinical effects are comparable and the incidence of side effects is not greater than that seen when compared to the preparation given in repeated, single doses (conventional dosage).

5. *Guidelines for evaluation of timed-release formulations.* Timed-release formulations generally fall into one of three major categorics: Extended release—those that provide for gradual and continuous release of active substance along the gastrointestinal tract; repeated action—those that provide two or more essentially discrete release times for the active constituents, e.g., coat/core formulations; and those that combine the mechanisms of both of the foregoing kinds of formulations.

Evaluation of any type of long-acting oral formulation should accomplish two objectives. First, it should establish that the dosage form provides delayed absorption of all or part of the drug(s) as claimed in the labeling. Secondly, it should establish that the formulation delivers the claimed dosage of the drug(s) to the patient.

There are basically two major methods of evaluating these specialized dosage forms:

a. *Clinical methods.* Controlled clinical tests, aimed at measuring the magnitude and duration of either the therapeutic effect or a characteristic pharmacologic effect resulting from timed-release drug as compared to the concentration or drug activity resulting from the usual dose administered in solution or a rapidly disintegrating solid dosage form, offers an ideal way of determining the safety and effectiveness of a timed-release dosage form of a drug. Unfortunately, however, there are few objective measurements currently available that will demonstrate drug action even though there are pharmacologic responses (see other sections of this document describing evaluation protocols for clincial studies). Where such methods are available, they should be the evaluative method of choice to compare the timed-release product with suitably repeated doses of the drug in a conventional formulation. In the absence of clinical trials of timed-release preparations, blood levels and urinary excretion determinations are acceptable if these measurements can be related to pharmacologic effects.

b. *Drug absorption methods.* (1) *Blood level measurements.* Long-acting dosage forms can be evaluated by methods that measure the rate and extent to which the active ingredients are absorbed into the bloodstream. A principal way of determining this drug absorption makes use of tests in which the blood levels of the drug are measured at specified time intervals after administration of the product.

The analytical method should permit quantitative evaluation of rates of absorption, peak drug levels, and peak time and areas under blood drug-level curves. The latter are particularly useful in evaluation of time-release formulations because the area under the blood drug-level curve of such a formulation should approximate that obtained with appropriately repeated doses of a conventional oral form of the drug. Thus, for example, two experimental approaches may be considered: For coat/core formulations, the aim is to establish whether the release time of each ingredient corresponds to the labeling claim, and then to determine whether the blood-level curve obtained with the core approximates that obtained with conventional tablets; and for other timed-release formulations one can also compare blood levels with those of a conventional form of the drug when each preparation has been administered at recommended time-intervals.

Where appropriate, it is preferable to measure blood levels of the parent drug and/or its metabolites; however, urinary excretion measurements offer an alternative approach.

(2) *Urinary excretion measurements.* There are many instances where adequate reproducible methods of determining blood levels have not yet been developed. In which case, urinary analytical methods offer an alternative to blood level measurements in evaluating a timed-release oral form of a drug. Urinary excretion measurements can provide quantitative data only when the drug is excreted unchanged in the urine or when the metabolism of the drug is well understood. In utilizing measurements of urinary levels and excretion rates, the timed-release product should also be compared with suitably repeated doses of a conventional oral form of the drug. With both preparations, the urinary excretion levels and rates over the test period should be roughly similar but need not be equal.

6. *Summary.* If claims of timed-release are made, these claims must be supported by evidence as compared to usual suitably repeated doses of the drug in a conventional oral formulation. Such evidence should be obtained from studies in humans, which are based upon the measurement of a therapeutic effect or acute pharmacologic effect of the drug or may be based upon the blood level and/or excretion characteristics of the drug.

The results obtained by suitable clinical methods or by blood level or urinary excretion methods should be correlated with appropriate in vitro dosage performance tests defined by the manufacturer. The in vitro tests should be incorporated into the quality control procedures as part of the Food and Drug Administration's regulations on good manufacturing practices identified in 21 CFR Part 211. The ongoing in vitro quality control procedure would assure product performance on a level in consonance with the in vivo results obtained during the initial stages of development of the particular timed-release product.

The Panel has reviewed § 200.31 (21 CFR 200.31) of the regulations, which regards a timed-release dosage form as a new drug when any such dosage form contains per dosage unit a quantity of active ingredient that is not generally recognized as safe (GRAS) for administration as a single dose under the conditions suggested in the labeling. In such cases, a new drug application (NDA) is required to demonstrate that the drug is properly formulated to release at a safe rate the total dose contained per dosage unit.

The Panel is concerned with the issue of sustained-release formulations of active ingredients placed in Category I. This concern relates to approval of dosage levels of Category I active ingredients in excess of the maximum effective dosage per dosage unit based upon sustained-release or timed-release characteristics of the particular product.

The issue facing the Panel is whether to recommend to the agency that timed-release products be reviewed on a product-by-product basis through the new drug application procedures or whether suitable standards can be developed for testing which can be included in the CCABA drug monograph. The Panel views the exclusive use of the new drug application procedures as eliminating any possible general recognition for timed-release products. The Panel is aware that the drug industry has developed appropriate test procedures for specific timed-release mechanisms which would assure that various timed-release products deliver an effective dosage of active ingredient over a claimed extended period of time between, e.g., 8 and 12 hours. The Panel encourages the drug industry with the assistance of the Food and Drug Administration to develop suitable tests for the standardization of all OTC timed-release CCABA products. The Panel recommends that 4 years be provided for the development of such testing procedures. The Panel is concerned, however, that in the interim some products would be marketed with timed-release claims which, due to poor formulations, would deliver unsafe or ineffective dosages of drugs to the consumer. To assure that safe and effective products are available to the consumer, the Panel recommends that, during this interim period while the drug industry is developing standards with the Food and Drug Administration, sustained-release claims not be permitted in the labeling unless data have been presented before marketing to the Food and Drug Administration documenting that the timed-release preparation exceeds the single therapeutic dosage by an amount sufficient to produce blood levels or other effects that approximate those achieved by multiple administration of single therapeutic dosage units at accepted intervals based on the absorption and/or excretion characteristics of the drug.

The Panel is concerned that after reviewing the safety and effectiveness of active ingredients, a timed-release formulation may modify the safety and ef-

fectiveness in such a way that in essence these products will not be as safe or as effective as the Panel intends.

Any active ingredients or combination of active ingredients that include a claim for time-release will therefore be placed in Category III unless appropriate data can be presented to the Food and Drug Administration as outlined above.

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F. DEFERRAL OF "SORE THROAT" CLAIM

The term "sore throat" is used by consumers to describe a symptom frequently accompanying cough, nasal congestion, or the symptom complex of the "common cold." Sore throat appears as an indication or claim for a variety of products included in submissions reviewed by the Panel.

Ingredients to which sore throat indications and claims are attributed include, in general, local anesthetics and antibacterials. The Panel, working in conjunction with the Food and Drug Administration, has determined that the expertise for evaluating these ingredients for safety and effectiveness resides in the OTC Oral Cavity Panel and has therefore referred these ingredients and the "sore throat" indication and claim to the Oral Cavity Panel.

The Panel notes, however, that while the sore throat may be due to simple irritation resulting from nasal congestion and consequent breathing through the mouth, it may also be due to an infection with potential for serious complications. In the latter circumstances, the patient should not self-medicate and suppress the pain of a sore throat because delay in obtaining medical attention can have serious consequences. Labeling for products intended for relief of sore throat should emphasize that such products are for use only for "minor throat irritation." The products should bear adequate warnings that they are not intended for persistent or chronic sore throat accompanied by fever or other symptoms like headache, rash, nausea or vomiting, or glandular swelling. Labeling should also indicate the potential seriousness of a sore throat and bear adequate instructions for obtaining medical consultation.

G. DRUG MISUSE AND ABUSE

Drug abuse, in its broadest sense, can be described as intentional consumption of a drug for reasons other than legitimate therapeutic uses, often in excess of normally acceptable doses and dosage intervals. Drug misuse generally refers to overuse of a drug for therapeutic purposes due to misinformation or ignorance about its rational use. To the extent that OTC drugs are able to suppress symptoms and through their pharmacological actions also affect other systems to produce overtly perceived effects, i.e., side effects, misuse and/or abuse of OTC products can be expected to occur. The Panel believes, however, that drugs having documented effectiveness, therapeutic utility, and safety when used prudently for self-diagnosable conditions in accordance with label instructions represent a valuable, national public health resource.

Misuse and abuse of drugs is an increasing problem in our society. The Panel is aware of this problem and has addressed it to a limited extent. Of those drugs reviewed by this Panel, the formerly exempt narcotics listed in Schedule V (21 CFR 1308.15), alcohol, sympathomimetics, and belladonna alkaloids appear to be most subject to abuse. It is not within the purview or charge to the Panel to evaluate the numerous psychological, sociological, or economic factors involved in drug abuse. Consequently, the following comments and recommendations are based on medical and scientific data related to safety and effectiveness of these OTC drugs.

The risk of misuse and/or abuse is minimized by restriction on the types of pharmacologic agents in available OTC products, limitations on dosage and concentration of active drug, and adequate and explicit directions for use coupled with appropriate warnings. The Panel also urges that all appropriate measures be directed to reducing the incidence and severity of accidental overdosage, including increased education of the consumer regarding storage of medications, limitations on dosage units per product packages, and employment of safety packaging.

In general, OTC products that have been carefully formulated, thoroughly tested, and adequately labeled are safe when taken in accordance with label instructions for use and dosage. However, when these products are misused or abused, they may have unusual, unexpected, and/or toxic effects. Such drug abuse affects not only the individual himself, but society as a whole. The drug abuse problem is a complex one requiring the joint effort for solution by health care professionals, government, industry, educational institutions, and consumers.

The Panel urges for a balance in educational programs directed to consumers, which illustrate not only the horrors of narcotic addiction, but also the beneficial properties of effective therapeutic agents, their contribution to man's well-being, their undesirable side effects as well as the dangers inherent in all drugs if not properly used. The Panel believes prevention to be the key to the solution of drug misuse and abuse problems, and education to be the key to prevention. Because of the progressive nature of involvement with drugs, it is mandatory that groundwork in drug abuse prevention be laid down for children at an early age and reinforced throughout their lifetime.

There is, at this time, a conspicuous lack of data available on the nature and extent of misuse and abuse of OTC products. The Panel believes it is an obligation of the industry, government, and health care professionals to find out how these products, and especially potentially abusable ones, are being used and misused. The Panel recognizes a need for and recommends attention be directed to definitive, properly conducted studies to provide an indication of the magnitude and severity of the problem attendant to misuse and abuse of OTC products, especially those affecting the central nervous system.

1. *Codeine abuse.* During the time the Panel was in session, the Food and Drug Administration issued a proposed regulation in the FEDERAL REGISTER of September 12, 1972 (37 FR 18741) which proposed to place codeine-containing cough preparations on prescription by modification of 21 CFR 329.20.

At the present time, codeine-containing cough syrups are available for purchase OTC after the patient has signed a registry which records the consumer's name, amount purchased, intended use, and date of purchase. The proposed regulation would have restricted the availability of codeine-containing cough preparations, making such preparations available only by a physician's prescription.

At the request of the Food and Drug Administration, the Panel reviewed the studies on the basis of which the Bureau of Narcotics and Dangerous Drugs (BNDD) (now the Drug Enforcement Administration) asked the Food and Drug Administration to revoke the OTC status and discussed these studies with representatives of the BNDD. In addition, the Panel discussed the potential for codeine abuse with representatives from Food and Drug Administration's Division of Neuropharmacologic Drug Products and discussed with Food and Drug Administration officials aspects of the national policy concerning opium products and production.

This policy was related to the need to reduce illicit drug traffic in narcotics by reducing national imports of opium. A high percentage of imported opium is processed to produce codeine, which is used in codeine-containing OTC cough

preparations. By placing these preparations in a "prescription only" category, their use would be severely reduced and thus the nation's need for imported opium reduced. In addition, BNDD had performed several studies that seemed to indicate a high incidence of abuse of codeine-containing cough preparations, possibly leading to drug addiction and contributing to the illicite drug traffic.

After review of all pertinent scientific data, the Panel concluded that codeine and its salts are safe and effective for OTC use as antitussives when used in accordance with instructions on the label. The potential for abuse of codeine is viewed by the Panel as negligible. When taken by mouth, codeine rarely causes physical dependence. Although codeine can partially suppress morphine withdrawal, it may require high doses in the range of 1,200 to 1,800 mg per day given by injection.

The Panel forwarded to the Commissioner the following statement:

Deliberations of the Panel have resulted in a statement that codeine is safe and effective for OTC use as a cough suppressant. It is further the opinion of the Panel that under usual conditions of therapeutic use, codeine has low dependence liability. On the basis of scientific and medical evidence alone, it is the Panel's opinion that codeine-containing cough suppressant preparations should continue to be available over-the-counter. The Panel recognizes, however, that in the matter now pending before the Food and Drug Administration (removal of prescription exemption for such preparations), considerations go beyond questions of safety and effectiveness alone. The Panel does not deem it part of its function to evaluate factors which are not directly concerned with medical safety and effectiveness. Because there appears to be a conflict between the findings regarding the basic safety and effectiveness of codeine and the removal of the prescription exemption, the Panel strongly urges that FDA clearly identify all factors which lead to FDA's final decision.

As a result, the Commissioner issued a notice withdrawing this proposal in the FEDERAL REGISTER of March 24, 1975 (40 FR 12998), thus retaining codeine-containing cough preparations on OTC status.

2. *Alcohol abuse.* Alcohol, in concentrations up to 42 percent, i.e., 84 proof, is present as a vehicle in a variety of OTC products reviewed by the Panel.

The Panel recognizes a potential for abuse of alcohol contained in OTC cold, cough, allergy, bronchodilator, and antiasthmatic products and recommendations directed to educational programs and need for studies to determine the incidence and severity of misuse and abuse of drugs apply equally to abuse and misuse of alcohol.

H. PEDIATRIC DOSAGE

The Panel is aware that data on the use in children of most drugs in CCABA products are negligible or nonexistent. Yet, pediatric patients comprise a substantial proportion of the population that receives these OTC products.

The dosage that will produce optimum therapeutic effects in a particular patient, adult or child, is dependent upon factors such as the drug itself, individual patient variables such as special sensitivity or tolerance to the specific agent, age, weight and metabolic, pathological, or psychological conditions. Children's dosage calculated by any method that does not take all of these variables into account, therefore, can only be considered general guides.

Definitive pediatric drug dosage should be derived from data obtained in clinical trials with children using protocols similar to those used in adult patients. The Panel recognizes the extreme difficulties attendant upon such trials but also recognizes the immediate need to make recommendations for pediatric dosage pending availability of such definitive data.

Traditionally, pediatric dosage calculations for infants and children have been based on body surface area, weight, or age of the child as a proportion of the "usual adult dose." Dosage calculated on the basis of the age of the child, although convenient, may be the least reliable method because of the large variation in the weight of patients at a specific age. However, for OTC products that have a relatively wide margin of safety, the Panel has concluded that dosage recommendations based on age are the most reasonable since they would be most easily understood by the consumer.

In order to provide the needed dosage recommendations for pediatric patients, the Panel sought the assistance of a panel of experts in pediatric drug therapy. This Special Panel on Pediatric Dosage was convened and met concurrently with this Panel on October 31 and November 1, 1974 and made recommendations. Members of the Pediatric Panel were:

Charles Janeway, M.D.
Sumner Yaffee, M.D.
Jennifer Loggie, M.D., B. Ch.
C. Warren Bierman, M.D.
Louie G. Linarelli, M.D.
Vincent D. Larkin, M.D.
Constantine Falliers, M.D.

Subsequently, the Special Panel on Pediatric Dosage conducted correspondence and review of all pediatric dosage recommendations. These recommendations have been considered in the preparation of this document.

Unless indicated contrarily, the Panel recommends the following guidelines for determining safe and effective pediatric dosages for the individual CCABA ingredients discussed in this document: For infants under 2 years of age, the pediatric dosage should be established by a physician. For children 2 to under 6 years of age, the pediatric dosage is ¼ the adult dosage; for children 6 to under 12 years of age, the dosage is ½ the adult dosage.

The Panel has determined that the labeling terms "baby" and/or "infant" on CCABA products implies that such products have been approved for use in children under 2 years of age. The Panel, therefore, concludes that CCABA products exclude from their labeling the imprecise terms "baby" and/or "infant" unless the ingredient(s) has been specifically demonstrated as safe and effective for children under 2 years of age. In addition, products shown to be safe and effective for children under 2 years of age must provide specific dosages in their labeling for that indication(s). Products with labeling claims for children under 2 years of age not shown to be safe and effective for that age group are considered Category II.

The differences between children under 2 years of age, and other age groups with respect to the anatomy and physiology disorders of their respiratory system, their responses to diseases affecting the respiratory system, and their responses to drugs make general labeling restrictions for this age group essential. For example, infants because of the smaller diameter of their respiratory airways are particularly prone to the complications of respiratory distress during an acute respiratory tract infection such as may occur in the "common cold." Therefore, parents of children under 2 years of age should be advised to consult a physician for diagnosis and individualized therapeutic recommendations, even for symptoms and conditions that are considered appropriate for self-medication in older children and adults. Because of these considerations, the Panel recommends that the general labeling of CCABA products for use in children under 2 years of age requires the advice and supervision of a physician.

The Panel concurs with accepted medical practice that recommends that children be administered a minimum amount or no alcohol. Therefore, alcohol in pediatric formulations should be maintained at the lowest possible concentration. If pharmaceutically possible, products should be formulated without alcohol. Therefore, the Panel recommends that CCABA products containing an alcoholic content greater than 10 percent (weight/weight) should not be given to children under 6 years except under the advice and supervision of a physician.

In the recommendation of the Special Panel on Pediatric Dosage, restrictions on the use of certain drugs were made because of the lack of data and/or experience in the pediatric population. Some drugs may be restricted because of the need for a physician's examination and evaluation of the medical problem for which a drug may be indicated. Still other drugs are not recommended for use in children because of inherent drug toxicity in the pediatric age group. This Panel will indicate, where applicable, pediatric dosages, limits, or warnings, in its discussion below of individual ingredients.

I. INACTIVE INGREDIENTS

A variety of inactive ingredients is used in the manufacture and formulation of products reviewed by the Panel. Such ingredients are intended as flavoring agents, aromatics, vehicles, colorants, sweeteners, etc.

Although the Panel did not review these inactive ingredients, it is the view of the Panel that their safety and the advisability of including them in drug products be reviewed by an appropriate body. Since many of these ingredients are used in the formulation of many drug

products other than those reviewed by this Panel, it is not appropriate that they be dealt with specifically and solely in relation to CCABA products.

For various reasons, individuals may wish to avoid using certain inactive ingredients found in drug products. These reasons may be allergic reactions, idiosyncratic responses, fear of safety (whether valid or not), or personal dislike. It is impossible to make a free choice in this regard unless the full contents of drug products are listed on the label. Therefore, this Panel strongly recommends that the Food and Drug Administration require full ingredient labeling of inactive as well as active ingredients in descending order of quantities present in all drug products. In support of this position the Panel notes that food products are already required to have such labeling, and since the purpose of a drug is to alleviate symptoms of disease, it would seem much more compelling to have this information on all drugs.

In line with the Panel's desire to expose the consumer to the smallest number of ingredients possible, the Panel has previously recommended that marketed products contain only those ingredients essential to the product. (See part II. paragraph C.2. above—Limitation of Ingredients in Combination Products.)

Although chloroform was reviewed, and considered by the Panel to be an inactive ingredient, it was reviewed again at the special request of the Food and Drug Administration, because of reports suggesting that it is carcinogenic (Refs. 1 and 2). A discussion can be found later in this document. (See part IV. paragraph B.2.b. below—Chloroform.)

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J. ADVANTAGES OF SINGLE INGREDIENT PRODUCTS

OTC drug combination products seem to provide the public with many options from which to select the preparation most likely to relieve a symptom or group of symptoms. The combinations available would seem on the surface to be rational. The Panel has discussed CCABA combination products earlier in this document. (See part II. paragraph C.1. above—General combination policy.) However, the individual may need or tolerate only one of the ingredients in the combination product and the presence of the others may be unnecessary or, because of side effects or idiosyncratic reactions, their presence may preclude use of the combination.

Great variability with regard to side effects induced by drugs is seen among patients. Common examples are drowsiness caused by antihistamines and nervousness and sleeplessness caused by ephedrine. Furthermore, the ratio in which the components exist in the combination will be unsuitable for some persons. Although these effects and the drugs producing them are familiar to physicians and pharmacists, the public is unlikely to identify the ingredient causing the side-effect if the ingredient is present in a combination. This difficulty is largely avoided with single ingredients, which many physicians prefer to prescribe. With a single ingredient, whether available OTC or on prescription only, the patient can recognize the drug's action with relative ease and can adjust the dosage according to need. Experience gained in this way could be very useful to the patient on occasions of future need for self medication.

Single ingredients are rarely available among CCABA OTC drugs. Since many physicians prefer to treat with single ingredients, it seems logical for the public to have the option to medicate themselves with single ingredients also.

In summary, availability of individual ingredients would provide increased opportunity for the public to evaluate OTC drugs and allow the public to avoid taking two or more drugs where one might suffice. This will promote more specific and possibly safer self-medication.

It is strongly recommended therefore, that any active ingredient marketed in OTC preparations for cold, cough, etc. be equally available OTC as a single ingredient and in a form equally convenient to administer.

K. ADVERTISING

The Panel is aware that the role of the Food and Drug Administration is to regulate labeling of over-the-counter drugs and the role of the Federal Trade Commission is to enforce adherence to such labeling in advertising. In addition to recommending specific labeling claims, warnings, and dosages, the Panel would like to make some general comments and recommendations regarding advertising of drugs.

Advertisements extend the label beyond the pharmaceutical counter or medicine cabinet. The public may well receive most of its attitude toward CCABA remedies from advertisements—particularly television advertisements.

For this reason the Panel strongly urges the Federal Trade Commission to challenge any advertisement which:

1. In any way negates or dilutes the information on the label, especially the contraindications and/or warnings;

2. Suggests or leans heavily on words, phrases, and portrayals that lead the lay person to assume that the product is to be used in any manner not recommended in the monograph established below, or that it cures when in reality it only alleviates symptoms.

The Panel further recommends that advertisements for CCABA remedies not be placed where they can promote or suggest use by children, and if such an advertisement is placed where numbers of children may learn of the indications for the product, that such advertisement contain clear and specific warnings and contraindications concerning child use.

L. STATEMENT ON CCABA COMBINATION PRODUCTS CONTAINING ASPIRIN

The Panel is aware that certain individuals develop manifestations simulating an allergic reaction within 15 to 45 minutes after taking 300 to 600 mg of aspirin (acetylsalicylic acid) (Ref. 1). Such reactions may occur even though aspirin has previously been well tolerated by these individuals for many years. The major manifestation of such an allergic type reaction to aspirin is asthma, which may be of such severity as to be life-threatening. These manifestations are those seen in acute allergic reactions. Other manifestations include intense nasal stuffiness and urticaria. However, all efforts to demonstrate an allergic mechanism to account for these reactions have failed.

In a study of nine analgesic drugs with respect to their capacity to induce bronchial reactions in aspirin-sensitive asthmatic patients and their ability to inhibit prostaglandin synthetase activity, those five drugs (aspirin, indomethacin mefenamic acid, flufenamic acid, and phenylbutazone) active in causing asthma were also active in inhibiting the enzymes (Ref. 2). Of the nine analgesics, four drugs (salicylamide, paracetamol, benzydamine, and chloroquine) lacking the capacity to induce asthma on challenge in aspirin-sensitive asthmatic patients also lacked the capacity to inhibit prostaglandin synthetase activity. Since some prostaglandins have bronchoconstrictor activity whereas others have bronchodilator activity, it was postulated that aspirin and other drugs giving asthma on challenge may do so by modifying prostaglandin synthesis. Inhibitors of prostaglandin biosynthesis such as aspirin should not be given to patients with aspirin-sensitive asthma (Ref. 2).

The available clinical evidence indicates that the presence of the acetyl group in aspirin is essential for such reactions to occur since sodium salicylate and other salicylates are well tolerated in aspirin-sensitive persons.

The frequency of adverse reactions to aspirin among asthmatic children 6 to 16 years of age is reported to be 1.9 percent (Ref. 3), and among adult asthmatics the reported frequency exceeds 3 percent and may be substantially higher (Refs. 1, 4, 5, and 6). There are at least two reports of death following the ingestion of aspirin (Refs. 7 and 8). Asthma may appear for the first time, after taking aspirin, in individuals who may have previously tolerated aspirin. Therefore, the Panel feels that a warning limited to the statement that aspirin-containing preparations be avoided by those with already existing asthma would be inadequate.

A common history in individuals who previously tolerated aspirin is long-standing perennial rhinitis, chiefly characterized by nasal stuffiness. Nasal polyps are very common but are not invariably present. Asthma may or may not have been present. The Panel is concerned that individuals having tolerated aspirin in the past may develop a severe reaction, usually an asthmatic attack, following the taking of a CCABA product containing aspirin. If aspirin is present in a combination drug product, aspirin is usually not recognized as the cause of

the reaction until such episodes occur once or twice more.

The association between nasal polyps, asthma, and aspirin sensitivity has been recognized for many years, and there are many reports in the literature (Refs. 1, 3, and 9). Eosinophilia is the rule in these patients and this should be considered as part of the syndrome. The yellow dye, tartrazine, and the anti-inflammatory drug, indomethacin, are also reported to cause asthma in these patients (Ref. 9).

The Panel recognizes that prevention is the logical course, which includes recognition of the syndrome and proper instruction given to the patient. However, the Panel notes that the presence of aspirin in combination with other drugs can lead to ingestion of aspirin by error, a point frequently made by patients. Furthermore, the first reaction of this kind in aspirin-sensitive individuals will often go unrecognized if aspirin is in combination with other drugs. For this reason the Panel concludes that the availability of aspirin in combination drug products can be expected to lead to more of these severe reactions than would occur if aspirin were only available as a single ingredient.

The OTC drugs under review by the Panel are frequently taken by consumers in whom reactions to aspirin are most frequent. The Panel notes that other analgesics like acetaminophen are available and may be included in specific combination products. (See part II. paragraph C. above—Principles Applicable to Combination Products.) For this reason, the Panel concludes that CCABA combination products containing aspirin (acetylsalicylic acid) should be labeled under the heading *"Warning":* "This product contains aspirin and should not be taken by individuals who are sensitive to aspirin."

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M. GENERAL STATEMENTS ON THE DETERMINATION OF SAFETY AND EFFECTIVENESS FOR CCABA PRODUCTS

1. *Determination of safety.* a. *Single drugs.* In deciding on the safety of a drug or combination of drugs, both animal and human studies were considered.

Although animal studies were of interest, they were seldom very helpful because it would be unusual for a drug to reach the market without satisfactory animal safety data. The animal data usually related to levels of the drug that might cause death and the effect of the drug on various organs such as the bone marrow, liver, and kidneys.

Major attention was paid to information related to adverse effects in humans, both adults and children. A knowledge of the pharmacology of the drug or drugs under consideration made it possible to look specifically for adverse effects in one or more systems. It was important that there be studies in which the drug was compared with a placebo. In addition, blood levels related to toxic effects were very useful and could be related to various dosages and routes of administration. Examples of the great variety of possible toxic effects are as follows:

(1) An adverse effect might be present but this might not be very serious and could be dealt with by careful labeling, e.g., the drowsiness caused by many antihistamine drugs.

(2) A drug might have abuse potential. For example, the abuse potential for codeine was considered small, but the abuse potential for stramonium was considered very high.

(3) The effect of repeated doses of the drug had to be considered, e.g., the rebound nasal congestion which can occur with repeated doses of nasal decongestant drops or sprays.

(4) A possible excessive therapeutic effect was considered, e.g., the drying effect of drugs from different pharmacologic groups (antihistamines and anticholinergics) on the bronchial tree.

(5) The possible depressant effect other than that related to the symptom under consideration, e.g., a cerebral depressant effect of an antitussive.

(6) The route of administration of drugs had to be considered, for example, the local effect on the bronchial tree of drugs used in the treatment of asthma where these were administered in an aerosol. Another example is the use of suppositories of theophylline that could be additive to theophylline given by mouth.

(7) The seriousness and frequency of known idiosyncratic reactions might be critical, e.g., the very serious adverse effects of aspirin in some patients with asthma.

(8) There might be interactions with other drugs such as the serious result of taking ephedrine with a monoamine oxidase inhibitor which would cause a severe rise in blood pressure.

All the above were considered, and in addition, information was sought regarding any differences that might occur when the drugs were given to children of various ages as compared with adults. Children less than 1 year tend to metabolize drugs differently from older children and, as this was difficult to predict, this was one factor leading to the decision of the Panel not to label drugs for OTC use in children under 2 years except under the advice and supervision of a physician. (See part II. paragraph H. above—Pediatric Dosage.)

The importance of clear labeling of warnings and cautions was continually considered, and it is recommended that the public be educated to read labels carefully and to take the warnings and cautions seriously.

b. *Drug interactions.* There is little, if any, documentation of drug interactions between OTC drug products or between OTC drug products and prescription products and only speculation can be offered regarding such potential interactions. Even well-documented drug interactions may depend on drug dosage levels not usually attained with OTC products. Therefore, in considering the safety of OTC drugs, one must consider not only possible effects of single drugs but also possible adverse effects of interactions between drug combinations. The Panel has recommended appropriate labeling warnings where there are serious concerns.

2. *Determination of effectiveness.* In determining effectiveness, it was necessary to consider each pharmacologic group separately although certain general principles applies to all groups.

Animal studies were seldom very helpful except in the case of antihistamines where one of the requirements for efficacy was the capacity of the drug to decrease or suppress anaphylaxis and the effects produced by histamine in animals.

Major attention was paid to clinical studies especially where the double-blind technique could be employed. In some situations the ability to do a crossover study was of additional value. Studies in which there were objective measurements with proper controls and statistical analysis were of considerable weight in the Panel's decision to place an ingredient in Category I. However, certain drug actions made such objective measurements extremely difficult or impossible and therefore, large well-controlled subjective studies were considered of reasonable use. Partially controlled and uncontrolled clinical studies were of very limited value but both were considered by the Panel. Clinical experience of a general nature, if documented by qualified experts, added somewhat to the final decision. It was considered particularly useful if similar results were obtained.

In some instances, the Panel considered the Drug Efficacy Study data. The Drug Efficacy Study of the National Academy of Sciences—National Research Council (NAS/NRC) reviewed the data submitted to the Food and Drug Administration to support effectiveness of only marketed products that had re-

ceived premarket clearance through a New Drug Application (NDA) for safety prior to 1962. The Panel in reaching its decision considered all the studies available including information from the Drug Efficacy Study.

Examples of the different types of studies (all of which should be placebo controlled) used by the Panel to assess different drug groups are as follows:

a. Antitussives are best assessed by objective cough-counting techniques. The antitussive can be tested by decreasing induced cough or by decreasing the cough in patients with chronic cough.

b. Expectorants may be assessed by large double-blind crossover subjective studies in patients with chronic lung disease or randomized double-blind studies in patients with acute upper respiratory infections. These studies are acceptable because objective techniques for assessing the expectorant action of a drug are not yet satisfactory and require further development.

c. Bronchodilators are best assessed by objective measurements of pulmonary function in asthmatics where a significant improvement in pulmonary function can be shown after the use of the drug.

d. Antihistamines require the study of large groups of patients with strict double-blind control using a subjective evaluation of the effect of the drug on allergic rhinitis or on the symptoms of the "common cold". These clinical subjective studies are acceptable as there is no definite objective technique for measuring the effect of antihistamines in these conditions. Anticholinergic drugs which are used in the treatment of rhinitis with rhinorrhea require clinical testing similar to that of the antihistamines.

e. Nasal decongestants which relieve obstruction to the nasal passages are best assessed by objective measurements of resistance to air flow through the nose. In this way comparisons of the drug and the placebo can be made using data of airway resistance measurements.

Although all the evidence related to the effectiveness of a drug was considered, the above studies in the various pharmacologic groups had the greatest influence in determining a Category I classification.

It was extremely difficult to judge the effectiveness of combinations of ingredients because of the many different dosages involved and the difficulty in determining the effect of each individual ingredient in the combination. The Panel considered it reasonable that Category I ingredients from different pharmacologic groups differed sufficiently from one another to reduce the likelihood of a competitive or potentiating effect between ingredients, and their combination was therefore considered effective. There are some exceptions to this and these exceptions are discussed in the section on combination drugs. (See part II. paragraph C.—Principles Applicable to Combination Products.)

To assist in the testing of ingredients in the future, the Panel developed clinical testing procedures for each pharmacologic group. These procedures have been included in the "Data Required for Evaluation" sections following the ingredient(s) statements for each pharmacologic group.

N. AEROSOL DOSAGE FORMS OF DRUGS UTILIZED IN CCABA PRODUCTS

The utilization of the pressurized, self-contained and self-propelled "aerosol" dosage forms in delivering pharmaceuticals was begun in the 1950's when advances in the technologies of propellants, valves, and containers made possible the accurate delivery of metered doses for direct inhalation into the respiratory system. Development in the areas of fine particle technology and different aerosol systems kept pace with the evolution of specialized valves and actuators, containers of diverse materials such as glass, coated metals and plastics, and a variety of propellant gases such as the halocarbons, compressed gases (nitrogen, carbon dioxide, nitrous oxide), and hydrocarbon gases (butane, isobutane, pentane).

The Panel is aware of the advantages and disadvantages of the pressurized drug products that were the subject of submissions to the Panel.

Among the advantages may be listed:

1. Aerosol products are permanently sealed units, and thus their contents are maintained in a stable form that is protected from accidental contamination by organisms, atmospheric gases, moisture, and sunlight that are sometimes encountered with the use of ordinary containers that are repeatedly opened.

2. The utilization of specialized valves and adapters permit the release of mists, sprays, or true aerosols (particles suspended in gas), in a controlled manner that assures the rapid administration of the aerosolized drug. This is particularly useful when prompt onset of action is desirable.

3. Metering valves and containers are available in compact form, so as to permit the consumer to carry the product on his person with little inconvenience and with quick accessibility when medication is required.

4. Aerosol products designed to emit an intermittent or continuous spray of medicaments into the atmosphere of a room are capable of producing aerosolized mists containing particles that are fine enough to be inhaled and thus exert their effect rapidly in the respiratory tract.

In recent years the advantages of the aerosolized forms of drugs for treatment of bronchial asthma and the transitory symptoms of the "common cold" have been challenged because of potential toxicities. These include the cardiotoxicity potential of the halocarbon propellent, fluorocarbon 11. Several studies have been reported that indicate that the propellant can be absorbed into the blood with a persistence of a small quantity in the blood after 1 hour.

Reports of accidental sudden deaths following the inhalation of aerosols emptied into a plastic bag indicate an abuse potential that cannot be overlooked.

More recently predictions based on the use of computer models have warned about the possibility that halocarbons released into the air from aerosol products may be the cause of depletion of the ozone layer in the stratosphere. Concern has been expressed that if these predictions are accurate then the protective elements of the stratosphere against ultraviolet radiation may become impaired.

The Panel, therefore, concludes that although aerosol products do possess inherent advantages for specialized application of drugs in bronchial asthma and other respiratory conditions, the possibility of toxic effects of the halocarbon propellants should be carefully evaluated by a suitable Panel of experts in this area.

O. CCABA PRODUCT LABELING CLAIMS NOT SUPPORTED BY SCIENTIFIC EVIDENCE

The Panel has reviewed the submitted labeling claims made for CCABA products. It is interesting to note that products sold for relief of symptoms of the "common cold" and allergies are probably the largest category of OTC drug products on the United States OTC drug market. In fact, there are estimates by the Food and Drug Administration that as many as 50,000 different OTC CCABA drug products are currently marketed. Because of this vast array of products, the consumer is often faced with a myriad of confusing claims, which are not only vague and hard to comprehend, but also make it almost impossible for the consumer to distinguish between these products.

One of the primary functions of this Panel is to minimize this confusion by clarifying the labeling. In that way the ordinary individual who purchases an OTC drug product for the relief of symptoms, e.g., of the "common cold" or allergies, will understand exactly what the product will do for him, the limits of the product's capability, and the cautions to be observed when using that product. It is also a basic function of the Panel to attempt to reduce confusing labeling claims to a reasonably concise number of understandable claims, permitting the consumer to easily distinguish between various CCABA products. The Panel believes that at the present time this is not possible since the labeling that appears on many currently marketed CCABA products tends to be overly complicated, vague, unsupported by scientific data, and in some cases is false and misleading.

The Panel understands the drug industry's desire to market OTC drug products for the relief of symptoms of the "common cold" or allergies by suggesting uniqueness or superiority of one product over another. But uniqueness or superiority must be proven scientifically or labeling will mislead and unduly confuse the consumer. For example, if one ingredient can be demonstrated to be superior to another because of greater effectiveness, then the consumer should be so informed. Conversely, if two ingredients are indistinguishable with regard to effectiveness, e.g., both are equally

effective in suppression of cough, then it is misleading to claim superiority for one of the ingredients. In this regard, the Panel wishes to make clear that its function is not to compare various ingredients in order to determine the OTC drug of choice. Rather, the Panel determines only safety and effectiveness for active OTC CCABA ingredients, as well as proper dosage ranges for OTC drug use. In reviewing the scientific literature for CCABA ingredients, it is clear that ingredients of the same pharmacologic group that are Category I, i.e., generally recognized as safe and effective, have similar effectiveness in the dosage ranges recommended. Consequently, the Panel concludes that all claims which imply superiority of one product over another, both of which contain Category I ingredients in the same pharmacological group, should be prohibited from the labeling of CCABA products. These claims would include such phrases as "Superior to ordinary" and "Specially improved or selected ingredients".

In addition, the Panel has determined that statements alluding to superiority due to greater potency, such as "extra strength" or "contains more active ingredient per dose", are also misleading unless fully documented. The Panel can find no justification for claiming more activity per dose for one Category I ingredient over another because there is no scientific merit from a therapeutic point of view between a product containing 15 mg of a drug A and another containing 30 mg of drug B if they are similarly effective. Unsubstantiated claims for "extra strength" or "contains more active ingredient per dose" or "higher dose level" or "stronger than" are therefore misleading. However, assuming that claims of greater potency were based on documented facts, such increase in potency might also indicate an increase in the potential side effects. Under such circumstances the Panel feels that such claims are misleading to the consumer.

Misleading superiority claims may also manifest themselves as claims that state or imply actions peculiar to a particular product, when in fact those claims are applicable to all OTC drug products or all Category I ingredients of the same pharmacologic group. Thus, for example, if two different OTC cough products contain different Category I antitussive ingredients, it would be misleading to make such claims as "specially formulated" or "specially selected ingredients". This view would, of course, also be applicable to combinations of appropriate CCABA ingredients or combinations of CCABA and non-CCABA ingredients. Thus, claims such as "teamed components" would also be considered misleading by the Panel.

Another area of concern to the Panel is claims implying a unique physiological action that either has no scientific foundation or meaning or that will be meaningless to the consumer. Such claims include pseudo-medical terms such as "antiallergic", or pseudo-medical activities such as "gets at the roots of", "fights", "wakes up", and "multiaction". Some claims mislead the consumer into believing a product has a unique action, when in fact that pharmacologic action is shared by all similar OTC drug products containing active ingredients from the same pharmacologic class. Examples include claims that an ingredient "travels through the bloodstream" or "works internally". All drugs taken internally "work internally" and virtually all drugs taken internally are absorbed into the bloodstream. Thus, these claims are also not appropriate in OTC labeling.

Finally, the Panel is concerned about vague generalizations relating to time that do not actually relate to the directions or indications. This is especially true where the time stated in the claim is indeterminate. Thus, claims such as "fast" and "prompt" should not appear on labels unless they are directly correlated to the directions for use permitted in the monograph.

P. CCABA PRODUCT NAMES AND LABELING CLAIMS ASSOCIATED WITH DISEASES AND RELATED SYMPTOMS

The Panel has made a clear distinction in this document between the treatment for the relief of the symptoms of a disease, e.g., cough, runny nose, and the treatment of the disease itself, e.g., "common cold." With few exceptions, CCABA products are indicated only for the treatment for the relief of symptoms. The most common disease associated with CCABA products is the "common cold." The Panel has discussed this respiratory disease earlier in this document. (See part II. paragraph B.3. above—The "common cold.") The Panel concludes that there is no demonstrated safe and effective OTC active ingredient or combination of active ingredients acceptable for specific treatment of the "common cold." Consequently, the Panel recommends that product names or labeling claims that infer or suggest a direct relationship to the "common cold," e.g., "cold medicine," "cold formula," "for relief of colds," should not be allowed. Such statements may mislead the consumer into believing that these products prevent, treat, or cure the disease itself.

The active ingredients reviewed by the Panel and included in currently marketed CCABA products are generally used for the treatment or relief of the symptoms of disease. The Panel concludes that if labeling is restricted to the proven pharmacologic activities of the active ingredients in CCABA products, reference in labeling to the specific activities of such ingredients in alleviating symptoms is acceptable. The Panel has summarized the commonly encountered symptoms and the acceptable pharmacologic groups earlier in this document. (See part II. paragraph B. above—Diseases and Related Symptoms Relieved by OTC Cold, Cough, Bronchodilator and Antiasthmatic Products.)

For drugs used to treat the symptoms of the "common cold," the Panel recommends that in addition to the acceptable claims (Category I) for specific pharmacologic groups, the following phrases may be used: "(symptoms) as may be associated with the 'common cold' " or "as may occur in the 'common cold' ". An example for a product containing an antitussive would be "For cough as may occur in the 'common cold'."

On the other hand, the Panel finds that certain OTC bronchodilator active ingredients are safe and effective for the treatment of asthma. This disease is effectively treated by OTC products but requires prior diagnosis of asthma by a physician. Bronchodilators serve to relieve the primary manifestations of asthma, shortness of breath, which is caused by widespread narrowing of the airways due to airway wall muscle spasm. The Panel recognizes that bronchodilators cannot prevent or cure the disease but are effective in relieving the primary symptoms. Because of these unique symptoms and because the Panel believes these products should be easily identifiable and accessible to those afflicted with the disease, the Panel concludes that use of the term "asthma" in labeling of products containing Category I bronchodilator active ingredients, either as part of a product name, e.g., "asthma medicine", or appearing alone in labeling claims, e.g., "treatment of asthma", is acceptable. The Panel is of the opinion that reference to asthma in labeling is not misleading and further, is essential for those individuals diagnosed by a physician as having the disease. This of course is acceptable, based upon the Panel's recommendation later in this document that the following warning be on all products containing bronchodilators: "Do not use this product unless a diagnosis of asthma has been made by a physician". (See part V. paragraph B.1. below—Category I Labeling.)

The Panel also recognizes that allergic rhinitis (such as hay fever) is a very common disease. Unlike the "common cold," most affected individuals understand the etiology of such a disease and realize that it cannot be prevented or cured by OTC antihistamines or nasal decongestants. However, as was the case with asthma, the manifestations of this disease can be treated with such a product. Here again, it is the Panel's conclusion that it is also acceptable for the terms "hay fever", and "allergic rhinitis", to appear in labeling of products containing Category I ingredients either as part of a product name, e.g., hay fever medicine, or appearing alone in labeling claims, e.g., "Dries running nose as may occur with allergic rhinitis", or "For treatment of hay fever".

Q. INGREDIENT EQUIVALENCE

The Panel recognizes that the ingredients submitted and reviewed may exist in chemical forms other than those considered in this document. The Panel notes that other salts, esters, and complexes of these ingredients may be available, which may be therapeutically equivalent to the forms of the ingredients considered by the Panel. In recognition of this fact, the Panel concludes that provided that there are suitable data to establish bioequivalence and safety, salts, esters, and complexes of ingredients dis-

cussed in the monograph would be acceptable. However, it is essential that the dosage used be equivalent to the dosage of the ingredient in the monograph.

INTRODUCTION TO PHARMACOLOGIC CLASSIFICATIONS

Not all CCABA products are used for the same purpose, nor should the requirements for effectiveness be the same. In an attempt to classify CCABA active ingredients and their products it was necessary to distinguish between the pharmacologic activities and resulting effectiveness for labeled claims of these products.

The following classifications of CCABA product ingredients was developed by the Panel in an attempt to simplify categorization of ingredients and thereby eliminate labeling confusion:

Antitussives
Expectorants
Bronchodilators
Anticholinergics
Antihistamines
Nasal decongestants
Miscellaneous active ingredients

III. ANTITUSSIVES

A. GENERAL DISCUSSION

An antitussive agent specifically inhibits or suppresses the act of coughing. Direct inhibtion may result from: depression of medullary or higher centers in the brain; diminishing the sensitivity of the cough receptors in the membranes lining the throat and respiratory passageway; interruption of the transmission of the cough impulses to the brain or to the muscles that are involved in the act of coughing; and by removal of irritants and excessive secretions through the improvement in bronchial drainage.

In theory, cough suppression may be produced indirectly by one of two mechanisms: A soothing action on the irritated or inflamed throat, which would in effect decrease the sensitivity of special nerve endings or cough receptors in such membranes; and a relief of spasm or localized constriction of the airway. This is known to occur in asthma or following the inhalation of an irritant.

The Panel has followed the presently accepted medical approach and has classified antitussives according to their principal site of action.

1. Centrally acting antitussive agents produce cough suppression by acting on the central nervous system to depress the medullary (brain) cough center and thus raise its threshold for afferent (incoming) cough impulses. These agents may be further subdivided into narcotic antitussives, such as codeine, and nonnarcotic antitussives such as dextromethorphan.

2. Peripherally acting antitussive agents act on the nerve receptors within the respiratory tract. Cough suppression may be produced by several different mechanisms such as a local anesthetic (pain deadening) or analgesic (pain suppressing) action on the mucosa of the respiratory tract; enhancing bronchial airway drainage by reducing the viscosity (thickness) of retained secretions, which may occur with effective expectorant agents or with adequate humidification of the airway; relaxation of the smooth muscle of the bronchial airway in the presence of spasm; or a soothing (demulcent) effect on the irritated throat and bronchial airway walls.

The narcotic antitussives have traditionally been the most effective agents available for suppressing cough. Because of its low abuse potential, codeine, the best known and most widely used antitussive in this group, has been considered safe for OTC use. Except in unusual circumstances in which cough is associated with pain, e.g., in pleurisy, the more potent narcotics such as morphine are not used because of their potential for acute toxicity from overdosage (respiratory depression) and abuse potential. Such drugs are best administered under medical supervision.

Nonnarcotic antitussives, such as dextromethorphan, act by selective suppression of the central cough mechanism and have no significant abuse liability. Therefore, they would seem to be more advantageous for use in treating cough and also for use in individuals who seem psychologically predisposed to drug dependence.

In general, the antitussives available for OTC use are and should be designed to diminish coughs associated with acute, self-limiting conditions that cause irritation to the respiratory airway. Since it is highly unlikely that such conditions would persist for more than 1 week, the Panel has limited the period of administration of these antitussives to a maximum of 7 days. A persistent cough for more than 1 week or one accompanied by high fever, rash, or persistent headache may be indicative of a serious disease, which should be treated by a physician and does not lend itself to self medication by antitussives. (See part II. paragraph B.4. above—Cough.) In asthma, bronchitis, pulmonary emphysema, and a number of other respiratory diseases, there is often an over production of secretions which accumulates in the airway and results in a cough productive of thick sputum. The suppression of cough by antitussives in such instances would impair clearing of the airway and could be harmful.

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Labeling

Consumers often have difficulty understanding the intended meaning of OTC drug labeling. The Panel concludes that use of vague words, or words which imply a greater effectiveness than other similar OTC products, is false and misleading. The Panel has reviewed the labeling that was submitted for antitussives and for other pharmacologic groups and has attempted to explain why some labeling is acceptable, objectionable, or questionable.

In the case of antitussives, the Panel has reviewed the symptoms of cough and the mechanisms by which the physiologic response is produced. Cough occurs in healthy individuals as a mechanism for clearing the airway of any obstructing mucus or inhaled foreign material. As indicated above, medications that suppress the act of coughing by reducing the number of coughs and/or the intensity of coughing are known as antitussive drugs. Based upon the previous discussion of cough and the discussion of antitussives, the Panel concludes that the following indications are acceptable labeling claims for generally recognized safe and effective antitussives (cough suppressants) for the temporary relief of cough: "Cough suppressant which temporarily reduces the impulse to cough". "For the temporary relief of coughs due to minor throat and bronchial irritation as may occur with the common cold or inhaled irritants". "Temporarily quiets coughing by its antitussive action". "Temporarily helps you cough less". "Temporarily helps to quiet the cough reflex that causes coughing".

Because of the lack of clinical studies in children under 2 years of age, the Panel was unable to determine an OTC dose for this age group. Based upon the lack of available data, the Panel recommends the following warning for products containing antitussives: "Do not give this product to children under 2 years except under the advice and supervision of a physician".

Since a persistent or chronic cough may be a sign of a serious condition requiring medical intervention and should be brought to the attention of a physician, the Panel recommends that all labeling for antitussive products bear the following warning: *"Caution:* A persistent cough may be a sign of a serious condition. If cough persists for more than 1 week, tends to recur, or is accompanied by high fever, rash or persistent headache, consult a physician".

In asthma, bronchitis, pulmonary emphysema, and a number of other respiratory diseases, there is often an overproduction of secretions, which accumulate in the airways and results in a cough that produces thick mucus. The suppression of cough by antitussives in such instances would impair clearing of the airway and could be harmful; therefore, the Panel recommends the following additional *"Warning"*: "Do not take this product for persistent cough such as occurs with smoking, asthma, emphysema, or where cough is accompanied by excessive secretions except under the advice and supervision of a physician".

B. CATEGORIZATION OF DATA

1. *Category I conditions under which antitussive ingredients are generally recognized as safe and effective and are not misbranded.*

Category I—active ingredients

The Panel has classified the following antitussive active ingredients as general-

ly recognized as safe and effective and not misbranded:

Codeine preparations: Codeine, Codeine alkaloid, Codeine phosphate, Codeine sulfate
Dextromethorphan
Dextromethorphan hydrobromide
Diphenhydramine hydrochloride

a. *Codeine preparations (codeine, codeine alkaloid, codeine phosphate, codeine sulfate).* The Panel concludes that codeine and its salts are safe and effective for OTC use as antitussives as specified in the dosage section discussed below.

(1) *Safety.* Side effects such as drowsiness, light headedness, excitement, loss of appetite, nausea, vomiting, headache, abdominal discomfort and constipation with oral doses of 20 mg of codeine have not been significantly greater than with placebo (Ref. 1). The Panel has reviewed the literature and finds that respiratory depression may occur but is usually seen when codeine products are used as prescription medication with dose levels of 120 mg every 4 hours which results in the codeine having analgesic activity similar to that of 10 mg of morphine (Ref. 2). Such high doses of codeine would present a real hazard in certain cases of respiratory disease associated with a tendency towards carbon dioxide retention. By central depression of respiration, the exchange of oxygen and carbon dioxide would be impaired and there would be a tendency for the carbon dioxide to accumulate in the blood resulting in or aggravating respiratory acidosis with a dulling of the senses progressing to coma. As little as 60 mg of codeine in adults has produced measurable respiratory depression, judging from carbon dioxide response curves (Refs. 3 and 4). This has not been apparent with the doses approved for OTC use. In an infant, doses of 10 mg every 2 hours for 10 doses has led to deep coma (Ref. 5). Death has occurred from overdosage with codeine in the range of 875 to 1,750 mg but effects were complicated by the presence of other central nervous system depressants (Ref. 6).

The Panel believes the potential for abuse of codeine is negligible (Refs. 7, 8, and 9). It is further the opinion of the Panel that under usual conditions of therapeutic use, codeine has low dependency liability. Codeine may cause addiction, but requires consistently high daily dosage (Ref. 9). (See part II. paragraph G. above—Drug Misuse and Abuse.)

(2) *Effectiveness.* A paper by Eddy et al. (Ref. 10) summarized all the data in animals and indicates the varied techniques used and results obtained. Practically all animal studies have demonstrated the ability of codeine to suppress the cough reflex.

Studies of experimentally produced cough in man were also reviewed by Eddy et al. (Ref. 10). Cough-inducing agents used were citric acid aerosol, ammonia vapour, acetylcholine aerosol, peppermint water spray, and paraldehyde. The dose of codeine ranged from 5 mg to 120 mg with most investigators using 15 to 30 mg and they were able to demonstrate a cough suppressant effect in humans.

Eddy's review of 33 clinical trials by 16 investigators (Ref. 10) indicated that codeine in doses ranging between 10 to 60 mg was an effective cough suppressant in a wide variety of disease states associated with cough. Twenty-four of these studies employed objective cough-counting techniques. All had placebo controls, and many compared codeine with other drugs as well. While all of the objective studies employed patients with chronic cough (Refs. 11 through 16), two of the subjective studies employed patients with an acute cough due to an upper respiratory infection (Refs. 17 and 18).

The technique of employing citric acid aerosols to stimulate the cough reflex in healthy subjects (Ref. 19) has also been used to demonstrate the effectiveness of codeine as an antitussive in dose ranges of 15 to 30 mg.

There are no well-controlled studies on the antitussive activity of codeine in children, and hence, dosage recommendations in children have been based on the general experience of a Pediatric Panel, which reviewed these recommended dosages. (See part II. paragraph H. above—Pediatric Dosage.) Because the majority of clinical trials have been in chronic cough, the Panel has accepted the principle that the effectiveness of codeine in coughs due to upper respiratory infection may, in large measure, be extrapolated from the information on antitussive activity in chronic cough. This is further supported by an extensive clinical experience with the use of codeine over the past 50 years.

Because of abuse liability of codeine if available as a single ingredient in unlimited supply, the Panel concurs with the present Drug Enforcement Agency regulations, which limit the sale of codeine over-the-counter. These regulations limit the amount of codeine or its salts contained in an OTC product to 200 mg per 100 ml for liquid preparations or 200 mg per 100 gm for solid dosage forms (21 CFR 1308.15(b)(1)). These regulations further specify that codeine for OTC purchase must include one or more nonnarcotic active medicinal ingredients in sufficient proportion to confer medicinal qualities upon the product other than those possessed by codeine alone (21 CFR 1308.15(b)). In addition, these regulations limit OTC sale of such codeine containing products to quantities not exceeding 120 ml or 24 dosage units (21 CFR 1306.32(b)).

(3) *Dosage.* Adult oral dosage is 10 to 20 mg every 4 to 6 hours not to exceed 120 mg in 24 hours. Children 6 to under 12 years oral dosage is 5 to 10 mg every 4 to 6 hours not to exceed 60 mg in 24 hours. Children 2 to under 6 years oral dosage is 2.5 to 5 mg every 4 to 6 hours not to exceed 30 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive ingredients. (See part III. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling claims referrable to a central mechanism of action: (i) *Indications.* "Calms the cough control center and relieves coughing".

(ii) *Warnings.* (*a*) "May cause or aggravate constipation".

(*b*) "Do not give this product to children taking other drugs except under the advice and supervision of a physician".

(*c*) "Do not take this product if you have a chronic pulmonary disease or shortness of breath except under the advice and supervision of a physician".

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b. *Dextromethorphan, dextromethorphan hydrobromide.* The Panel concludes that dextromethorphan and dextromethorphan hydrobromide are safe and effective for OTC use as antitussives as specified in the dosage section discussed below.

(1) *Safety.* Dextromethorphan is the dextrorotatory isomer of the morphinan molecule which, unlike the levo isomer, has no analgesic or addictive properties (Ref. 1). With usual antitussive doses, no effect has been noted on respiration, the cardiovascular system, or the gastrointestinal tract. With very large doses such as occur in drug abuse or accidental poisoning, respiratory depression has been noted (Refs. 2 and 3). However, no fatalities have been reported, even with doses in excess of 100 times the normal adult dose. Abuse has been reported by Degkwitz (Ref. 4) with doses of 300 to 1,500 mg several times daily, resulting in intoxication with bizarre behavior but no physical dependence.

(2) *Effectiveness.* Dextromethorphan is an active antitussive comparable to codeine on a mg-for-mg basis for cough suppression. Studies involving many species of animals and many methods for inducing cough have demonstrated that effectiveness of dextromethorphan as an antitussive is comparable to codeine (Refs. 5 through 7). Two studies (Refs. 8 and 9) reported that dextromethorphan was less effective than codeine in equivalent doses. It has been demonstrated that dextromethorphan, like codeine, acts through central (brain) inhibition of incoming cough stimuli (Refs. 10 and 11).

There have been a large number of studies in man over the past 20 years. These have consisted of: Experimentally induced cough with controlled double-blind crossover designs (Refs. 12 through 15) in which all but one (Ref. 13) showed effective antitussive activity; controlled subjective studies in pathologic cough (Refs. 13, 16 through 18); controlled objective studies in pathologic cough (Refs. 19 and 20); and uncontrolled subjective studies in a variety of disease states resulting in cough (Refs. 21 and 22).

The wide range of safety and low order of toxicity in clinical trials has been documented by Ralph (Ref. 21). The lack of addiction liability has been confirmed recently by Mansky and Jasinski (Ref. 23).

The majority of these clinical studies demonstrate effective antitussive activity. Even though a few of the studies questioned the effectiveness of dextromethorphan, the Panel concluded that based on the evidence presented, dextromethorphan is generally recognized as effective, and because of its low order of toxicity it is probably the safest antitussive presently available.

(3) *Dosage.* Adult oral dosage is 10 to 20 mg every 4 hours or 30 mg every 6 to 8 hours not to exceed 120 mg in 24 hours. Children 6 to under 12 years oral dosage is 5 to 10 mg every 4 hours or 15 mg every 6 to 8 hours not to exceed 60 mg in 24 hours. Children 2 to under 6 years oral dosage is 2.5 to 5 mg every 4 hours or 7.5 mg every 6 to 8 hours not to exceed 30 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients. (See part III. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling claims referrable to a central mechanism of action and its nonnarcotic designation: (i) *Indications.* (*a*) "Calms the cough control center and relieves coughing".

(*b*) "Non-narcotic cough suppressant for the temporary control of coughs".

(*c*) "Calms cough impulses without narcotics".

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c. *Diphenhydramine hydrochloride.* The Panel concludes that diphenhydramine hydrochloride is safe and effective for OTC use as an antitussive as specified in the dosage section discussed below.

(1) *Safety.* Diphenhydramine was the first of the antihistamines to be developed in the U.S. and was first used in 1946, clinically, for the relief of a wide variety of allergic symptoms. Diphenhydramine had a low order of toxicity in laboratory animals combined with a high degree of antihistaminic action. The Panel reviewed a number of studies contained in the submissions (Refs. 1 and 2) and concluded that with the exception of sedation, adverse effects have been rare and the drug is safe. The Panel has also found the drug to be safe for use

as an antihistamine and this use is discussed elsewhere in this document. (See part VII. paragraph B.1.c. below—Diphenhydramine hydrochloride.)

Clinical experience indicates that about 50 percent of persons have drowsiness as a side effect when 50 mg is given (Ref. 3). A double-blind controlled study in 20 males showed no evidence of interference with tests for memory, rotary pursuit, or reaction time with diphenhydramine hydrochloride in doses of 12.5 and 25 mg (Ref. 4). In a double-blind controlled subjective study on 546 patients with acute upper respiratory infection, drowsiness was reported in 11 of 269 patients receiving 25 mg diphenhydramine 4 times daily over a 3 day period (Ref. 5). Two of 277 patients receiving placebo also reported drowsiness. In infants, high doses of diphenhydramine may cause excitement and convulsions (Ref. 1). The acute toxicity of diphenhydramine in a variety of animal species is similar to other antihistamines such as pyribenzamine (Ref. 6). In children, 20 to 30 tables or capsules containing 50 mg each may represent a lethal or near lethal dose (Ref. 3).

The Panel has recommended specific warnings (see below) because an atropine-like effect is described by patients which includes a drying sensation of the mouth and nose and difficulty with urination in patients with enlarged prostates.

The Panel is aware that recently there was some concern expressed about the potential for misuse and abuse of diphenhydramine. This concern was contained in the statement of the Commissioner of Food and Drugs, which was included in the preamble to the report of the OTC Advisory Panel on Sedatives, Tranquilizers and Sleep-Aid Drug Products and published in the FEDERAL REGISTER of December 8, 1975 (40 FR 57292). This Panel will not attempt to comment on the findings of the other Panel or on the societal impact or abuse potential of diphenhydramine when used as an OTC nighttime sleep-aid. However, after a review of all the available data, the Panel concluded that diphenhydramine, as well as the other antihistamines reviewed, have a very low abuse potential and that there is little if any evidence of tolerance or habituation. However, the Panel does recognize that doses of diphenhydramine higher than those recommended for OTC use are likely to result in some side effects but that these side effects are sufficient to discourage abuse or misuse. In addition, the two pharmacologic groups for which this Panel is recommending diphenhydramine for OTC use, i.e., as an antitussive and as an antihistamine, are not recognized as being abusable by the drug abusing subculture. It should also be noted that diphenhydramine is available without a prescription for use as an antihistamine in Canada, the United Kingdom, and many other industralized countries of the world. The Panel was unable to determine that significant abuse of this ingredient was a problem in any of these countries.

The Panel concludes that diphenhydramine hydrochloride is safe for OTC use as an antitussive in the dosage ranges described below.

(2) *Effectiveness.* A number of animal studies employing chemical and mechanical methods for inducing cough (Refs. 7 through 9), including stimulation of the superior laryngeal nerve, the nerve that supplies the larynx and upper airway (Ref. 10), have demonstrated a reduction in cough frequency, which ranges from 25 percent to 120 percent of that produced by codeine depending on the species of animal employed and the method for inducing cough. The exact mechanism of action of diphenhydramine is not precisely known. However, because of its ability to inhibit the cough reflex resulting from stimulation of the superior laryngeal nerve, the Panel believes a central site of activity of diphenhydramine is a reasonable mode of action. Furthermore, the animal studies are cited as evidence that cough inhibition is not due to a general depression of the central nervous system but to a specific action, similar to codeine, on the "cough center".

Studies in man have consisted of: Experimentally induced cough employing a controlled double-blind crossover design in which both the 25 and 50 mg dose of diphenhydramine hydrochloride produced significant cough suppression equivalent to 15 mg of codeine (Refs. 11 through 13); two double-blind controlled objective studies in chronic cough, which showed antitussive activity for both 25 and 50 mg diphenhydramine hydrochloride as compared with placebo (Refs. 14 and 15), and the most common adverse reaction was drowsiness; controlled subjective study in chronic cough (Ref. 16) demonstrating antitussive activity superior to placebo but less than codeine; two subjective studies in acute upper respiratory infections, one controlled and one uncontrolled (Refs. 5 and 17), yielding equivocal results; and two objective cough counting studies in chronic cough, which were uncontrolled and showed a decrease in cough with all treatments (Refs. 18 and 19).

While drowsiness did not appear to be a major problem in the single dose studies, it is quite conceivable that repetitive doses may cause profound drowsiness in susceptible individuals. Furthermore, the drying effect of the drug's antihistaminic action could hinder bronchial drainage in patients with productive cough by making the secretions thicker and more difficult to expectorate.

(3) *Dosage.* Adult oral dosage is 25 mg every 4 hours not to exceed 150 mg in 24 hours. Children 6 to under 12 years oral dosage is 12.5 mg every 4 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients. (See part III, paragraph B.1 below—Category I Labeling.) In addition, the Panel recommends the following specific labeling claims referable to a central mechanism of action and its nonnarcotic designation: (i) *Indications.* (*a*) "Calms the cough control center and relieves coughing".

(*b*) "Non-narcotic cough suppressant for the temporary control of coughs".

(*c*) "Calms cough impulses without narcotics".

(ii) *Warnings.* (a) "May cause marked drowsiness".

(*b*) "May cause excitability especially in children".

(*c*) "Do not take this product if you have glaucoma or have difficulty in urination due to enlargement of the prostate gland except under the advice and supervision of a physician".

(*d*) *"Caution.* Avoid driving a motor vehicle or operating heavy machinery".

(*e*) "Do not give this product to children under 6 years except under the advice and supervision of a physician".

(iii) *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 6.25 mg every 4 hours not to exceed 37.5 mg in 24 hours.

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Category I Labeling

The Panel recommends the following Category I labeling for antitussive active ingredients to be generally recognized as safe and effective and not misbranded as well as the specific labeling discussed in the individual ingredient statements:

a. *Indications.* (1) "Cough suppressant which temporarily reduces the impulse to cough".

(2) "For the temporary relief of cough due to minor throat and bronchial irritation as may occur with the common cold (cold) or with inhaled irritants".

(3) "Temporarily quiets coughing by its antitussive action".

(4) "Temporarily helps you cough less".

(5) "Temporarily helps to quiet the cough reflex that causes coughing".

b. *Warnings.* (1) "Do not give this product to children under 2 years except under the advice and supervision of a physician".

(2) "Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, or emphysema, or where cough is accompanied by excessive secretions except under the advice and supervision of a physician".

(3) "*Caution:* A persistent cough may be a sign of serious condition. If cough persist for more than 1 week, tends to recur or is accompanied by high fever, rash or persistent headache, consult a physician".

2. *Category II conditions under which antitussive ingredients are not generally recognized as safe and effective or are misbranded.* The use of antitussives under the following conditions is unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel concludes that the following ingredients and labeling should be removed from the market until scientific testing supports their use.

Category II Active Ingredients

The Panel has classified the following antitussive active ingredients as not generally recognized as safe and effective or as misbranded:

Hydrocodone bitartrate (dihydrocodeinone)

Turpentine oil (spirits of turpentine) (oral)

a. *Hydrocodone bitartrate (dihydrocodeinone).* The Panel concludes that hydrocodone bitartrate (dihydrocodeinone) is safe for prescription use but that its addiction potential and other adverse reactions, including respiratory depression, are so serious that it is not appropriate for OTC use. The Panel concludes that the current prescription status of hydrocodone bitartrate under the Federal Controlled Substances Act is appropriate and that the ingredient should not be available as an OTC antitussive.

(1) *Safety.* Pharmacologically, hydrocodone is a more potent antitussive and analgesic than codeine and its adverse reactions, including addiction potential, are greater than codeine (Refs. 1 through 3). Depression of respiration has been noted in animals (Ref. 4) and man (Ref. 5). The addiction problem, which approaches that of the more potent narcotics such as morphine, has been reviewed by Rosenwald and Russell (Ref. 6). Because its potency as a narcotic falls between morphine and codeine, respiratory depression can be a real hazard with hydrocodone, especially in patients with chronic obstructive pulmonary disease.

(2) *Effectiveness.* Hydrocodone is an active antitussive with a potency approximately three times that of codeine on a weight basis.

A number of uncontrolled clinical trials (Refs. 7 through 10) suggest effective antitussive activity in chronic lung disease, including pulmonary tuberculosis lasting for 8 to 12 hours. A subsequent double-blind clinical trial (Ref. 11) and experimental cough-challenge study (Ref. 12) confirmed its antitussive activity.

(3) *Evaluation.* The Panel concludes that the activity of hydrocodone bitartrate in chronic and serious diseases make it a valuable drug for use under proper medical supervision and for that reason recommends that its availability continue to be restricted to prescription use only, under the Federal Controlled Substances Act.

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b. *Turpentine oil (spirits of turpentine) (oral).* The Panel concludes that oil of turpentine is not safe for OTC use when taken orally as an antitussive.

(1) *Safety.* Oil of turpentine is a volatile oil distilled from turpentine, an oleoresin obtained from the pine tree. It has a characteristic odor and taste. The substance has been administered orally, topically, and by inhalation.

In doses of 15 ml in children and 150 ml in adults fatal poisoning may occur (Ref. 1). Excessive oral doses produce marked irritation of the alimentary tract, especially of the stomach and of the pelvic organs. Toxic symptoms include vomiting, diarrhea, acute pain, renal irritation, bloody stools and hyperemia of all abdominal organs. Continued use may lead to cloudy swelling and fatty degeneration of the liver. Abnormal central nervous system symptoms may develop (Refs. 2 and 3).

Since no safe oral dose has been established for effective use as an antitussive, the Panel concludes that turpentine oil should not be available for oral OTC use as an antitussive. However, elsewhere in this document, the Panel concludes that the ingredient is safe when applied topically or used as an inhalant but that there are insufficient data to permit final classification of its effectiveness for inhalant or topical use as an antitussive. (See part III. paragraph B.3.1. below—Turpentine oil (spirits of turpentine) (topical/inhalant).)

(2) *Effectiveness.* Oil of turpentine is irritating and its chief suggested uses are based on this property (Refs. 1 and 4). There is no evidence to support its effectiveness as an antitussive when taken orally.

(3) *Evaluation.* The Panel is unable to determine a safe oral dose for turpentine oil for use as an antitussive. The Panel is of the opinion that the risk from oral administration outweighs whatever benefit might occur. Therefore, the Panel concludes that turpentine oil is not safe for oral use as an antitussive.

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Category II Labeling

The Panel concludes that the use of certain labeling claims related to the safety and/or effectiveness of the product is unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel has previously discussed such labeling. (See part II. paragraph O. above—CCABA Product Labeling Claims Not Supported by Scientific Evidence.) However, labeling that is descriptive of the product such as its taste or appearance is acceptable.

Unacceptable claims for antitussives include any statement containing the term chest or lung congestion. The term "congestion", which may be interpreted by the target population to denote a discomfort of the chest, may result from a variety of causes, several of which may be of a most serious nature and require professional attention.

All claims that state or imply a therapeutic action or safety property peculiar to the preparation that cannot be demonstrated in controlled studies are not acceptable, e.g., "specially formulated", "improved", or "selected", "natural", "extra strength", "teamed components", "superior to ordinary", "modern", and "superior".

Statements alluding to greater potency, such as "extra strength" or "contains more antitussive per dose" are misleading because there are no acceptable controlled studies documenting that one preparation is more potent than another, particularly for Category I drugs. There is also no justification for claiming more antitussive per dose because there is no scientific merit from a therapeutic point of view between 15 mg of drug A and 30 mg of drug B if they are both effective. Therefore, any claim for "extra strength" or "higher dose level" may be misleading in that the product is no more effective and in fact may increase the potential for side effects. Under such circumstances the Panel feels that all such claims are misleading to the consumer.

Claims implying a physiological effect that either has no foundation or meaning will be meaningless to the public are unacceptable; such as, "gets to the roots of", "recommended by doctors", "travels through the blood stream", "works internally".

Claims for relief where time is indeterminate and not supported by scientific data are unacceptable; such as, "fast" and "prompt".

Statements such as "a dramatic advance", "the greatest advance in cough relief", "the modern way to stop coughs" etc., are vague generalizations, which imply a superiority of a product. These statements cannot be supported by scientific evidence, and since they are meaningless, can only have the effect of misleading the consumer.

The Panel concludes that such labeling should be removed from the market until scientific testing supports their use.

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel concludes adequate and reliable scientific evidence is not available at this time to permit final classification of the claimed ingredients and conditions listed below. The Panel believes it reasonable to provide 4 years for the development and review of such evidence. Marketing need not cease during this time if adequate testing is undertaken. If adequate effectiveness data are not obtained within 4 years, however, the ingredients and conditions listed in this category should no longer be marketed in over-the-counter products. Effectiveness as an antitussive must be demonstrated by controlled objective studies employing cough-counting techniques. Subjective data, alone, are unacceptable because of the marked variability in the subjective awareness of cough. Studies have shown (Refs. 1 and 2) that there is a poor correlation in the subjective appraisal of the effectiveness of the cough suppressant and the actual objective studies done by employing cough-counting techniques.

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Category III Active Ingredients

The Panel concludes that the available data are insufficient to permit final classification of the following claimed antitussive active ingredients:

Beechwood creosote
Camphor (topical/inhalant)
Caramiphen edisylate (caramiphen ethanedisulfonate)
Carbetapentane citrate
Cod liver oil
Elm bark
Ethylmorphine hydrochloride
Eucalyptol/eucalyptus oil (topical/inhalant)
Horehound (horehound fluidextract)
Menthol/peppermint oil (topical/inhalant)
Noscapine (noscapine hydrochloride)
Thymol (topical/inhalant)
Turpentine oil (spirits of turpentine) (topical/inhalant)

a. *Beechwood creosote.* The Panel concludes that beechwood creosote is safe in the dosage range used as an antitussive, but there are insufficient data to permit final classification of its effectiveness for OTC use as an antitussive.

(1) *Safety.* Clinical experience has confirmed that beechwood creosote in the usual doses contained in lozenges or cough mixtures for antitussive activity is safe.

Creosote is a distillate of wood tar and has a smokey color and a pungent taste. Dosages in excess of 4 gm 3 times daily produce giddiness, dimness of vision, circulatory collapse, convulsions and coma (Ref. 1). Because of the taste, it is normally given well-diluted (Ref. 2). Occasional adverse gastrointestinal side effects are mentioned in one report but are poorly documented (Ref. 3). Based on the available data and the presence of beechwood creosote on the market for many years, the Panel concludes that this ingredient is safe for OTC use.

(2) *Effectiveness.* There are no well-controlled objective studies documenting the effectiveness of beechwood creosote, alone, as an antitussive. Only one submission to the Panel (Ref. 4), reports a double-blind controlled study, for a combination product containing creosote, in 25 patients with chronic cough employing cough-counting techniques, which is said to show transient drug activity with statistical significance at 1 hour after drug administration. The statistical analysis and methodology is cumbersome and confusing. It is unclear whether a significant difference from the placebo was obtained. Because the dose of the product is unstated there is a lack of information regarding the smoking habits of the subjects in this study, and no evidence to indicate that the high speed, automatic electronic counter is accurate and reliable by comparing it with actual cough counts, serious questions are raised by the Panel about the acceptability of this study.

According to the standard compendia (Refs. 1 and 5), an average dose of beechwood creosote is 250 mg 3 or 4 times daily. In the two submissions to the panel listing of creosote, the dosages are 3.29 mg/lozenge and 33 mg/15 ml every 3 hours (Ref. 6). This 40 to 80 fold differ-

ence in dose (3.29 mg/lozenge, 8 doses/daily) appears illogical, and there is no evidence to indicate that creosote is effective in such low doses. The Panel concludes that further studies are needed to determine effectiveness.

(3) *Proposed dosage.* Adult oral dosage is 250 mg every 4 to 6 hours not to exceed 1500 mg in 24 hours. Children 6 to under 12 years oral dosage is 125 mg every 4 to 6 hours not to exceed 750 mg in 24 hours. Children 2 to under 6 years oral dosage is 62.5 mg every 4 to 6 hours not to exceed 375 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness as an antitussive will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

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b. *Camphor (topical/inhalant).* The Panel concludes that camphor is safe in the dosage ranges used when applied topically or as an inhalant, but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as an antitussive.

(1) *Safety.* Clinical experience has confirmed that camphor (topical/inhalant) is safe in the dose ranges used as an antitussive.

Camphor is a local irritant producing skin redness when rubbed on the skin. However, when not vigorously applied, it may produce a feeling of coolness on the skin as does menthol. It acts similarly on the respiratory tract. Taken orally in small doses it produces a feeling of warmth and comfort in the stomach, but in larger doses it is irritating and can cause nausea and vomiting. Camphor also has a mild local anesthetic action, and its application to the skin may be followed by numbness. The systemic effects are primarily related to stimulation of the central nervous system. The ingestion of solid camphor by children can cause convulsions (Ref. 1). As little as 0.75 gm of camphor (equivalent to a teaspoonful of liniment of camphor or camphorated oil, which contain 20 percent camphor) has been fatal to a child. Commercially available ointments containing mixtures of volatile substances for use as decongestants or antitussives contain about 5 percent camphor. Since it is conceivable that ingestion of a sufficient amount of such a preparation could produce toxic effects in a young child, a suitable warning should be present on the label. The ingestion of 2 gm of camphor generally produces toxic effects in an adult, although up to 45 gm has been ingested with recovery (Ref. 2).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of camphor (topical/inhalant) as an antitussive. Its effectiveness is uncertain due to lack of properly controlled studies of the substance by itself.

Studies involving objective measurement of antitussive activity of camphor primarily involve mixtures of volatile substances topically applied as ointments (Refs. 3 and 4), as steam inhalations (Refs. 5 through 7), and as lozenges (Refs. 8 and 9), evaluated against artificially induced cough in normal subjects by the citric acid aerosol method. In these studies, significant antitussive activity is demonstrated for a mixture of volatile substances containing camphor compared to placebo, but the contribution of the camphor component to this effect is not evident. In a crossover study involving 16 subjects, the effects of 5.3 percent camphor in a petrolatum ointment applied to the chests of subjects were compared to an ointment containing several volatile substances including 5.3 percent camphor and to a placebo (petrolatum) in suppressing a citric acid aerosol-induced cough. The combination ointment containing camphor induced a significant decrease in cough counts at all challenge times from ½ hour through 2 hours averaging about 20 percent decrease in cough counts at the ½- and 1-hour intervals, whereas the single ingredient camphor ointment yielded a significant decrease in cough counts just at the ½- and 1-hour intervals averaging about 10 percent reduction, and the petrolatum yielded no significant difference in cough counts compared with base line (Ref. 3).

(3) *Proposed dosage.* Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 5 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapors rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 7 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl or wash basin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For topical use as a lozenge 0.02 to 15 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every ½ to 1 hour.

For children under 2 years, there is no recommended topical or inhalant dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients. (See part III. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: *Warning:* "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: *Warning:* "For steam inhalation only. Do not take by mouth".

(5) *Evaluation.* The Panel made the following recommendations:

(i) For topical ointment use: Data to demonstrate effectiveness will require only one additional controlled cough-counting objective study in patients with coughs due to respiratory disease in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

(iii) For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

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c. *Caramiphen edisylate (caramiphen ethanedisulfonate).* The Panel concludes that caramiphen edisylate is safe but there are insufficient data to permit final determination of its effectiveness for OTC use as an antitussive.

(1) *Safety.* Clinical experience has confirmed that caramiphen edisylate is safe in the dose ranges used as an antitussive. Acute and chronic toxicity studies in animals indicate a wide margin of safety, and caramiphen was judged to be considerably less toxic than codeine (Ref. 1). Instances of dizziness and drowsiness have been reported with dosage levels of 10 mg of caramiphen edisylate 3 times daily (Ref. 2). The incidence of these mild reactions increased when the dose was doubled, and one patient experienced a transient period of disorientation (Ref. 2). In a number of clinical trials, 12 of 172 patients reported adverse reactions, 4 of which were probably not drug related (Ref. 3). Although caramiphen pharmacologically is anticholinergic, with ½ to 1/10 the drying (antisecretory) effects of atropine, there have been no reports concerning its effect on bronchial secretions and no difficulty with retained secretions (Ref. 4).

At the average dose of 10 to 20 mg 3 to 4 times daily, few toxic reactions have been reported. Reported side effects have included slight nausea, dizziness, and occasional drowsiness, which appeared to be dose related. Until additional experience has accumulated, the labeling warning below concerning glaucoma and enlarged prostate, which may cause a block to the flow of urine, is deemed necessary in view of the drug's anticholinergic properties (Ref. 4).

(2) *Effectiveness.* There are no well-controlled objective, clinical studies documenting the effectiveness of caramiphen edisylate as an antitussive.

Studies in animals indicate that caramiphen is a centrally acting antitussive (Refs. 1 and 5). Cough suppression is due to an increase in the central threshold for cough. Almost all of the reports of studies are uncontrolled, subjective clinical trials (Refs. 6 and 7). Two controlled studies with induced cough showed 10 mg caramiphen to be singificantly superior to placebo but slightly less active than codeine 15 mg (Refs. 8 and 9). The only well-controlled crossover study was performed by Abelmann, Gaensler and Badger (Ref. 2), who concluded that caramiphen was superior to placebo but not as effective as codeine or dihydrocodeinone as a cough suppressant by subjective criteria, and that it decreased the amount of sputum in 61 percent of patients but without evidence of retention of secretions.

A controlled cough-counting study was recently reported in 25 patients with chronic cough (Ref. 10). The results of this study failed to show the efficacy of a single dose of 20 mg caramiphen as compared with placebo, but offered to show a significant antitussive effect after the fourth and fifth doses of the drug. Because of a lack of information regarding the smoking habits of the subjects in this study, and no evidence to indicate that the high speed, automatic electronic counter is accurate and reliable by comparing it with actual cough counts, serious questions about the acceptability of this study are raised.

(3) *Proposed dosage.* Adult oral dosage is 10 to 20 mg every 4 to 6 hours not to exceed 80 mg in 24 hours. Children 6 to under 12 years oral dosage is 5 to 10 mg every 4 to 6 hours not to exceed 40 mg in 24 hours. Children 2 to under 6 years oral dosage is 2.5 to 5 mg every 4 to 6 hours not to exceed 20 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients. (See part III. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific claims referrable to a central mechanism of action and its non-narcotic designation: (i) *Indications.* (*a*) "Calms the cough control center and relieves coughing".

(*b*) "Non-narcotic cough suppressant for the temporary control of coughs".

(*c*) "Calms cough impulses without narcotics".

(ii) *Warnings.* (*a*) "Do not take this product if you have glaucoma or have difficulty in urination due to an enlarged prostate gland except under the advice and supervision of a physician".

(*b*) *"Caution:* Do not give this product to children taking other drugs except under the advice and supervision of a physician".

(5) *Evaluation.* Data to demonstrate effectiveness will be required from only one additional well-controlled cough-counting objective study in patients with cough due to respiratory disease in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

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d. *Carbetapentane citrate.* The Panel concludes that carbetapentane citrate is safe but there are insufficient data to permit final determination of its effectiveness for OTC use as an antitussive.

(1) *Safety.* Clinical experience has confirmed that carbetapentane citrate is safe in the dose range used as an antitussive.

Studies in several animal species revealed a low order of toxicity, which was comparable to codeine phosphate (Ref. 1). Intravenous administration resulted in slight transient falls in blood pressure with no effect on respiration. In addition, carbetapentane possesses marked antispasmodic (relieves spasms) activity with weak anticholinergic (atropine-like) and local anesthetic properties. Adverse reactions in humans consisted for the most part of mild dryness of the mouth (Ref. 2). In this study, nine of 31 patients reported this side effect. An additional patient complained of severe nausea and loss of appetite and discontinued medication.

At an average dose of 25 mg 4 times daily, few side effects have been reported, and have consisted mostly of dryness of the mouth. On the whole, this atropine-like effect was mild and did not interfere with sputum production (Ref. 3), but the labeling warning (see below) concerning glaucoma and enlarged prostate is deemed necessary because of the anticholinergic properties of carbetapentane.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of carbetapentane citrate as an antitussive.

Animal studies employing a variety of methods for experimentally inducing cough as well as pathologic cough in dogs indicate that the onset of action and duration of cough suppression is equivalent to codeine (Refs. 1 and 4), but in a review of the literature (Ref. 5) there was considerable disagreement as to carbetapentane's relative antitussive potency as compared with codeine. Clinical studies were all subjective in type and only one had a placebo control (Ref. 6). At doses ranging between 7 and 25 mg 3 to 4 times daily, most investigators have reported "good" to "excellent" antitussive effect. Many of the clinical trials were of short duration in acute respiratory conditions and were uncontrolled (Refs. 3, and 7 through 9). The Council on Drugs of the American Medical Association has stated that, "available clinical evidence suggests that the effectiveness of the drug is limited to the acute (short duration) type of cough. Further and better controlled observations are

needed to establish its clinical usefulness" (Ref. 10). However, other investigators (Refs. 5, 11, and 12) have found carbetapentane to be effective in all types of cough. In one study, carbetapentane was not as effective as codeine for severe (intense and frequent) cough (Ref. 13). None of these clinical studies employed objective cough-counting techniques and few were adequately controlled.

(3) *Proposed dosage.* Adult oral dosage is 15 to 30 mg every 4 to 6 hours not to exceed 180 mg in 24 hours. Children 6 to under 12 years oral dosage is 7.5 to 15 mg every 4 to 6 hours not to exceed 90 mg in 24 hours. Children 2 to under 6 years oral dosage is 3.75 to 7.5 mg every 4 hours not to exceed 45 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients. (See part III. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific claims referable to a central mechanism of action and its nonnarcotic designation: (i) *Indications.* (*a*) "Calms the cough control center and relieves coughing".

(*b*) "Non-narcotic cough suppressant for the temporary control of coughs".

(*c*) "Calms cough impulses without narcotics".

(ii) *Warnings.* (*a*) "Do not take this product if you have glaucoma or have difficulty in urination due to an enlarged prostate gland except under the advice and supervision of a physician".

(*b*) "Do not give this product to children under 2 years except under the advice and supervision of a physician".

(*c*) *"Caution:* Do not give this product to children taking other drugs except under the advice and supervision of a physician".

(5) *Evaluation:* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

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e. *Cod liver oil.* The Panel concludes that cod liver oil is safe but there are insufficient data to determine its effectiveness for OTC use as an antitussive.

(1) *Safety.* Clinical experience has confirmed that cod liver oil is safe in the dose ranges used as an antitussive. Clinical experience over more than 100 years of use has demonstrated that cod liver oil is safe, and no significant evidence of toxicity has been reported when used in a wide variety of disease states as well as for vitamin supplementation. Rare instances of hypervitaminosis with resulting nausea, vomiting, and diarrhea have been reported with excessive doses (Ref. 1).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of cod liver oil as an antitussive. Except for a brief statement that cod liver oil is also given with benefit in "respiratory catarrhs" in subacute and chronic bronchitis, "catarrhal pneumonia," and frequent and persistent "colds" in children and the aged (Ref. 1), there is no actual reference to its value as a cough suppressant. In fact, all of the available references state that the value of cod liver oil in therapeutics lies in its high content of vitamins A and D (Refs. 2 and 3).

(3) *Proposed dosage.* The usual dosage is said to be 5 ml (1 teaspoon), which contains no less than 3,900 USP units of vitamin A and 386 USP units of vitamin D which provides the daily requirements for children and adults of both these vitamins (Refs. 3 and 4). The dosage of an emulsion containing 50 percent cod liver oil is 15 ml or 1 tablespoon (Ref. 2). However, all of these dosage forms refer to its use as a vitamin supplement.

The Panel is aware of one reference to a dosage of 2 teaspoons after each meal in convalescence from respiratory diseases. The duration of therapy is not stated (Ref. 2). The Panel concludes that the pharmaceutical industry should consult with the Food and Drug Administration as to a suitable proposed dosage for testing. Otherwise, the Panel recommends that each drug manufacturer evaluate the dosage as labeled on the manufacturer's marketed product(s).

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients. (See part III. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

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f. *Elm Bark.* The Panel concludes that elm bark (slippery elm, ulmus rubra) is safe but there are insufficient data to determine its effectiveness for OTC use as an antitussive.

(1) *Safety.* Clinical experience has confirmed that elm bark is safe in the dose ranges used as an antitussive. Clinical experience over a period of several hundred years has yielded no evidence of toxicity when used either as a lozenge, infusion for internal consumption, or as a poultice applied to the skin for antitussive action.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of elm bark as an antitussive. Elm bark was used by the Indians and early settlers of North America in the form of poultices and liquids for the treatment of fevers and colds with cough. It is referred to by Schopf in 1787 as "salve bark" (Ref. 1). The mucilaginous quality of these preparations is said to confer excellent protective demulcent properties, which were employed in the form of lozenges to relieve irritation of the pharynx (Ref. 2).

(3) *Proposed dosage.* The Panel is unable to determine a proposed dosage. Troches or lozenges of slippery elm are listed as containing 0.2 gm of elm per troche with the dosage being one troche, and the frequency of administration is given as "ad libitum" (Ref. 3). A warm infusion was prepared by stirring 1 oz of the powdered bark in a pint of hot water, which was then taken "ad libitum" (Ref. 2). The Panel concludes that the pharmaceutical industry should consult with the Food and Drug Administration as to a suitable proposed dosage for testing. Otherwise, the Panel recommends

that each drug manufacturer evaluate the dosage as labeled on the manufacturer's marketed product(s).

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients. (See paragraph III. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

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g. *Ethylmorphine hydrochloride.* The Panel concludes that ethylmorphine hydrochloride is safe but there are insufficient data to permit final determination of its effectiveness for OTC use as an antitussive.

(1) *Safety.* Clinical experience has confirmed that ethylmorphine hydrochloride is safe in the dose range used as an antitussive.

There are few well-documented studies in animals and man defining the incidence of adverse reactions. Ethylmorphine is the ethyl ether of morphine and its pharmacologic properties are similar to codeine, the methyl ether of morphine. Tolerance and physical dependence have been reported after prolonged use of ethylmorphine (Ref. 1). Other adverse reactions, such as constipation and respiratory depression, are similar to those of codeine. Topically, ethylmorphine is an irritant to mucous membranes and causes an inflammatory reaction with increased secretion of mucus (Ref. 2).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of ethylmorphine as an antitussive.

Animal studies employing induced cough showed ethylmorphine to have some antitussive activity (Refs. 3 and 4).

Since the early 1900's, ethylmorphine has been used clinically at approximately the same dosage level as codeine. Because of its failure to demonstrate any advantage over codeine, it never attained the popularity of codeine as an antitussive (Ref. 5), and hence there are few studies demonstrating its use as an antitussive. Only one paper reported that ethylmorphine in a dose of 15 to 22.5 mg was as effective as 30 to 60 mg of codeine in suppressing cough due to tuberculosis (Ref. 6). Unlike codeine, there are no objective clinical trials or well-controlled subjective studies in the literature.

Dosage range and pharmacologic activity, including adverse reactions and abuse potential, are similar to codeine. While ethylmorphine is regulated under the Federal Controlled Substances Act, it has not been tested at the Addiction Research Center, Lexington, KY because of its infrequent use (Ref. 5).

(3) *Proposed dosage.* Adult oral dosage is 15 mg every 4 to 6 hours not to exceed 90 mg in 24 hours. Children 6 to under 12 years oral dosage is 7.5 mg every 4 to 6 hours not to exceed 45 mg in 24 hours. Children 2 to under 6 years oral dosage is 3.75 mg every 4 to 6 hours not to exceed 22.5 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the labeling for Category I antitussive active ingredients. (See part III. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific claims referrable to its central mechanism of action: (i) *Indications.* "Calms the cough control center and relieves coughing".

(ii) *Warnings.* (*a*) "May cause or aggravate constipation".

(*b*) "Do not give this product to children taking other drugs except under the advice and supervision of a physician".

(*c*) "Do not take this product if you have a chronic pulmonary disease or shortness of breath except under the advice and supervision of a physician".

(5) *Evaluation:* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

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h. *Eucalyptol/eucalyptus oil (topical/inhalant).* The Panel concludes that eucalyptol/eucalyptus oil is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as an antitussive.

(1) *Safety.* Clinical experience has confirmed that eucalyptol/eucalyptus oil (topical/inhalant) is safe in the dose ranges used as an antitussive.

Eucalyptus oil is about 70 percent active eucalyptol. Fatalities have followed doses of the oil as small as 3.5 ml, although recovery has occurred after doses of 20 and even 30 ml. Symptoms include epigastric burning with nausea and vomiting, vertigo, ataxia, muscle weakness and stupor (Refs. 1 and 2). A study of 223 subjects in which an ointment containing several volatile substances, including eucalyptus oil 1.3 percent, was applied for 48 hours to areas of intact skin under a patch and to abraded skin, revealed no instances of irritation, inflammation, wheal or hives following the period of exposure (Ref. 3). A study of 10 subjects who received application of an ointment containing several volatile substances, including eucalyptus oil 1.3 percent, to their trunks 3 times daily for 3 weeks, then 1 week off followed by another 1 week of treatment, revealed no local reactions during this subsequent challenge phase (Ref. 4). A study of infants and children with respiratory infection who received an ointment containing a mixture of volatile oils, including eucalyptus oil 1.3 percent, applied to the chest and neck demonstrated no adverse effect from inhaled vapors by that route of administration on the rate of clearing of laryngeal edema (Ref. 5).

Vapors are also produced by placing a liquid mixture of volatile substances, including eucalyptus oil 1.7 percent, in the water of a hot steam vaporizer and administered via inhalation. Exaggerated-use studies in adults and children, i.e., exposure for several hours to higher than recommended exposure concentrations of these vapors either due to sitting in closer proximity to the vaporizer or placing two to five times the recommended dose of the volatile substance in the vaporizer, were not associated with irritating or toxic effects (Refs. 6 and 7).

A series of studies assessing buccal safety and overt side effects from lozenges containing a mixture of volatile oils was conducted in over 300 subjects (Refs. 8 through 11). Lozenges containing up to 5.5 mg eucalyptus oil were dissolved in the mouth every hour for 8 hours on 2 successive days. Mild erythema of the buccal mucosa and tongue was observed but did not differ appreciably from the response to dissolving lozenge sugar base without volatile oils. The incidence of gastrointestinal symptoms did not differ from control either (Refs. 8 through 11).

An aerosolized dosage form of volatile substances including 1 percent eucalyptus oil has also been utilized for treatment of nasal congestion. In humans, such aerosol sprays have been generally safe when used as directed, but there have been reports of deaths from deliberate sniffing abuse, particularly when the subject inhales from a plastic bag into which the material has been sprayed (Ref. 12). Furthermore, one commercial preparation containing a particular solvent (1,1,1-trichloroethane) was recently

recalled from the market due to potential hazards of this substance (Ref. 13).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of ecualyptol/eucalyptus oil (topical/inhalant) as an antitussive. Its effectiveness is uncertain due to lack of properly controlled studies of the substance by itself.

Eucalyptus oil is a component of a number of currently marketed OTC topically applied preparations utilized as antitussives, e.g., ointments, steam inhalation, and lozenges. In a crossover study involving 16 subjects, the effects of a 1.3 percent eucalyptus oil in petrolatum ointment applied to the chests of the subjects was compared to an ointment containing several volatile substances, including 1.3 percent eucalyptus oil, and to petrolatum in suppressing a citric acid aerosol induced cough. The combination ointment containing eucalyptus oil induced a significant decrease in cough counts at all challenge times from ½ hour through 2 hours averaging about 20 percent decrease at the ½ and 1 hour intervals, whereas the single ingredient eucalyptus oil ointment yielded a significant decrease in cough counts at the ½ hour through 1 and ½ hour intervals averaging about 15 to 18 percent reduction at these times, and the petrolatum yielded no significant decrease in cough counts compared with base line (Ref. 14). Similar results with a combination ointment containing 1.3 percent eucalyptus oil were obtained in two additional induced cough studies conducted by the same investigator (Refs. 14 and 15).

A single-blind crossover cough counting study of 27 patients exhibiting stabilized chronic cough, utilized twice daily chest application of either the ointment containing several volatile substances an ointment containing several volatile oils including 1.3 percent eucalyptus oil or a placebo (petrolatum base). Neither the ointment mixture of volatile substances nor the eucalyptus oil ointment induced a significant decrease in cough counts compared to placebo after the morning application, but a significant 20 percent cough count reduction compared to placebo was obtained following the afternoon dose of the ointment mixture. An average reduction in cough counts of about 10 percent compared to placebo was noted following the afternoon dose of eucalyptus oil ointment but this was not statistically significant (Ref. 16).

A liquid mixture of volatile substances was evaluated. The mixture was added to water of a hot steam vaporizer and administered via inhalation, and contains menthol 3.66 percent, camphor 7 percent, eucalyptus oil 1.7 percent and tincture of benzoin 5 percent. Three crossover studies compared the effects of this volatile substance containing liquid in steam (1 tablespoonful per quart of water) to steam alone in suppressing coughs artificially induced by the citric acid aerosol technique. In each case, both steam and medicated steam induced a statistically significant reduction in cough counts during the period of administration. In two of the studies the cough reduction with the medicated steam was statistically greater than with steam alone and persisted beyond the period of actual administration to the subjects (Refs. 17 through 19). In an objective cough counting study on patients with acute upper respiratory disease, the medicated steam showed significantly lower cough counts than the unmedicated steam for the 4 hours the patients were exposed to vaporization, and for 2 additional hours after vaporizer therapy was discontinued (Ref. 20). Subjective evaluation studies of adults and infants with cough associated with respiratory infection demonstrated statistically significant antitussive effectiveness of both the volatile substances in steam (1 tablespoon per quart) and of steam alone. In some of these studies the effect of the medicated steam was judged statistically superior to the steam alone (Refs. 21 and 22).

The variety of lozenge preparations containing a mixture of volatile substances that include eucalyptus oil have been studied for their ability to suppress citric acid aerosol induced cough in normal subjects. Since each of these lozenge preparations contain different concentrations of eucalyptus oil and other volatile substances, the study results will be individually summarized. The general study format involved a single blinded crossover design in which a group of cough standardized normal subjects were tested with each of two lozenge formulations, i.e., the active formulation and its vehicle control against cough artificially induced by the citric acid aerosol technique.

Two studies involving a total of 40 subjects used similar active formulations consisting of menthol 9.6 mg and eucalyptus oil 5.5 mg per lozenge. In these studies the active formulation produced significant cough reductions at the 10 to 40 minute challenge periods, reaching a peak of 25 to 35 percent reduction at the 10 and 20 minute intervals, whereas the control lozenge produced a significant reduction, 10 to 15 percent maximum, at only the 10 minute challenge (Refs. 23 and 24). In a study of 9 subjects receiving a two lozenge dose of menthol (1.0 mg/lozenges) and eucalyptol (7.6 mg/lozenge) elevated citric acid thresholds of 130 to 146 percent of control for 3 to 5 hours after dosing were obtained, although a placebo control lozenge was not utilized in this study for comparison (Ref. 25). Another study of 20 subjects utilizing a formulation of menthol 2.78 mg, eucalyptus oil 0.77 mg plus smaller amounts of camphor, thymol, and tolu balsam, produced significant cough reductions at the 10 through 40 minute challenge periods reaching a peak of 35 percent reduction at the 10 and 20 minute intervals whereas a control lozenge produced a significant reduction of 11 to 17 percent maximum at the 10 and 20 minute challenge periods only (Ref. 26). Similar results were obtained in 16 subjects using an active formulation containing menthol, eucalyptus oil, camphor, thymol and tolu balsum present in about one-half the amounts utilized in the preceding study (Ref. 27).

The effect of rinsing and gargling twice daily with an aqueous mixture of volatile substances on the incidence of colds and the severity of the symptoms associated with colds was evaluated in a long-term double-blind, placebo-controlled, subjective study in school children. The results of the study revealed milder nasal symptoms and cough symptoms in individuals using the medicated mouthwash as compared to the placebo. Although the medicated mouthwash contained 0.91 mg/ml eucalyptol, the results did not demonstrate the contribution of this component to the overall alleviation of symptoms (Ref. 28).

(3) *Proposed dosage.* Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 1.3 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapors rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 1.7 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl, or washbasin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For topical use as a lozenge 0.2 to 15 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every ½ to 1 hour.

(iv) For use as a mouthwash 0.91/mg/ml solution: Gargle with ⅔ oz (20 ml) twice daily.

For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients. (See part III. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: *Warning*: "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: *Warning*: "For steam inhalation only. Do not take by mouth".

(5) *Evaluation.* The Panel made the following recommendations:

(i) For topical ointment use: Data to demonstrate effectiveness will be required from only one additional controlled cough-counting objective study in patients with coughs due to respiratory disease in accordance with the guidelines set forth below for testing antitussive drugs.(See part III. paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

(iii) For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

(v) For use as a mouthwash: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

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(28) OTC Volume 040278.

i. *Horehound (horehound fluidextract)*. The Panel concludes that horehound (marrubium) is safe but there are no data to evaluate its effectiveness for OTC use as an antitussive.

(1) *Safety*. Clinical experience has confirmed that horehound is safe in the dose ranges used as an antitussive. Horehound has been used for many centuries in the folk medicine of Europe in the form of a sweetened tea or bitter flavoring agent in decoctions and candies (Ref. 1). No adverse reactions have been cited and on the basis of long clinical experience, the Panel concludes that it is safe at the dose ranges employed for OTC use.

(2) *Effectiveness*. There are no well-controlled studies documenting the effectiveness of horehound as an antitussive. There is no information available as to the effectiveness of horehound. It is stated that it was formerly used as an expectorant in various types of bronchitis but "has been abandoned by physicians" (Ref. 2). Another text (Ref. 1) states that it was dropped from the "Primary List" of drugs in 1910.

(3) *Proposed dosage*. The Panel is unable to determine a proposed dosage.

One marketed product for children contains the following dosage range: Children over 5 years oral dosage is 44 mg. Children 2 to 5 years oral dosage is 22 mg (Ref. 3). The Panel concludes that the pharmaceutical industry should consult with the Food and Drug Administration as to a suitable dosage for testing. Otherwise, the Panel recommends that each drug manufacturer evaluate the dosage as labeled on the manufacturer's marketed product(s).

(4) *Labeling*. The Panel recommends the Category I labeling for antitussive active ingredients. (See part III. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation*. Data to demonstrate effectiveness will be required according to the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.) However, the Panel notes that if claims for antitussive activity were withdrawn, this preparation could be considered a pharmaceutical necessity or flavoring agent.

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j. *Menthol/peppermint Oil (topical/inhalant)*. The Panel concludes that menthol/peppermint oil is safe in the dosage ranges used when applied topically as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as an antitussive.

(1) *Safety*. Clinical experience has confirmed that menthol/peppermint oil (topical/inhalant) is safe in the dosage ranges used as an antitussive.

Menthol is the chief constituent of peppermint oil comprising not less than 50 percent. It may be obtained by distillation of the oil or by synthesis (Ref. 1). Toxic effects with an excess ingestion of peppermint oil or mentholated products can include abdominal pain, nausea, vomiting, and symptoms of central nervous system depression such as dizziness, staggering gait, slowed respiration, flushed face, sleepiness, and coma (Refs. 2 and 3). The fatal oral dose of menthol itself in man is about 2 gm (Ref. 4). Topically applied menthol produces a cooling sensation presumably due to stimulation of the cold sensory receptors, whereas higher concentrations have irritant properties. In one study, a 20 percent solution of menthol in oil rubbed on to the skin induced an intense and lasting cooling sensation followed by numbness with slight burning and skin redness. A 0.5 percent solution applied to the nasal or oral mucosa was subjectively irritating, whereas a 0.2 percent solution was judged nonirritating (Ref. 5). A study of 223 subjects in which an ointment containing several volatile substances including menthol 2.8 percent was applied for 48 hours to areas of intact skin under a patch and to abraded skin revealed no instances of inflammation, wheal, hives, or primary irritation following the period of exposure (Ref. 6). Repeated topical application of mentholated products has been reported to give rise to hypersensitivity reactions, including contact der-

matitus (Ref. 4). A study of ten subjects who received an application of an ointment containing several volatile substances including menthol 2.8 percent to their trunks 3 times daily for 3 weeks, then 1 week off, followed by another week of treatment, revealed no local reactions during this subsequent challenge phase (Ref. 7). The incidence of hypersensitivity to menthol appears to increase with increased duration of use. For example, one survey revealed an incidence of less than 1 percent menthol hypersensitivity in 542 patients using a mentholated ointment for less than 10 years, whereas an incidence of 3.4 percent hypersensitivity was seen in 414 patients using this type of a preparation for longer than 10 years (Ref. 8).

In infants and small children under 2 years, intranasal use of ointments or drops containing high percentages of menthol may cause spasm of the glottis. A case of dangerous asphyxiation has been reported in a 3-week-old infant following intranasal application (Ref. 9). For this reason a warning against the topical application of menthol-containing products directly to the nostrils of infants has been recommended (Refs. 4 and 9). A study of infants and children with respiratory infection was made. They received an ointment containing a mixture of volatile oils including 2.8 percent menthol applied to the chest and neck; the study demonstrated no adverse effect from the inhaled vapors by that route of administration on the rate of clearing of laryngeal inflammation. In this study 35 children, 23 under 2 years of age, with respiratory infection received only standard forms of therapy, e.g., antibiotics and fluids, while 37 children, 30 under 2 years of age, received standard therapy plus the mentholated ointment to the chest and neck. Laryngoscopic examination revealed comparable rates of clearing of laryngeal inflammation (Ref. 10).

A liquid mixture of volatile substances including 3.66 percent menthol is placed in the water of a hot steam vaporizer and administered via inhalation. A number of studies involving nearly 900 subjects in which this mixture was administered at recommended doses was not associated with significant complaints of subjectively perceived adverse effects (Refs. 11 through 23). Exaggerated-use studies in adults and children, i.e., exposure for several hours to higher than recommended exposure concentrations, either due to sitting in closer proximity to the vaporizer or placing 2 to 5 times the recommended dose of the volatile substance in the vaporizer was not associated with irritating or toxic effects (Refs. 24 and 25).

In two studies, 40 healthy subjects who were each asked to dissolve two candy-base lozenges, each lozenge containing 1.36 mg of menthol together with other volatile oils, every 20 minutes for 2 hours exhibited no adverse effects with the exception of one report of nausea and vomiting. This was attributed to a dislike for the wild cherry flavor of the lozenge (Refs. 26 and 27). In a group of 70 healthy subjects, 50 adults and 20 children ages 8 to 12, half dissolved a menthol-eucalyptus lozenge containing 9.62 mg menthol and 5.55 mg eucalyptus oil every 4 to 8 hours on 2 successive days, the other half dissolved the cough drop base without the aromatics. In this intensive dosage schedule, a slightly larger number of subjects demonstrated mild irritation of the oral mucosa on days 1 and 2, but there were no differences between the two groups in the severity of irritation or residual findings after day 2. No systemic complaints were reported (Ref. 28). A similar study using a lozenge formulation containing menthol 8.14 mg and eucalyptus oil 4.625 mg versus a lozenge base without volatile substances produced comparable results (Ref. 29).

An aerosolized dosage form of volatile substances including 1 percent menthol has also been utilized for treatment of nasal congestion and cough symptoms. Rats exposed to acute overdoses of the spray in a confined chamber for 6 hours revealed no untoward behaviorial responses or airway tissues abnormality upon autopsy examination (Ref. 30). A group of four monkeys were exposed to 200 gm per day of the aerosol, i.e., 2 gm of menthol total dose in divided doses over an 8 hour period for 14 consecutive days in a confined chamber. Eye irritation was the only pharmacotoxic sign observed during the study (Ref. 31). In humans, such aerosol sprays have been generally safe when used as directed, but there have been reports of deaths from deliberate sniffing abuse, particularly when the subject inhales from a plastic bag into which the material has been sprayed (Ref. 32). Furthermore, one commercial preparation containing a particular solvent, 1,1,1-trichloroethane, was recently recalled from the market due to potential hazards of this substance (Ref. 33).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of menthol/peppermint oil (topical/inhalant) as an antitussive. Its effectiveness is uncertain due to lack of properly controlled studies of the substance by itself.

The local anesthetic effect of menthol vapor has been the justification for including menthol in topically administered ointments and lozenges for alleviation of cough. In a crossover study involving 16 subjects, the effects of a 2.8 percent mentholated petrolatum ointment applied to the chest of the subjects was compared to an ointment containing several volatile substances including 2.8 percent menthol, and to petrolatum in suppressing a citric acid aerosol induced cough. A combination ointment containing menthol induced a significant decrease in cough counts at all challenge times from ½ hour through 2 hours, averaging about 20 percent decrease at the ½ and 1 hour intervals, whereas the single ingredient menthol ointment yielded a significant decrease in cough counts just at the ½ and 1 hour intervals, averaging about 10 percent reduction. The petrolatum yielded no significant decrease in cough counts compared with base line (Ref. 34). Similar results with the combination ointment containing 2.8 percent menthol were obtained in two additional induced-cough studies conducted by the same investigator (Refs. 34 and 35).

A single-blind crossover cough-counting study of 27 patients exhibiting stabilized chronic cough, utilized twice daily chest applications of either the ointment containing several volatile substances including 2.8 percent menthol, an ointment containing 1.3 percent eucalyptus oil, or petrolatum base. Neither the ointment mixture nor the eucalyptus oil ointment induced a significant decrease in cough counts compared to placebo after the morning application, but a significant 20 percent cough-count reduction compared to placebo was obtained following the afternoon dose of the ointment mixture. An average reduction in cough counts of about 10 percent compared to placebo was noted following the afternoon dose of eucalyptus oil ointment, but this was not statistically significant (Ref. 36).

A liquid mixture of volatile substances added to the water of a hot steam vaporizer and administered via inhalation contained menthol 3.66 percent, camphor 7 percent, eucalyptus oil 1.7 percent, and tincture of benzoin 5 percent. Three crossover studies compared the effects of this volatile substance containing liquid in steam, 1 tablespoonful per quart of water, to steam alone in suppressing coughs artificially induced by the citric acid aerosol technique. In each case, both steam and medicated steam induced a statistically significant reduction in cough counts during the period of administration. In two of the studies the cough reduction with the medicated steam was statistically greater than with steam alone and persisted beyond the period of actual administration to the subject (Refs. 37, 38, and 39). In an objective cough-counting study on patients with acute upper respiratory disease, the medicated steam showed significantly lower cough counts than does unmedicated steam for the 4 hours the patients were exposed to vaporization and for 2 additional hours after vaporizer therapy was discontinued (Ref. 40). Subjective evaluation studies of adults and infants having cough associated with respiratory infection demonstrated statistically significant antitussive effectiveness of the volatile substances in steam, 1 tablespoon per quart of water, and of steam alone. In some of these studies the effect of the medicated steam was judged statistically superior to the steam alone (Refs. 41 and 42).

The variety of lozenge preparations containing a mixture of volatile substances including menthol have been studied for their ability to suppress citric acid aerosol induced cough in normal subjects. Since each of these lozenge preparations contain different concentrations of menthol and other volatile substances, the results of the study will be individually summarized. The general study format involved an unblinded crossover design in which a group of

cough-standardized normal subjects were tested with each of two lozenge formulations, i.e., the active formulation and its vehicle control, against cough artificially induced by the citric acid aerosol technique. Two studies involved lozenges in which menthol was the principal active ingredient and consequently represent an indication of the effectiveness of this mode of administering menthol to suppress cough. One of the studies involving 16 subjects used a lozenge containing menthol 2.64 mg and peppermint oil 2.29 mg plus benzyl alcohol 5.76 mg. The active formulation produced significant cough reductions at the 10 to 40 minute challenge periods, reaching a peak of 30 to 35 percent at the 10 and 20 minute intervals, whereas the control lozenge produced a significant reduction of 15 to 20 percent at the 10 and 20 minute intervals only (Ref. 43). The other study of 10 subjects, utilizing a lozenge containing menthol 1.13 mg plus citric acid flavoring, produced greater cough reduction than the control lozenge at the 10 through 30 minute challenge periods, although both the active and control lozenges in this study produced cough reductions at these time intervals (Ref. 44).

Two studies involving a total of 40 subjects used similar active formulations consisting of menthol 9.6 mg and eucalyptus oil 5.5 mg per lozenge. In these studies the active formulation produced significant cough reductions at the 10 to 40 minute challenge periods, reaching a peak of 25 to 35 percent reduction at the 10 and 20 minute intervals, whereas the control lozenge produced a significant reduction of 10 to 15 percent maximum at only the 10 minute challenge (Refs. 45 and 46). In a study of nine subjects receiving lozenge doses of menthol 1.5 mg and eucalyptol 0.35 mg, elevated citric acid thresholds of 130 to 146 percent of control for 3 to 5 hours after dosing were obtained, although a placebo control lozenge was not utilized in this study for comparison (Ref. 47). Another study of 20 subjects utilizing a formulation of menthol 2.78 mg, eucalyptus oil 0.77 mg, plus smaller amounts of camphor, thymol, and tolu balsam, produced significant cough reductions at the 10 through 40 minute challenge periods, reaching a peak of 35 percent reduction at the 10 and 20 minute intervals, whereas a control lozenge produced a significant reduction of 11 to 17 percent maximum at the 10 and 20 minute challenge periods only (Ref. 48). Similar results were obtained in 16 subjects using an active formulation containing menthol, eucalyptus oil, camphor, thymol and tolu balsam present in about ½ the amounts utilized in the preceding study (Ref. 49).

The effect of rinsing and gargling twice daily with an aqueous mixture of volatile substances on the incidence of colds and the severity of the symptoms associated with colds was evaluated in a long-term, double-blind, placebo-controlled, subjective study in school children. The results of the study revealed milder nasal symptoms and cough symptoms in individuals using the medicated mouthwash as compared to the placebo. Although the medicated mouthwash contained 0.42 mg/ml menthol, the results did not demonstrate the contribution of this component to the overall alleviation of symptoms (Ref. 50).

(3) *Proposed dosage.* Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 2.8 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapors rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 3.66 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl, or washbasin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For topical use as a lozenge 1.0 to 15 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every ½ to 1 hour.

(iv) For use as a mouthwash 0.42 mg/ml solution: Gargle with ⅔ oz (20 ml) twice daily.

For children under 2 years, there is no recommended topical or inhalant dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients. (See part III. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: *Warning:* "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: *Warning:* "For steam inhalation only. Do not take by mouth".

(5) *Evaluation.* The Panel made the following recommendations: (i) For topical ointment use: Data to demonstrate effectiveness will be required from only one additional controlled cough-counting objective study in patients with coughs due to respiratory disease in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

(iii) For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

(iv) For use as a mouthwash: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

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k. *Noscapine (noscapine hydrochloride).* The Panel concludes that noscapine is safe but there are insufficient data to determine its effectiveness for OTC use as an antitussive.

(1) *Safety.* Clinical experience has confirmed that noscapine is safe in the dosage ranges used as an antitussive. Noscapine belongs to the isoquinoline alkaloids of opium and, like papaverine, has a weak spasmolytic (relieves spasm) effect on smooth muscle but little or no effect on the heart or gastrointestinal tract (Ref. 1). There is no evidence that it causes addiction, and it is not subject to the Federal Controlled Substances Act. A large margin of safety in both animals and man has been reported (Refs. 2 and 3). Nausea, drowsiness, and lightheadedness have been reported in a few instances, but this was similar to the incidence in placebo reactors (Ref. 4). Bellville et al. (Ref. 5) found no depression of respiration with doses as high as 90 mg.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of noscapine as an antitussive. Effectiveness has not been established by objective, controlled clinical trials.

For the most part, the animal studies employing a variety of methodologies for inducing cough by mechanical and chemical means have shown noscapine to have an antitussive effect equivalent to codeine (Refs. 6, 7, and 8). Controlled studies in man using experimentally induced cough have been conflicting (Refs. 4, 9, and 10). Most of the clinical trials reported have been poorly controlled subjective studies. The majority of these studies indicate that noscapine is equal to codeine in clinical effectiveness (Refs. 3 and 11 through 15).

Unlike the narcotic antitussives, respiratory depression and constipation have not been reported for noscapine. Doses as high as 90 mg have been given with no significant increase in toxicity (Ref. 16).

(3) *Proposed dosage.* Adult oral dosage is 15 to 30 mg every 4 to 6 hours not to exceed a total of 180 mg in 24 hours. Children 6 to under 12 years oral dosage is 7.5 to 15 mg every 4 to 6 hours not to exceed 90 mg in 24 hours. Children 2 to under 6 years oral dosage is 3.75 to 7.5 mg every 4 to 6 hours not to exceed 45 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients. (See part III. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific claims referable to its central mechanism of action and its nonnarcotic designation:

(i) *Indications.* (*a*) "Calms the cough control center and relieves coughing".

(*b*) "Non-narcotic cough suppressant for the temporary control of coughs".

(*c*) "Calms cough impulses without narcotics".

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.) The Panel recommends that one experimentally induced cough study and one controlled study in patients with cough due to respiratory illness employing objective cough-counting techniques be performed in order to establish effectiveness as an antitussive.

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1. *Thymol (topical/inhalant).* The Panel concludes that thymol is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as an antitussive.

(1) *Safety.* Clinical experience has confirmed that thymol (topical/inhalant) is safe in the dosage ranges used as an antitussive.

Thymol is an alkyl derivative of phenol and has bactericidal, fungicidal and anthelmintic properties (Ref. 1). When hydrogenated, thymol is converted to the closely related drug, menthol (Ref. 2). The LD_{50} of thymol in mice is 1800 mg/kg orally (Ref. 3). No data were found bearing on the drug's toxicity in man. In view of thymol's relative inactivity compared to menthol, of which 50 to 120 gm "would have to be absorbed to cause poisoning" (Ref. 4), thymol is presumably relatively nontoxic.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of thymol (topical/inhalant) as an antitussive. Experiments in anesthetized rabbits have indicated that thymol administered by steam inhalation augmented the concentration of soluble mucous in the respiratory tract fluid (Ref. 2). The dose administered was unknown but the concentration in the vaporizer was in excess of 81 mg/kg. The volume of secretions did not change. Much lower concentrations of menthol were effective (1 mg/kg). In man no data on effectiveness of thymol alone were found although a mixture containing thymol, menthol, eucalyptol and propylene glycol appeared to suppress citric acid induced cough (Ref. 5) and to reduce resistance in the nasal and bronchial airways (Ref. 6).

Studies involving the objective measurement of the antitussive activity of thymol were done with mixtures of volatile substances, topically applied as ointments (Refs. 7, 8 and 9), and in steam inhalations (Refs. 10 and 11). Although significant antitussive activity as compared to placebo was demonstrated, it was not evident whether the thymol component contributed to this effect.

The effect of rinsing and gargling twice daily with an aqueous mixture of volatile substances on the incidence of colds and the severity of the symptoms associated with colds was evaluated in a long-term, double-blind, placebo-controlled, subjective study in school children. The results of the study revealed milder cough symptoms in individuals using the medicated mouthwash as compared to placebo. Although the medicated mouthwash contained 0.63 mg/ml thymol the results did not demonstrate the contribution of this component to the overall alleviation of symptoms (Ref. 12).

(3) *Proposed dosage.* Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 0.1 percent preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapors rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For inhalation use as a 0.13 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl or washbasin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For inhalation use as a 0.1 percent room spray: Spray room for 15 to 20 seconds in the vicinity of the patient. May be repeated at ½ to 1 hour intervals as needed.

(iv) For topical use as a lozenge 0.2 to 15 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every ½ to 1 hour.

(v) For use as a mouthwash 0.63 mg/ml solution: Gargle with ⅔ oz (20 ml) twice daily.

For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients. (See part III. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: *Warning:* "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: *Warning:* "For steam inhalation only. Do not take by mouth".

(5) *Evaluation.* The Panel made the following recommendations: (i) For topical use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

(ii) For inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

(iii) For inhalation use as a room spray: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

(iv) For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

(v) For use as a mouthwash: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

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m. *Turpentine oil (spirits of turpentine) (topical/inhalant).* The Panel concludes that turpentine oil is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as an antitussive.

(1) *Safety.* Clinical experience has confirmed that turpentine oil is safe when applied topically or used as an inhalant in the dosage ranges used as an antitussive. The Panel concludes that oil of turpentine is safe when applied externally or vaporized in boiling water as a steam inhalant. However, the Panel has determined elsewhere in this document that it is not safe for OTC use when used orally as an antitussive. (See part III. paragraph B.2.b. above—Turpentine oil (spirits of turpentine) (oral).)

Oil of turpentine is a volatile oil consisting of a mixture of pinenes derived from the oleoresin obtained from Pinus palustrus. Nelson et al. (Ref. 1) found exposure to a vapor of 420 to 560 mcg/l acceptable to most of their human subjects. The threshold for industrial exposure for 8 hours has been set at 560 mcg/l. The maximum concentration obtainable with a currently marketed OTC preparation is 36 mcg/l (Refs. 2 and 3). No histological evidence of pulmonary lesions were seen in mice and rats exposed to lethal concentrations of turpentine vapors (Ref. 4). Inhalation of 300 mcg/l of turpentine vapor by mice for 15 minutes did not influence the electrocardiogram, respiratory minute volume, pulmonary airway, resistance, or compliance (Ref. 5). One study in mice using a mixture of volatile oils, one of which was turpentine, showed a decrease in pulmonary antibacterial activity (Ref. 6). Two other studies showed no change when the mixture was used (Refs. 7 and 8).

In several studies in children and infants suffering from minor breathing discomforts associated with the "common cold" no side effects that were drug related were observed when a medicated steam was administered (Refs. 9 through 13). Turpentine has been widely used as a part of a mixture of volatile oils for many years with approximately two complaints per million packages purchased (Ref. 14).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of turpentine oil (topical/inhalant) as an antitussive. Its effectiveness is uncertain due to a lack of properly controlled studies of the substance by itself.

(3) *Proposed dosage.* Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 4.0 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapor rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 5.5 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl, or washbasin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

For children under 2 years, there is no recommended topical or inhalant dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antitussive active ingredients. (See part III. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: *Warning:* "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: *Warning:* "For steam inhalation only. Do not take by mouth".

(5) *Evaluation.* The Panel made the following recommendations:

(i) For topical ointment use: Data to demonstrate effectiveness will be required from only one additional well-controlled cough-counting objective study in patients with coughs due to respiratory disease in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing antitussive drugs. (See part III. paragraph C. below—Data Required for Evaluation.)

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Category III Labeling

The Panel concludes that the available data are insufficient to permit final classification of the labeling claims identified below for antitussives. The Panel concludes that certain words used in the context of claims for antitussives are statements which have no scientific meaning and therefore are misleading to the consumer. Additional data are required to support the following antitussive claims:

a. The term "soothing" in labeling such as "Calms coughing by soothing the irritated throat".

b. The term "throat soothing" in labeling such as "Throat soothing and recommended for coughs due to colds and dry, husky or tickling throats".

c. The term "smooth coating" in labeling such as "Produces a smooth coating that gives quick comfort to irritated throats and helps relieve coughs".

d. The terms "demulcent action" and "soothes" in labeling such as "Demulcent action which gently sooths cough-irritated throat membranes".

e. Statements referring to "duration of action" unless there is acceptable documentation to verify this.

f. Terms relating to sleep such as "Quiets annoying cough and lets you sleep". An antitussive is capable of quieting annoying cough, but has not been demonstrated to be directly related to sleep.

g. The term "soothing" has not been scientifically demonstrated to have an antitussive effect. In fact, none of the antitussive ingredients reviewed by the Panel have any "soothing" properties since the Panel cannot determine what such a property would be. The same is true for the term "smooth". Again, the Panel is unaware of how the ingredients act to smooth an irritated throat or sooth membranes by a "demulcent" action.

C. DATA REQUIRED FOR EVALUATION

The Panel has agreed that the protocols recommended in this document for the studies required to bring a Category III drug into Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved methodology in the future.

1. *Principles in the design of an experimental protocol for testing antitussive drugs.* a. *General principles.* The effectiveness of an antitussive agent is dependent on its ability to relieve the coughing of patients with a variety of disease conditions associated with cough. Relief of coughing may occur with a reduction in the frequency or number of coughs, or with a decrease in the intensity of the coughing, or both. Because coughing is such a common symptom occurring in health as well as disease, adaptation readily occurs to the extent that many patients are unaware of the extent of their coughing, and hence any subjective evaluation is apt to be highly variable and with an unacceptable margin for error. Objective studies employing the actual recording of the cough are re-

quired to document a decrease in cough frequency and/or intensity.

b. *Selection of patients.* The study design will depend on whether the patients in the study have chronic lung disease or acute self-limiting illnesses. For a cough study in patients with chronic lung disease, a crossover design could be used in a small group of 10 to 20 patients whose underlying chronic pulmonary disease is relatively stable so that daily fluctuations in the recorded cough counts performed prior to drug administration are minimized. The smoking habit of the patients must be carefully documented and maintained at the same level throughout the clinical trials. No smoking would be permitted during the actual recording sessions. For a cough study in patients with acute upper respiratory infection, a larger number of patients, averaging between 50 and 100, would have to be studied because of the marked variation in cough from day to day and hour to hour in upper respiratory infection. The patients would have to be assigned in a randomized design to either the placebo or drug groups. The sensitivity of this type of study could be improved by matching the groups for age, sex, severity of cough, and smoking habit.

c. *Methods of study.* To establish effectiveness of a drug as an antitussive, objective controlled studies employing cough-counting techniques are recommended. Two types of investigation are acceptable to the Panel. These are:

(1) A study may be done in a small group of healthy volunteers, approximately 10 to 20 in number, who are preferably nonsmokers. If smokers are included, their smoking habits must be well documented and remain at the same level during the entire course of the study. Any departure from smoking habits must be documented and made part of the evaluation of data. The data obtained in such a study including smokers and nonsmokers should be evaluated separately before combined. A challenge technique employing an irritant aerosol such as citric acid is used to assess effectiveness, dose, and time responses against the experimentally induced cough. This is performed under controlled laboratory conditions with a double-blind or suitably blinded, crossover design in suitably trained individuals.

(2) A double-blind, controlled study may be done in patients with cough due to respiratory disease. The dose and formulation of the drug to be tested would be as recommended for OTC use. Coughs are recorded and counted for stated periods before and after giving the drug or placebo so that adequate comparisons can be made concerning the onset and duration of antitussive activity following a single dose, as well as the effect of multiple doses. As a model for OTC drugs, however, the requirement for long periods of testing would be unnecessary since effective relief should be obtained fairly rapidly and, in most instances, after 1 or, at most, 2 days.

d. *Interpretation of data.* Evidence of drug effectiveness is required from a minimum of two positive studies based on the results of two different investigators or laboratories. All of the required studies in man should employ objective cough-counting techniques for recording the cough reflex. In the reevaluation of those drugs for which there was insufficient evidence of antitussive effectiveness and for the assessment of drugs that have not been submitted for review by the Panel, the two required studies should consist of either one challenge study with experimentally induced cough plus a study with cough in respiratory disease, or, alternatively, two studies by different investigators in patients with respiratory disease. A significant reduction in cough when compared with placebo by acceptable statistical analysis of the data will permit reclassification of such drugs into Category I.

All data submitted to the Food and Drug Administration must present both favorable and unfavorable results.

e. *Evaluation of safety.* Tests for safety should involve the usual tests for toxicity relevant to the known possible adverse effects of the drugs under testing. Tests should be done in the form of dose-response curves up to maximum therapeutic effectiveness.

IV. EXPECTORANTS

A. GENERAL DISCUSSION

Expectorants are agents that are used to promote or facilitate the evacuation of secretions from the bronchial airways to provide for the temporary relief of coughs due to minor throat and bronchial irritation as may occur with upper respiratory infection. This may be accomplished by reducing the thickness of these secretions or by augmenting the formation of a more fluid secretion. The secretions (sputum or phlegm) expectorated consists in part of respiratory tract fluids (RTF) together with a varying mixture of saliva and postnasal secretions.

In general, the mechanisms of action of the expectorants have been shown to be due to one or more of the following: The stimulation of reflexes from the stomach (the major action of certain drugs that are irritants to the gastrointestinal tract and act through their nauseant effect which increases the output from the secretory glands of the gastrointestinal as well as the respiratory tracts); stimulation of vagal nerve endings in the glands of the bronchial tubes; direct effect on the secretory cells lining the airway when administered by inhalation or if excreted by the respiratory tract; and stimulation of centers in the brain such as the vomiting center.

By facilitating the evacuation of secretions from the bronchial airway, local irritants are removed. In addition, by increasing the amount of mucous that covers and protects the lining of the throat and the bronchial airway, it is claimed that a "soothing" or demulcent" action is exerted which relieves irritated membranes in the respiratory passages. While these effects may indirectly serve to diminish the tendency to cough, the mechanism of this indirect action is quite different from that of an antitussive which is specifically designed to inhibit or suppress cough. Any claim relating to the amelioration of cough must be supported by the type of studies suggested above for evaluation of antitussives. (See part III. paragraph C. above—Data Required for Evaluation.) Expectorants would be expected to have their major usefulness in the irritative nonproductive cough as well as those coughs productive of scanty amounts of thick, sticky secretions.

As a group, the expectorant drugs have been widely used for many decades in the form of liquid preparations. By and large, in the dosages used for OTC administration, these drugs have had a good safety record. The few exceptions, where hypersensitivity reactions or cumulative toxicity represents a distinct hazard, have been discussed under the individual sections. While the expectorants have been traditionally used for their effect on aiding in the expectoration of phlegm (sputum) and thus relieving certain aspects of difficulty in breathing, there is little or no evidence to document this. In summary, the Panel concludes that while many of the expectorants on the market with long usage are generally safe, most lack evidence of efficacy and furthermore, all expectorants must be clearly identified on the labels of drug products as having a primary effect on respiratory sputum and not primarily as an antitussive.

B. CATEGORIZATION OF DATA

1. *Category I conditions under which expectorant ingredients are generally recognized as safe and effective and are not misbranded.*

Category I Active Ingredient

The panel was unable to classify a claimed expectorant active ingredient as generally recognized as safe and effective and not misbranded.

Category I Labeling

The Panel recommends the following Category I labeling for expectorant active ingredients to be generally recognized as safe and effective and not misbranded:

a. *Indications.* (1) "Helps loosen phlegm (sputum)".

(2) "Helps rid the passageways of bothersome mucus".

(3) "Expectorant action to help loosen phlegm (sputum) and bronchial secretions".

(4) "Helps drainage of the bronchial tubes by thinning the mucus".

(5) "Relieves irritated membranes in the respiratory passageways by preventing dryness through increased mucus flow".

b. *Warnings.* (1) "Do not give this product to children under 2 years except under the advice and supervision of a physician".

(2) "Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, or emphysema, or where cough is accompanied by excessive secretions except under the advice and supervision of a physician".

(3) *"Caution:* A persistent cough may be a sign of a serious condition. If cough

persists for more than 1 week, tends to recur or is accompanied by high fever, rash or persistent headache, consult a physician".

2. *Category II conditions under which expectorant ingredients are not generally recognized as safe and effective or are misbranded.* The use of expectorants under the following conditions is unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel concludes that the following ingredients and labeling should be removed from the market until scientific testing supports their use.

Category II Active Ingredients

The Panel has classified the following expectorant active ingredients as not generally recognized as safe and effective or as misbranded:

Antimony potassium tartrate
Chloroform
Iodides: Calcium iodide anhydrous, Hydriodic acid syrup, Iodized lime, Potassium iodide
Ipecac fluidextract
Squill preparations: Squill, Squill extract
Turpentine oil (spirits of turpentine) (oral)

a. *Antimony potassium tartrate.* The Panel concludes that antimony potassium tartrate is not safe for OTC use as an expectorant.

(1) *Safety.* Antimony potassium tartrate is not safe in the dosage range used as an expectorant.

The trivalent salts of antimony are potent inducers of vomiting; they act on centers in the brain as well as locally on the stomach walls. Because the antimony ingredient in this preparation tends to accumulate in the body and not to be excreted in a manner similar to arsenic, the danger of toxic reactions increases with repetitive or chronic use. These toxic reactions consist of marked irritation of the stomach and intestinal mucosa. Pain in joints and muscles are common, and the muscles of the heart may be depressed. Abdominal pain, rash and vascular collapse as well as a number of cases of hemolytic anemia, some fatal, have been reported (Ref. 1). Such toxic effects have been seen with the use of the trivalent compound at higher doses for the treatment of helminthic infections; but even in doses suitable for expectorant activity, antimony potassium tartrate is considered too toxic because of its cumulative properties to be used as an OTC product (Ref. 1).

(2) *Effectiveness.* There is no evidence that antimony potassium tartrate is effective as an expectorant.

When administered in subemetic doses, antimony potassium tartrate theoretically exerts its expectorant activity through reflex stimulation of the salivary and bronchial glands (Ref. 2). There is, however, not one documented study in either animals or man demonstrating its effect on cough, sputum production or respiratory tract secretions (Ref. 3).

(3) *Evaluation.* Because of its toxicity and tendency to accumulate in the body, the Panel is of the opinion that even subemetic doses present risks which outweigh whatever benefit theoretically might occur since there is no evidence to support effectiveness.

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(2) "Drill's Pharmacology in Medicine," 2d Ed., Edited by DiPalma, J. R., McGraw-Hill, New York, p. 689, 1958.

(3) OTC Volume 040190.

b. *Chloroform.* The Panel concludes that chloroform is not effective for OTC use as an expectorant. The Panel is aware that the safety of chloroform is being questioned at present and has therefore limited its use only as a flavoring agent in CCABA preparations.

(1) *Safety.* The Panel concludes that the question of safety is dependent on dosage and abuse potential.

In doses of 4 to 8 ml orally, chloroform has been known to produce a narcotism similar to that occurring when administered by inhalation but developing more slowly and of longer duration (Ref. 1). The mean lethal dose by ingestion is approximately 30 ml (Ref. 2), although as little as a teaspoonful has produced serious illness. Symptoms of toxicity due to chloroform ingestion are often delayed for 2 or more days (Ref. 3). The problem of abuse at a "chloroform party" has recently been reported (Ref. 4).

Three documents concerning the safety of chloroform were submitted to the Panel for review and appropriate action. These pertained to the possible carcinogenicity of chloroform (Refs. 5 and 6) and the acute toxicity of chloroform in rats with an extrapolation to a suggested "maximum permissible limit" in humans (Ref. 7).

The first document was a review of a report by Harris on the implications of cancer causing substances in Mississippi River water (Ref. 5). A detailed analysis of the epidemiological data, presented together with a review of the statistical methods and the animal studies, is reported in full in the minutes of the 17th meeting of the Panel, Appendix 9 (Ref. 8). The Panel recognizes that there are serious inconsistencies in the report which makes the extrapolation of the data to possible risks of cancer from chloroform in drinking water unacceptable. Furthermore, the evidence of carcinogenicity in mice is conflicting and inconclusive and its extrapolation to another species, man, is open to serious question. Accordingly, the Panel concludes that for the report pertaining to the possibility of chloroform being a carcinogen in drinking water there is no evidence to support this possible carcinogenic hazard in the recommended dosages. This view is supported by an ad hoc Study Group on "Assessment of Health Risk from Organics in Drinking Water" in their report to the Hazardous Materials Advisory Committee of the Environmental Protection Agency (Ref. 9).

The second document (Ref. 7) attempts to establish some guidelines on permissible limits of solvent residues in chemicals. The authors list the obvious limitations of their study, i.e., the difficulty of extrapolating from rat to man; an acute single dose study does not provide an answer regarding the effect of chronic exposure; and the questionable use of arbitrary conversion factors that have no scientific basis. Their revised figure for the permissible limit for chloroform is 0.25 ml/60 kg. The Panel's recommended concentration of 0.4 percent by volume is therefore well within the authors' suggested permissible limit. The Panel recommends that chloroform be available only as a flavoring agent at a maximum concentration of 0.4 percent which represents 0.004 ml/ml or 0.02 ml/5 ml (teaspoon) of a product dosage. This is well within their revised permissible limit of 0.25 ml/60 kg. of body weight.

The third document is a preliminary report from the National Cancer Institute entitled, "Report on Carcinogenesis Bioassay of Chloroform" dated February 1976 (Ref. 6). The protocol consisted of a total of 400 rats and mice with suitable control animals receiving daily doses of chloroform orally for a total of 546 days. The treated animals were divided into low and high dose groups.

For rats, the results of the study showed a decreased survival rate which appeared dose related. Clinical evidence of toxicity appeared during the first 10 weeks but became more apparent during the second year of the study. The control groups also showed these signs by the 70th week. Transient palpable nodules were noted in both test and control groups by the end of the second year. The incidence of "all tumors" in both treated and control rats did not differ. Significant differences from control groups occurred with kidney tumors in male rats which appeared dose related and thyroid tumors in the female rats but the thyroid tumors were not considered relevant to the study because of the known incidence of spontaneously occuring thyroid tumors in this strain of rat. Neoplastic nodules of the liver occurred with equal frequency in test and matched controls (5 percent). Necrosis of hepatic parenchyma occurred with slightly greater frequency in the chloroform-treated rats.

For mice, results of the study showed that there were no significant differences in survival rate between the controls and treated mice except for the high dose female group. Beginning after 42 weeks of treatment, the chloroform-treated mice began to exhibit a bloated appearance with abdominal distention. The incidence of "all tumors" in the treated groups was significantly higher, and this was solely due to the presence of hepatocellular cancer.

The conclusions to be drawn from this study are that orally administered chloroform can produce hepatic neoplasms in this strain of mice when administered at these levels and for a prolonged period of time. There was a less striking correlation of kidney tumors with chloroform ingestion in the rat species. But the lack of any increase in hepatic tumors in the rats or kidney tumors

in the mice is attributed by the authors as illustrating "species differences in organ specificity and sensitivity." The Panel questions whether this then can be extrapolated to other species such as dog or man.

The Panel has considered the dosage of chloroform administered in the study. The average 400-gm rat received 36 to 80 mg/day for 546 days or a total of 19.-656 to 43.680 gm. The average 30-gm mouse received 4 to 14 mg/day for 546 days or a total of 2.184 to 7.644 gm. In terms of an average 60-kg human, the equivalent doses would be 5.4 to 12.0 gm/day or a total of 2,984.4 to 6,552 gm for 546 days. If the mouse dosage is extrapolated, the human dose would be 8.0 to 28.0 gm/day or a total of 4,368 to 15,288 gm. The Panel finds that the use of chloroform as a flavoring agent at a maximum allowable concentration of 0.4 percent or 0.4 gm/100 ml would require the consumption of 1.35 to 7 liters/day for a total of 737.1 to 8,822 liters in 546 days. If the usual cough mixture is dispensed in a 120 ml bottle, this would represent the consumption of 31,850 bottles in a 2-year period. The Panel questions how many other drugs, food stuffs, flavoring agents, etc. would be toxic or even carcinogenic at these levels.

In the final analysis, the Panel is unable to determine from the available data the lack of safety of chloroform in man at the 0.4 percent concentration proposed for use as a flavoring agent. Obviously, there is a dose-response relationship with respect to toxicity and the potential for abuse exists just as with alcohol.

(2) *Effectiveness.* There is no evidence that chloroform is effective as an expectorant or that it ameliorates cough.

There is no documentation of the expectorant activity of chloroform. One report (Ref. 9) states that it is "probably harmless as well as useless in the dosages used." *The U.S. Dispensatory* reports that chloroform has been added to cough mixtures as a respiratory sedative, but its action is too fleeting to be of any great value (Ref. 1). *Remington's Practice of Pharmacy* (Ref. 10) classifies chloroform as a pharmaceutical necessity.

(3) *Evaluation.* The Panel concludes that chloroform should be restricted to use as a flavoring agent (pharmaceutical necessity) in amounts not to exceed 0.4 percent by volume in an OTC CCABA product.

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c. *Iodides (calcium iodide anhydrous, hydriodic acid syrup, iodized lime, potassium iodide).* The Panel concludes that the iodides are neither safe nor effective for OTC use as expectorants.

(1) *Safety.* At a dosage that may be effective, iodides are not considered safe as OTC preparations.

The action and toxic effects of these compounds are due to the iodide content. The iodides are readily absorbed from the gastrointestinal tract and concentrated primarily in the secretions of the respiratory tract. The Panel is unaware of any animal studies on the safety of the iodides. There are no controlled studies on short-term use of iodides as expectorants. The incidence of side effects and toxicities are directly proportional to the dose and duration of therapy, and practically all persons continually treated with high doses will manifest symptoms of iodism which may simulate the symptoms of the "common cold". Some individuals, though not frequently, are highly sensitive to iodides and will react to the first few doses with serious consequences (Ref. 1). The clinical experience with iodides has been mostly in the treatment of chronic diseases, such as bronchial asthma, chronic bronchitis, bronchiectasis and emphysema; therefore, most of the toxicity has been related to chronic administration. The effective dose is 900 mg daily in divided doses (Refs. 2 and 3). Leonardy (Ref. 4) estimates the optimal dose at 25 to 35 mg/kg daily in divided doses. At these doses, there is a high incidence of toxic effects varying in seriousness from mild iodism to generalized papulovesicular eruptions, hypothyroidism, edema of the glottis, submandibular adenitis (Ref. 1), and iodide fever (Ref. 5).

Murray and Stewart (Ref. 6) reported two cases of iodide goiter and found at least 170 cases in the literature as well as several other cases through personal communications. Carswell, Kerr and Hutchison (Ref. 7) reported iodide-induced goiters in the fetuses of pregnant women. Two cases of neonatal death apparently due to congenital goiter caused by iodides compressing the trachea are reported by Galina, Avnet and Einhorn (Ref. 8). Continued heavy use in children and adults may produce goiter and/or hypothyroidism (Refs. 9 and 10). *The Medical Letter* (Ref. 11) discusses the hazards of drug-induced goiters and cites iodides as the most frequent cause. The blood levels needed to induce goiter could not be established. Falliers et al. (Ref. 2), in a double-blind crossover study of 52 asthmatic children, found a high incidence of adverse effects. One child could not complete the study because of the development of a severe generalized papulovesicular eruption. Sixteen adolescents developed acne-form lesions. Eighteen showed thyroid enlargement but no evidence of suppressed thyroid functions. Leonardy (Ref. 4), in discussing the use of iodides in the treatment of bronchial asthma, cites a review by Peacock and Davison (Ref. 12) of 500 cases in which 13.5 percent of patients receiving iodides had sufficient side effects to warrant discontinuing the drug.

There is a wide variety of diseases which contraindicate the use of iodides or require caution that the consumer does not have the expertise to determine, such as hypersensitivity to iodides, thyroid disease, psoriasis (Refs. 3 and 13) and various types of dermatoses.

Because of the high incidence of untoward effects and the potential for toxicity, iodides should be used only under the advice and supervision of a physician.

(2) *Effectiveness.* Iodides may be effective as an expectorant when given in adequate doses in some chronic respiratory disease. There is no evidence that they are efficacious in acute upper respiratory infections.

Animal studies have demonstrated the presence of iodides in the respiratory tract fluid (RTF) and an increase in the amount of RTF or a decrease in its viscosity (Refs. 14 and 15). Numerous investigators have reported observations on the expectorant action of iodides (Ref. 14). Many cite the rapid appearance of iodides in the RTF after the administration (Refs. 16, 17, and 18). The mechanism of the action of iodides as expectorants is not clear. Their presence in the RTF does not necessarily indicate increased amounts of RTF or decreased viscosity. It has been suggested by Lieberman and Kurnick (Ref. 19) that the iodides may liquefy purulent sputum by inducing the enzymatic hydrolysis of proteins. In asthmatics, no consistent change in viscosity resulting from iodides was reported by Leonardy (Ref. 4), citing as evidence a number of studies. Hirsh et al. (Ref. 20), using a new technique to measure viscosity, have been able to obtain consistent and reproducible results, but no final answer is yet available.

Falliers et al. (Ref. 2), in a 3-year double-blind study of 52 children with chronic asthma, demonstrated a statistically significant improvement in the children receiving potassium iodide 300 mg 3 times daily. The population receiving iodides improved but there was a wide variability in the response of the individuals in the study, and there is no an-

swer to why. It may be due to some other property than that of its expectorant property.

While the iodides are possibly expectorants, there are insufficient studies to confirm this. This would suggest the need for more controlled studies and better techniques for evaluation of the action of iodides.

(3) *Evaluation.* The Panel concludes that iodides are not safe for OTC use. Because of the wide variety of diseases which contraindicate their use and because of the potential for toxicity and untoward effects, iodides should be used only under the advice and supervision of a physician.

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d. *Ipecac fluidextract.* The Panel concludes that ipecac fluidextract is not safe for OTC use as an expectorant.

(1) *Safety.* Based on its long history of use, it is generally accepted that syrup of ipecac is safe although no studies can be found to substantiate this belief (Ref. 1). The fluidextract of ipecac, however, is 14 times more potent than the syrup (Ref. 2) possessing a 2 percent total alkaloidal content. The chief alkaloids of ipecac are emetine and cephaeline varying in ratio from equal parts to a fourfold preponderance of emetine. These alkaloids are responsible for its therapeutic and toxic manifestations (Ref. 3).

Toxic, even fatal doses may occur in man at 2 oz of the fluidextract. A dose of 10 ml produced death in a 4-year-old child (Ref. 4). Death from the ingestion of the syrup has not been reported. However, it is believed that many cases of overdosage result from mistaking the fluidextract for the syrup. Toxic manifestations of overdosage include nausea, bloody stools, and vomitus, cramping, and abdominal pain. Myocardial manifestations have also been reported (Ref. 3).

The Panel is aware of a reference to an expectorant dose of the fluidextract of 0.2 to 0.5 ml (Ref. 5), however the Panel feels that the syrup possesses a superior benefit-to-risk ratio and that ipecac fluidextract should not be available for OTC use as an expectorant.

(2) *Effectiveness.* Ipecac fluidextract has both local and central effects; however, there are no acceptable clinical studies to substantiate its use as an expectorant.

(3) *Evaluation.* The Panel is unable to determine a safe dose for ipecac fluid extract for use as an expectorant. Because of its documented toxicity and since there is no evidence to support effectiveness, the Panel concludes that ipecac fluidextract is not safe for use as an expectorant.

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e. *Squill preparations (squill, squill extract).* The Panel concludes that squill preparations are not safe or effective for OTC use as expectorants.

(1) *Safety.* Squill is a toxic substance capable of causing nausea, vomiting, and violent purging. It contains scillarin A and scillarin B, glycosides that may be toxic to the heart. The powdered drug and extracts from it have been used as rat poison. As a rat poison, red squill is usually preferred but all squill preparations have the same general properties (Ref. 1). Although the market experience would indicate that squill is probably safe, the doses used are small and there are no data available to relate this dose to effectiveness or to the lower limits of toxic doses (Ref. 2). Available information relates to sources and methods for preparation. The lowest toxic dose is currently estimated at 50 mg/kg (Ref. 3).

(2) *Effectiveness.* Squill is an irritant to the gastric mucosa and produces a reflex expectorant action. In larger doses it is an emetic (Refs. 1, 4, and 5). There are no available data to relate these effects to dose. Squill is practically always given as one of several drugs in various preparations and there are no data to indicate whether it does or does not contribute to the expectorant action of the preparation.

(3) *Evaluation.* Because of its known toxicity and historical use as a rat poison, and since there are no data available to relate marketed doses as an expectorant to the lower limits of toxic doses, the Panel is of the opinion that the risks outweigh whatever benefit might occur. Therefore, the Panel concludes that squill preparations are not safe or effective for OTC use.

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f. *Turpentine oil (spirits of turpentine) (oral).* The Panel concludes that oil of turpentine is not safe for OTC use when taken orally as an expectorant.

(1) *Safety.* Oil of turpentine is a volatile oil distilled from turpentine, an oleoresin obtained from the pine tree. It has a characteristic odor and taste. The substance has been administered orally, topically and by inhalation.

In doses of 15 ml in children and 150 ml in adults fatal poisoning may occur (Ref. 1). Excessive oral doses produce marked irritation of the alimentary tract, especially of the stomach and of the pelvic organs. Toxic symptoms include vomiting, diarrhea, acute pain,

renal irritation, bloody stools and hyperemia of all abdominal organs. Continued oral use may lead to cloudy swelling and fatty degeneration of the liver. Abnormal central nervous system symptoms may develop (Refs. 2 and 3).

Since no safe oral dose has been established for effective use as an expectorant, the Panel concludes that turpentine oil should not be available for oral OTC use as an expectorant. However, elsewhere in this document, the Panel concludes that the ingredient is safe when applied topically or used as an inhalant but that there are insufficient data to permit final classification of its effectiveness for inhalant or topical use as an expectorant. (See part IV. paragraph B.3.n. below—Turpentine oil (spirits of turpentine) (topical/inhalant).)

(2) *Effectiveness.* Oil of turpentine is irritating and its chief suggested uses are based on this property (Refs. 1 and 4). There is no evidence to support its effectiveness as an expectorant when taken orally.

(3) *Evaluation.* The Panel is unable to determine a safe oral dose for turpentine oil for use as an expectorant. The Panel is of the opinion that the risk from oral administration outweighs whatever benefit might occur. Therefore, the Panel concludes that turpentine oil is not safe for oral use as an expectorant.

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Category II Labeling

The Panel concludes that the use of certain labeling claims related to the safety and/or effectiveness of the product are unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel has previously discussed such labeling. (See part II. paragraph O. above—CCABA Product Labeling Claims Not Supported by Scientific Evidence.) However, labeling that is descriptive of the product such as its taste or appearance are acceptable.

The Panel concludes that the following claims are misleading and are unacceptable for preparations used as expectorants. These and similar claims are unsupported by scientific data. The term "congestion", which may be interpreted by the target population to denote a discomfort of the chest, may result from a variety of causes, several of which may be of a most serious nature and require professional attention. Other terms and phrases are descriptive, but vague, and cannot be scientifically evaluated. Statements or phrases which allude to greater potency or suggest superiority of a product are not acceptable.

All claims that state or imply a therapeutic action or safety property peculiar to the preparation that cannot be demonstrated in controlled studies are not acceptable, e.g., "specially formulated", "improved", "selected", "natural", "extra strength", "teamed components", "superior to ordinary", "modern", and "superior".

Claims implying a physiological effect that has no foundation or meaning or will be meaningless to the public are unacceptable; such as "antiallergic", "gets at the roots of", "fights", "wakes up", "recommended by doctors", "multiaction", and "travels through the blood stream", "works internally", and "actively moistens".

Claims for relief where time is indeterminate and not supported by scientific data are unacceptable, such as "fast" and "prompt". Using the above criteria the Panel feels that the following specific claims are unacceptable:

a. *Unacceptable claims because of vagueness and the inability to evaluate them scientifically.* (1) "Temporarily relieves cough congestion by working internally to break up phlegm".

(2) "Help decongest bronchial passage".

(3) "To help clear congestion".

(4) "Frees secretions along lower respiratory tract".

(5) "Helps loosen congestion so you can cough it up and get it off your chest".

(6) "Works internally".

(7) "Actively moistens the bronchial lining".

(8) "Soothes tired throats".

(9) "Promotes free breathing".

(10) "Restores free breathing".

(11) "Eases breathing".

b. *Unacceptable because the claims allude to greater potency or suggest superiority of a product which is not supported by scientific data.* (1) "Full expectorant".

(2) "Combines modern expectorant".

(3) "Superior expectorant".

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel concludes adequate and reliable scientific evidence is not available at this time to permit final classification of the claimed conditions listed below. Because of the lack of suitable objective criteria for evaluating expectorant activity and the need to rely on subjective assessment of highly variable symptoms, the Panel believes it reasonable to provide 5 years for the development and review of such evidence. Marketing need not cease during this time if adequate testing is undertaken. If adequate effectiveness data are not obtained within 5 years, however, the conditions listed in this category should no longer be marketed as over-the-counter products.

Category III Active Ingredients

The Panel has concluded that the available data are insufficient to permit final classification of the following claimed expectorant active ingredients:

Ammonium chloride
Beechwood creosote
Benzoin preparations (inhalant): Compound tincture of benzoin, Tincture of benzoin
Camphor (topical/inhalant)
Eucalyptol/eucalyptus oil (topical/inhalant)
Glyceryl guaiacolate
Ipecac syrup
Menthol/peppermint oil (topical/inhalant)
Pine tar preparations: Extract white pine compound, Pine tar, Syrup of pine tar, Compound white pine syrup, White pine
Potassium guaiacolsulfonate
Sodium citrate
Terpin hydrate preparations: Terpin hydate, Terpin hydrate elixir
Tolu preparations: Tolu, Tolu balsam, Tolu balsam tincture
Turpentine oil (spirits of turpentine) (topical/inhalant)

a. *Ammonium chloride.* The Panel concludes that ammonium chloride is safe in the dosage range used as an expectorant but there are insufficient data to permit final classification of its effectiveness for OTC use as an expectorant.

(1) *Safety.* Clinical experience has confirmed that ammonium chloride is safe in the dosage ranges used as an expectorant.

Several studies have documented the occurrence of severe acidosis, especially in patients with renal or hepatic dysfunction (Refs. 1 through 3). Most of these occurred with doses in excess of 6 to 8 gm per day where it was being used as a diuretic. Relman, Shelburne and Talman (Ref. 4) reported two near fatal cases following ingestion of huge amounts, 82 gm taken in a 48 hour period; while Ticktin, Fazekas and Evans (Ref. 5) described a case report of hepatic coma precipitated by 6 gm in a patient with congestive heart failure. At the dose ranges of 250 to 500 mg 4 to 6 times daily, which is the customary dose as an expectorant, the major adverse reaction has been nausea and emesis (Ref. 6).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of ammonium chloride as an expectorant. No objective evaluations have been reported. Partially controlled subjective studies (Ref. 7) showed no significant change in either sputum volume or viscosity. Several investigators (Refs. 8 through 10) felt that sputum was more fluid and easier to raise when given at doses 0.3 gm every 2 hours, and Basch, Holinger and Poncher (Ref. 11) reported a decrease in visocity and pH (acidity) in patients with damaged bronchial tubes and infection.

(3) *Proposed dosage.* Adult oral dosage is 300 mg every 2 to 4 hours. Children 6 to under 12 years oral dosage is 150 mg every 2 to 4 hours. Children 2 to under 6 years oral dosage is 75 mg every 4 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Warnings.* (i) *"Caution:* This product must be taken with adequate amounts (½ to 1 glass) of fluids with each dose".

(ii) "Do not take this product if you have heart trouble or chronic kidney or lung disease except under the advice and supervision of a physician".

(5) *Evaluation.* Data to demonstrate effectiveness as an expectorant will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

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b. *Beechwood creosote.* The Panel concludes that beechwood creosote is safe in the dosage range used as an expectorant but there are insufficient data to permit final classification of its effectiveness for OTC use as an expectorant.

(1) *Safety.* Clinical experience has confirmed that beechwood creosote in the usual dosages contained in lozenges or cough mixtures for expectorant activity is safe.

Creosote is a distillate of wood tar and has a smokey color and a pungent taste. Dosages in excess of 4 gm 3 times daily produces giddiness, dimness of vision, circulatory collapse, convulsions and coma (Ref. 1). Because of the taste, it is normally given well-diluted (Ref. 2). Occasional adverse gastrointestinal side effects are mentioned in one report but are poorly documented (Ref. 3). Based on the available data and the presence of beechwood creosote on the market for many years, the Panel concludes that this ingredient is safe for OTC use.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of beechwood creosote as an expectorant. No controlled or partially controlled studies were submitted to the Panel documenting its effectiveness as an expectorant. Only one reference (Ref. 3) was found that reported some increase of respiratory tract fluid (RTF) in animals given high dosages but the authors expressed doubt as to the applicability of these data to man. According to the standard compendia (Refs. 1 and 4), an average dose of beechwood creosote is 250 mg 3 or 4 times a day. In the two submissions to the Panel listing creosote, the dosages are 3.29 mg/lozenge and 33 mg/15 ml every 3 hours (Ref. 5). This 40 to 80-fold difference in dosage (3.29 mg/lozenge, 8 dosages daily) appears illogical and there is no evidence to indicate that creosote is effective in such low doses. The Panel concludes that further studies are needed to determine effectiveness.

(3) *Proposed dosage.* Adult oral dosage is 250 mg every 4 to 6 hours not to exceed 1,500 mg in 24 hours. Children 6 to under 12 years oral dosage is 125 mg every 4 to 6 hours not to exceed 750 mg in 24 hours. Children 2 to under 6 years oral dosage is 62.5 mg every 4 to 6 hours not to exceed 375 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness as an expectorant will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

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c. *Benzoin preparations (compound benzoin tincture, tincture of benzoin) (inhalant).* The Panel concludes that tincture of benzoin and compound benzoin tincture are safe in the dosage ranges used as an expectorant but there are insufficient data to permit final classification of its effectiveness for OTC use as an expectorant.

(1) *Safety.* Clinical experience has confirmed that benzoin tincture and compound benzoin tincture are safe in the dosage ranges used in boiling water as a steam inhalant for expectorant purposes.

Benzoin is the balsamic resin obtained from *Styrax benzoin* Dryander or Styrax paralleloneurus Perkins, known in commerce as Sumatra Benzoin or from *Styrax* tonkinensis (Pierre) Craib ex Hartwich, or other species of the Section *Anthostyrax* of the genus Styrax, known in commerce as Siam benzoin (San. *Styraceae*) (Ref. 1).

Benzoin is used in preparing official preparations, e.g., compound benzoin tincture, United States Pharmacopeia XIX (Ref. 1) and benzoin tincture, National Formulary XI (Ref. 2). Compound benzoin tincture contains 74 to 80 percent alcohol and is prepared by a maceration process incorporating benzoin, aloe, storax and tolu balsam using alcohol as a menstruum (Ref. 1). Benzoin tincture contains 75 to 83 percent alcohol and is also prepared by macerating benzoin, the final product being a 20 percent solution of benzoin (Ref. 2). These preparations are used topically as a protectant and antiseptic and by steam inhalation as an expectorant (Refs. 3 and 4). It is generally recognized as safe when administered by steam inhalation in accordance with recommended concentrations. The alcohol content would be responsible for the major toxic signs and symptoms arising from oral administration of the tincture (Ref. 5).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of tincture of benzoin and compound benzoin tincture as an expectorant.

Although compound benzoin tincture and benzoin tincture have been advocated and used for generations as a component of steam inhalations to promote an expectorant action, no studies demonstrating this effect have been found in the literature or OTC submissions.

(3) *Proposed dosage.* Dosage for adults and children 2 to under 12 years of age is as follows: Add 1 teaspoonful of compound benzoin tincture or benzoin tincture to a pint of water in a hot steam vaporizer, bowl or washbasin. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV, paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Warning:* "For use by steam inhalation only. Do not take by mouth".

(5) *Evaluation.* Data to demonstrate effectiveness as an expectorant will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

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d. *Camphor (topical/inhalant)*. The Panel concludes that camphor is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as an expectorant.

(1) *Safety*. Clinical experience has confirmed that camphor (topical/inhalant) is safe in the dosage ranges used as an expectorant.

Camphor is a local irritant producing skin redness when rubbed on the skin. However, when not vigorously applied, it may produce a feeling of coolness on the skin as does menthol. It acts similarily on the respiratory tract. Taken orally in small doses it produces a feeling of warmth and comfort in the stomach but in larger doses it is irritating and can cause nausea and vomiting. Camphor also has a mild local anesthetic action and its application to the skin may be followed by numbness. The systemic effects are primarily related to stimulation of the central nervous system. The ingestion of solid camphor by children can cause convulsions (Ref. 1). As little as 0.75 gm of camphor equivalent to a teaspoonful of linament of camphor or camphorated oil that contains 20 percent camphor has been fatal to a child. Commercially available ointments containing mixtures of volatile substances for use as decongestants or antitussives contain about 5 percent camphor. Since it is conceivable that ingestion of a sufficient amount of such a preparation could produce toxic effects in a young child, a suitable warning should be present on the label. The ingestion of 2 gm of camphor generally produces toxic effects in an adult although up to 1.5 oz has been ingested with recovery (Ref. 2).

(2) *Effectiveness*. There are no well-controlled studies documenting the effectiveness of camphor (topical/inhalant) as an expectorant. Its effectiveness is uncertain due to lack of properly controlled studies of the substance by itself.

A standard text indicates that camphor may have a slight expectorant action (Ref. 1). Well-controlled specific studies to document this effect have not been found in the literature.

(3) *Proposed dosage*. Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 5 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapor rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 7 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl, or washbasin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For topical use as a lozenge 0.02 to 15 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every ½ to 1 hour.

For children under 2 years, there is no recommended topical or inhalant dosage except under the advice and supervision of a physician.

(4) *Labeling*. The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: *Warning*: "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: *Warning*: "For steam inhalation only. Do not take by mouth".

(5) *Evaluation*. The Panel made the following recommendations: (i) For topical ointment use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below— Data Required for Evaluation.)

(iii) For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

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e. *Eucalyptol/eucalyptus oil (topical/inhalant)*. The Panel concludes that eucalyptol/eucalyptus oil is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as an expectorant.

(1) *Safety*. Clinical experience has confirmed that eucalyptol/eucalyptus oil (topical/inhalant) is safe in the dosage ranges used as an expectorant.

Eucalyptus oil is about 70 percent active eucalyptol. Fatalities have followed doses of the oil as small as 3.5 ml although recovery has occurred after doses of 20 and even 30 ml. Symptoms include epigastric burning with nausea and vomiting, vertigo, ataxia, muscle weakness and stupor (Refs. 1 and 2). A study of 223 subjects in which an ointment containing several volatile substances, including eucalyptus oil 1.3 percent, was applied for 48 hours to areas of intact skin under a patch and to abraded skin, revealed no instances of irritation, inflammation, wheal or hives following the period of exposure (Ref. 3). A study of ten subjects who received application of an ointment containing several volatile substances including eucalyptus oil 1.3 percent to their trunks 3 times daily for 3 weeks, then 1 week off followed by another 1 week of treatment, revealed no local reactions during this subsequent challenge phase (Ref. 4). A study of infants and children with respiratory infection who received an ointment containing a mixture of volatile oils, including eucalyptus oil 1.3 percent, applied to the chest and neck demonstrated no adverse effect from inhaled vapors by that route of administration on the rate of clearing of laryngeal edema (Ref. 5). In another study, the vapors were produced by placing a liquid mixture of volatile substances, including eucalyptus oil 1.7 percent, in the water of a hot steam vaporizer and administered via inhalation. Exaggerated use studies in adults and children, i.e., exposure for several hours to higher than recommended exposure concentrations either due to sitting in closer proximity to the vaporizer or placing 2 to 5 times the recommended dose of the volatile substance in the vaporizer, were not associated with irritating or toxic effects (Refs. 6 and 7).

A series of studies assessing buccal safety and overt side effects from lozenges containing a mixture of volatile oils was conducted in over 300 subjects (Refs. 8 through 11). Lozenges containing up to 5.5 mg eucalyptus oil were dissolved in the mouth every hour for 8 hours on 2 successive days. Mild erythema of the buccal mucosa and tongue was observed but did not differ appreciably from the response to dissolving lozenge sugar base without volatile oils. Incidence of gastrointestinal symptoms did not differ from control either (Refs. 8 through 11).

An aerosolized dosage form of volatile substances including 1 percent eucalyptus oil has also been utilized for treatment of nasal congestion. In humans, such aerosol sprays have been generally safe when used as directed but there have been reports of deaths from deliberate sniffing abuse, particularly when the subject inhales from a plastic bag into which the material has been sprayed (Ref. 12). Furthermore, one commercial preparation containing a particular solvent (1,1,1-trichloroethane) was recently recalled from the market due to potential hazards of this substance (Ref. 13).

(2) *Effectiveness*. There are no well-controlled studies documenting the effectiveness of eucalyptol/eucalyptus oil (topical/inhalant) as an expectorant. Its effectiveness is uncertain due to lack of properly controlled studies of the substance by itself.

Eucalyptus oil is traditionally assumed to have an expectorant action by virtue

of direct stimulation of bronchial secretory cells following inhalation (Ref. 14). In one study, eucalyptus oil was administered via steam inhalation to rabbits and respiratory tract fluid collected (Ref. 15). At normal doses eucalyptus oil did not increase the volume or decrease the specific gravity of the collected fluids. Larger doses were required for eucalyptus oil to produce this effect, and these doses led to local inflammation and several animal deaths (Ref. 15). In a later study, this group administered eucalyptol by stomach tube to anesthetized animals. Eucalyptol was shown to be an expectorant in rats, guinea pigs, rabbits, cats, and dogs. The effect was not influenced by section of the afferent gastric nerves. From this observation the authors concluded that eucalyptol does not act by a reflex mechanism in the stomach but directly upon the secretory cells of the respiratory tract (Ref. 16). Conclusive studies to confirm this expectorant property in humans are lacking.

(3) *Proposed dosage.* Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 1.3 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapors rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 1.7 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl or washbasin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For topical use as a lozenge 0.2 to 15.0 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every ½ to 1 hour.

For children under 2 years, there is no recommended topical or inhalant dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: *Warning:* "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: *Warning:* "For steam inhalation only. Do not take by mouth".

(5) *Evaluation.* The Panel made the following recommendations: (1) For topical ointment use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

(iii) For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

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1. Glyceryl guaiacolate. The Panel concludes that glyceryl guaiacolate is safe in the dosage ranges used as an expectorant but there are insufficient data to permit final classification of its effectiveness for OTC use as an expectorant.

(1) *Safety.* Clinical experience has confirmed that glyceryl guaiacolate is safe in the dosage ranges used as an expectorant.

Acute and chronic toxicity studies in animals demonstrated no adverse pathologic findings (Ref. 1). A number of studies in humans also demonstrates the safety of glyceryl guaiacolate over a wide range of dosages (Refs. 2, 3, and 4). Carter (Ref. 5) administered 100 mg/lb of body weight to 18 children with cerebral palsy for periods of 1 month. One child complained of loss of appetite and two exhibited nausea and vomiting. All laboratory data remained within normal limits (blood chemistry, complete blood count, and urine). An epidemiological study (Ref. 6) indicates that glyceryl guaiacolate is one of the most widely used medications with few reported adverse reactions.

Inhibition of in vitro platelet aggregation in the blood with prolongation of coagulation time of activated plasma has been described (Refs. 7 and 8) but appears to have no clinical significance (Refs. 9 and 10). Glyceryl guaiacolate may interfere with certain laboratory tests, such as 5-hydroxyindoleacetic acid and vanillyl mandelic acid (Refs. 11 and 12) which are employed as screening tests for carcinoid (hormone secreting) tumors and pheochromocytoma.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of glyceryl guaiacolate as an expectorant.

Earlier animal studies, in which glycerol guaiacolate was reported as increasing respiratory tract fluid (Refs. 13 and 14) were subsequently revised to indicate that the expectorant activity of glyceryl guaiacolate occurred only at extremely high doses (Ref. 15).

There have been a large number of clinical studies in man. Even in the early studies, the lack of acceptable standard techniques for evaluation was recognized. These studies can be subdivided into subjective uncontrolled reports (Refs. 16, 17, and 18) claiming effectiveness in the management of cough and good patient acceptance; subjective controlled or semicontrolled studies (Refs. 19 and 20) claiming superiority of glyceryl guaiacolate (100 to 200 mg 4 times daily) over placebo with respect to ease of raising sputum, and ameliorating the unproductive cough and objective controlled studies in which the flow properties of sputum were measured or the clearance rates of inhaled radioactive tracer particles were determined. Hirsch et al. (Ref. 2) and Hirsch, Viernes and Kory (Ref. 21) found glyceryl guaiacolate at dosages of 800 to 1,600 mg daily to be no more effective than placebo in lowering sputum consistency, increasing sputum volume or improving ventilatory function. The subjective ease of expectoration was also no different than with placebo. Chodosh (Ref. 22) and Chodosh, Medici and Enslein (Ref. 23), on the other hand, dispute these findings and in a letter to the editor of *Chest*, Chodosh and Medici (Ref. 24) claim improvement in subjective symptoms, pulmonary function tests, and sputum stickiness (adhesiveness) with 2.4 gm glyceryl guaiacolate daily. Perhaps the most striking point in his discussion is that even at 2.4 gm daily the most significant changes were noted only after 10 days

although trends could be detected at 7 days. The report by Thomson, Pavia and McNicol (Ref. 25) showing a significantly faster clearance of inhaled radioactive particles over the first 5 hours with glyceryl guaiacolate in single doses of 200 mg as compared to placebo in bronchitic patients in a double-blind crossover study is of special interest both in the evaluation of glyceryl guaiacolate and as an objective type of assessment for expectorant drugs. This is a new approach to the study of expectorants and is objective in design. If results can be confirmed, it may represent a "breakthrough" in methodology.

If glyceryl guaiacolate requires 7 to 10 days to begin to demonstrate a significant expectorant effect, it is obviously not suited for OTC use where rapid relief of symptoms in a self-limited illness of relatively short duration is desired. It should be emphasized that the study by Thomson, Pavia and McNicol (Ref. 25) suggesting drug activity is a single study that has not been confirmed by any other investigator. Hirsch et al. (Ref. 2) and Hirsch, Viernes and Kory (Ref. 21), employing another objective controlled method of study, were unable to demonstrate effectiveness. It would appear that the contradictory results of these two studies cancel each other out in a manner of speaking.

A recent subjective double-blind study was submitted in which there were 121 patients in a placebo group and 118 who received 200 mg every 6 hours for a period of 72 hours (Ref. 26). Statistical analysis of the data was reported as showing a significant reduction in cough frequency and intensity in the patients on glyceryl guaiacolate. However, this conclusion by a subjective method of evaluation is unacceptable as a claim for suppression of cough frequency or intensity in keeping with the Panel's statement that effectiveness of a drug with respect to antitussive activity must be assessed by objective techniques, such as cough-counting methods as described in the section under evaluation of antitussives. (See part III, paragraph C. below—Data Required for Evaluation.)

In addition, this study reported that glyceryl guaiacolate administration was associated with the production of a significantly thinner sputum and was effective in increasing sputum volume and facilitating the raising of secretions in patients with a productive cough. In examining the data, it was noted that one investigator in this multidisciplinary study submitted two separate studies with a total of 76 subjects which accounted for approximately one-third of the total subject population. Another investigator presented data that showed no significant difference from placebo and a third investigator showed a significant trend in favor of glyceryl guaiacolate. Because of the conflicting results of the different investigators on this study and the likelihood that the data from the single investigator referred to above would bias the results of the study when all the information is pooled, serious questions are raised as to the validity of the study. Retrospective analysis of the data with respect to smoking showed that there was no bias introduced by the incidence of smoking of the subjects (Ref. 27).

There are a number of controlled, objective studies with combinations of theophylline and glyceryl guaiacolate in reversible airway obstruction studies but these were not relevant to its expectorant acivity.

There is considerable dispute as to the effective dosage. From the more recent reports in the literature it would appear to be 2 to 4 times higher than the customary dose of 100 mg.

(3) *Proposed dosage.* Adult oral dosage is 200 to 400 mg every 4 hours not to exceed 2400 mg in 24 hours. Children 6 to under 12 years oral dosage is 100 to 200 mg every 4 hours not to exceed 1200 mg in 24 hours. Children 2 to under 6 years oral dosage is 50 to 100 mg every 4 hours not to exceed 600 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. Effectiveness to be established by only one additional controlled study which in view of the difficulty in obtaining objective criteria for such evaluations, could be a well-designed subjective study. (See part IV. paragraph C. below—Data Required for Evaluation.)

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(27) OTC Volume 040280.

g. *Ipecac syrup.* The Panel concludes that ipecac syrup is safe in the dosage ranges used as an expectorant but there are insufficient data to permit final classification of its effectiveness for OTC use as an expectorant.

(1) *Safety.* Clinical experience has confirmed that syrup of ipecac is safe in the dosage ranges used as an expectorant but there are no known studies to substantiate this belief. There are no known studies on the toxicity of ipecac as a single ingredient. The chief alkaloids of ipecac, emetine and cephaeline, are very toxic (Ref. 1). It has been shown that when these alkaloids are given parenterally (by injection), they are cumulative with toxic effects on the heart, liver, kidney, intestinal tract, and skeletal muscle (Refs. 1 and 2); however,

when given orally, there is no information on the absorption of small doses from the gastrointestinal tract, or on the cumulative effects of repeated administration. In view of possible cumulative effects from oral administration, the Panel recommends a 1-week time limit of use for any ipecac preparation except when given under the advice and supervision of a physician.

Based on the long history of use and on the available data, the Panel concludes that when given in small doses as proposed below, ipecac syrup is safe for OTC use.

(2) *Effectiveness.* In large doses, ipecac is an emetic. However, in the subemetic dosages used as an expectorant, its effectiveness is questionable. There are no acceptable clinical studies to substantiate its use as an expectorant.

Practically all the work with ipecac was done more than 2 decades ago. Animal studies using varying preparations of ipecac indicate that this drug may increase the flow of respiratory tract fluid (Refs. 3 through 7). Several controlled studies in humans with chronic cough did not demonstrate that ipecac was effective as an expectorant (Refs. 8, 9, and 10). In one study, bronchial fluid collected by bronchoscopic drainage revealed lowered viscosity following ipecac administration (Ref. 11). The available data is insufficient to make a determination that ipecac is effective, and the Panel recommends further study.

(3) *Proposed dosage.* Adult oral dosage is 0.5 to 1 ml of a syrup containing not less than 123 mg and not more than 157 mg of total ether-soluble alkaloids of ipecac per 100 ml 3 to 4 times daily. Children 6 to under 12 years oral dosage is 0.25 to 0.5 ml of syrup 3 to 4 times daily. For children under 6 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Warning:* "Do not give this product to children under 6 years except under the advice and supervision of a physician".

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

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h. *Menthol/peppermint oil (topical/inhalant).* The Panel concludes that menthol/peppermint oil is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectivness for topical or inhalant OTC use as an expectorant.

(1) *Safety.* Clinical experience has confirmed that menthol/peppermint oil (topical/inhalant) is safe in the dosage ranges used as an expectorant.

Menthol is the chief constituent of peppermint oil, comprising not less than 50 percent. It may be obtained by distillation of the oil or by synthesis (Ref. 1). Toxic effects with an excess ingestion of peppermint oil or mentholated products can include abdominal pain, nausea, vomiting and symptoms of central nervous system depression, such as dizziness, staggering gait, slowed respiration, flushed face, sleepiness, and coma (Refs. 2 and 3). The fatal oral dose of menthol itself in man is about 2 gm (Ref. 4). Topically applied menthol produces a cooling sensation presumably due to stimulation of the cold sensory receptors, whereas higher concentrations have irritant properties. In one study, a 20 percent solution of menthol in oil rubbed on to the skin induced an intense and lasting cooling sensation followed by numbness with slight burning and skin redness. A 0.5 precent solution applied to the nasal or oral mucosa was subjectively irritating whereas a 0.2 percent solution was judged nonirritating (Ref. 5). A study of 223 subjects in which an ointment containing several volatile substances including menthol 2.8 percent was applied for 48 hours to areas of intact skin under a patch and to abraded skin revealed no instances of inflammation, wheal, hives, or primary irritation following the period of exposure (Ref. 6). Repeated topical application of mentholated products has been reported to give rise to hypersensitivity reactions, including contact dermatitis (Ref. 4). A study of ten subjects who received an application of an ointment containing several volatile substances including menthol 2.8 percent to their trunks 3 times daily for 3 weeks, then 1 week off, followed by another week of treatment, revealed no local reactions during this subsequent challenge phase (Ref. 7). One study suggests that the incidence of hypersensitivity to menthol appears to increase with increased duration of use. This survey revealed an incidence of less than 1 percent menthol hypersensitivity in 542 patients using a mentholated ointment for less than 10 years, whereas an incidence of 3.4 percent hypersensitivity was seen in 414 patients using this type of a preparation for longer than 10 years (Ref. 8).

In infants and small children, nasal ointment or drops containing menthol may cause spasm of the glottis and cases of dangerous asphyxiation have been reported in infants following local application of menthol. For this reason a warning against the topical application of menthol-containing products directly to the nostrils of infants has been recommended (Refs. 4 and 9). A study of infants and children with respiratory infection who received an ointment containing a mixture of volatile oils including 2.8 percent menthol applied to the chest and neck demonstrated no adverse effect from the inhaled vapors by that route of administration on the rate of clearing of laryngeal inflammation. In this study 35 children, 23 under 2 years of age, with respiratory infection received only standard forms of therapy, e.g., antibiotics and fluids, while 37 children, 30 under 2 years of age, received standard therapy plus the mentholated ointment applied to the chest and neck. Laryngoscopic examination revealed comparable rates of clearing of laryngeal inflammation (Ref. 10).

A liquid mixture of volatile substances including 3.66 percent menthol is placed in the water of a hot steam vaporizer and administered via inhalation. A number of studies involving nearly 900 subjects in which this mixture was administered at recommended doses was not associated with significant complaints of subjectively perceived adverse effects (Refs. 11 through 23). Exaggerated-use studies in adults and children, i.e., exposure for several hours to higher than recommended exposure concentrations either due to sitting in closer proximity to the vaporizer or placing 2 to 5 times the recommended dose of the volatile substance in the vaporizer was not associated with irritating or toxic effects (Refs. 24 and 25).

In two studies, 40 healthy subjects asked to dissolve two candy-base lozenges, each lozenge containing 1.36 mg of menthol together with other volatile oils, every 20 minutes for 2 hours exhibited no adverse effects with the exception of one report of nausea and vomiting. This was attributed to a dislike for the wild cherry flavor of the lozenge (Refs. 26 and 27). In a group of 70 healthy subjects, 50 adults and 20 children ages 8 to 12, half dissolved a menthol-eucalyptus lozenge containing

9.62 mg menthol and 5.55 mg eucalyptus oil every 4 to 8 hours on 2 successive days, the other half dissolved the cough drop base without the aromatics. In this intensive dosage schedule, a slightly larger number of subjects demonstrated mild irritation of the oral mucosa on day 1 and day 2, but there were no differences between the two groups in the severity of irritation or residual findings after day 2. No systemic complaints were reported (Ref. 28). A similar study using a lozenge formulation containing menthol 8.14 mg and eucalyptus oil 4.625 mg versus a lozenge base without volatile substances produced comparable results (Ref. 29).

An aerosolized dosage form of volatile substances including 1 percent menthol has also been utilized for treatment of nasal congestion and cough symptoms. Rats exposed to acute overdoses of the spray in a confined chamber for 6 hours revealed no untoward behaviorial responses or airway tissues abnormality upon autopsy examination (Ref. 30). A group of four monkeys were exposed to 200 gm per day of the aerosol, i.e., 2 gm of menthol total dose in divided doses over an 8-hour period for 14 consecutive days in a confined chamber. Eye irritation was the only pharmacotoxic sign observed during the study (Ref. 31). In humans, such aerosol sprays have been generally safe when used as directed, but there have been reports of deaths from deliberate sniffing abuse, particularly when the subject inhales from a plastic bag into which the material has been sprayed (Ref. 32). Furthermore, one commercial preparation containing a particular solvent, 1,1,1-trichloroethane, was recently recalled from the market due to potential hazards of this substance (Ref. 33).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of menthol/peppermint oil (topical/inhalant) as an expectorant. Its effectiveness is uncertain due to lack of properly controlled studies of the substance by itself.

The local anesthetic effect of menthol vapor has been the justification for including menthol in topically administered ointments and lozenges for alleviation of cough. In a crossover study involving 16 subjects the effects of a 2.8 percent mentholated petrolatum ointment applied to the chest of the subjects was compared to an ointment containing several volatile substances including 2.8 percent menthol, and to petrolatum in suppressing a citric acid aerosol-induced cough. A combination ointment containing menthol induced a significant decrease in cough counts at all challenge times from ½ hour through 2 hours, averaging about 20 percent decrease at the ½ and 1 hour intervals, whereas the single ingredient menthol ointment yielded a significant decrease in cough counts just at the ½ and 1 hour intervals, averaging about 10 percent reduction. The petrolatum yielded no significant decrease in cough counts compared with base line (Ref. 34). Similar results with the combination ointment containing 2.8 percent menthol were obtained in two additional induced-cough studies conducted by the same investigator (Refs. 34 and 35).

A single-blind crossover cough-counting study of 27 patients exhibiting stabilized chronic cough utilized twice daily chest applications of either the ointment containing several volatile substances including 2.8 percent menthol, an ointment containing 1.3 percent eucalyptus oil, or petrolatum base. Neither the ointment mixture nor the eucalyptus oil ointment induced a significant decrease in cough counts compared to placebo after the morning application, but a significant 20 percent cough-count reduction compared to placebo was obtained following the afternoon dose of the ointment mixture. An average reduction in cough counts of about 10 percent compared to placebo was noted following the afternoon dose of eucalyptus oil ointment, but this was not statistically significant (Ref. 36).

A liquid mixture of volatile substances added to the water of a hot steam vaporizer and administered via inhalation contained menthol 3.66 percent, camphor 7 percent, eucalyptus oil 1.7 percent, and tincture of benzoin 5 percent. Three crossover studies compared the effects of this volatile substance containing liquid in steam, 1 tablespoonful per quart of water, to steam alone in suppressing coughs artifically induced by the citric acid aerosol technique. In each case both steam and medicated steam induced a statistically significant reduction in cough counts during the period of administration. In two of the studies the cough reduction with the medicated steam was statistically greater than with steam alone and persisted beyond the period of actual administration to the subject (Refs. 37, 38, and 39). Subjective evaluation studies of adults and infants having cough associated with respiratory infection demonstrated statistically significant antitussive effectiveness of the volatile substances in steam, 1 tablespoon per quart of water, and of steam alone. In some of these studies the effect of the medicated steam was judged statistically superior to the steam alone (Refs. 40, 41, and 42).

The variety of lozenge preparations containing a mixture of volatile substances including menthol have been studied for their ability to suppress citric acid aerosol induced cough in normal subjects. Since each of these lozenge preparations contain different concentrations of menthol and other volatile substances, the results of the study will be individually summarized. The general study format involved an unblinded crossover design in which a group of cough-standardized normal subjects were tested with each of two lozenge formulations, the active formulation and its vehicle control, against cough artificially induced by the citric acid aerosol technique. Two studies involved lozenges in which menthol was the principal active ingredient and consequently represent an indication of the effectiveness of this mode of administering menthol to suppress cough. One of the studies involving 16 subjects used a lozenge containing menthol 2.64 mg and peppermint oil 2.29 mg plus benzyl alcohol 5.76 mg. The active formulation produced significant cough reductions at the 10- to 40-minute challenge periods, reaching a peak of 30 to 35 percent at the 10- and 20-minute intervals whereas the control lozenge produced a significant reduction of 15 to 20 percent at the 10- and 20-minute intervals only (Ref. 43). The other study of ten subjects utilizing a lozenge containing menthol 1.13 mg plus citric acid flavoring produced greater cough reduction than the control lozenge at the 10- through 30-minute challenge periods although both the active and control lozenges in this study produced cough reductions at these time intervals (Ref. 44).

Two studies involving a total of 40 subjects used similar active formulations consisting of menthol 9.6 mg and eucalyptus oil 5.5 mg per lozenge. In these studies the active formulation produced significant cough reductions at the 10- to 40-minute challenge periods, reaching a peak of 25 to 35 percent reduction at the 10- and 20-minute intervals whereas the control lozenge produced a significant reduction of 10 to 15 percent maximum at only the 10-minute challenge (Refs. 45 and 46). In a study of nine subjects receiving lozenge doses of menthol 1.5 mg and eucalyptol 0.35 mg, elevated citric acid thresholds of 130 to 146 percent of control for 3 to 5 hours after dosing were obtained, although a placebo control lozenge was not utilized in this study for comparison (Ref. 47). Another study of 20 subjects utilizing a formulation of menthol 2.78 mg, eucalyptus oil 0.77 mg plus smaller amounts of camphor, thymol, and tolu balsam, produced significant cough reductions at the 10- through 40-minute challenge periods, reaching a peak of 35 percent reduction at the 10- and 20-minute intervals whereas a control lozenge produced a significant reduction of 11 to 17 percent maximum at the 10- and 20-minute challenge periods only (Ref. 48). Similar results were obtained in 16 subjects using an active formulation containing menthol, eucalyptus oil, camphor, thymol, and tolu balsam present in about ½ the amounts utilized in the preceding study (Ref. 49).

(3) *Proposed dosage.* Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 2.8 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapors rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 3.66 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl, or washbasin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For topical use as a lozenge 1.0 to 12 mg: Allow lozenge to dissolve

slowly in mouth. May be repeated every ½ to 1 hour.

For children under 2 years, there is no recommended topical or inhalant dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: *Warning:* "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: *Warning:* "For steam inhalation only. Do not take by mouth".

(5) *Evaluation.* The Panel made the following recommendations: (i) For topical ointment use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

(iii) For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

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1. *Pine tar preparations (extract white pine compound, pine tar, syrup of pine tar, compound white pine syrup, white pine).* The Panel concludes that pine tar preparations are safe in the dosage range used as expectorants but effectiveness at those dosages has not been established.

(1) *Safety.* Clinical experience has confirmed that the pine tar preparations are safe in the dosage ranges used as expectorants. The above preparations are administered orally for an expectorant activity. The active ingredient is pine tar, a product obtained by the destructive distillation of wood of various species of pine, usually "Pinus palustrus." It is a viscid blackish-brown noncrystalline

liquid. It has a turpentine-like odor and a sharp taste of organic decomposition. It has been used mainly for diseases of the skin, being slightly irritating, antiseptic, and with local anesthetic properties.

The Panel is unaware of any studies to evaluate the safety of pine tar. It is probably safe in the recommended doses since it has been used for decades without any recorded reports of adverse effects (Refs. 1 through 4).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of pine tar preparations as expectorants. The use of pine tar preparations as expectorants appears to be based solely on tradition. There is no evidence that they are effective as an expectorant when taken orally.

(3) *Proposed dosage.* Adult oral dosage is 1.6 mg every 3 to 4 hours. Children 6 to under 12 years oral dosage is 0.8 to 1.0 mg every 3 to 4 hours. Children 2 to under 6 years oral dosage is 0.4 to 0.5 mg every 3 to 4 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness as an expectorant will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

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j. *Potassium guaiacolsulfonate.* The Panel concludes that potassium guaiacolsulfonate is safe in the dosage ranges used as an expectorant but there are insufficient data to permit final classification of its effectiveness for OTC use as an expectorant.

(1) *Safety.* Clinical experience has confirmed that potassium guaiacolsulfonate is safe in the dosage ranges used as an expectorant. There is no evidence of toxicity in the available literature. Information is sparse, and there is no documentation of adverse reactions.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of potassium guaiacolsulfonate as an expectorant. While subjective studies would indicate that it is ineffective as an expectorant (Refs. 1 and 2), potassium guaiacolsulfonate has been used empirically, for many decades, in expectorant mixtures. Connell, et al. (Ref. 3) showed no change in water content of the respiratory tract of rats. Two papers cited that potassium guaiacolsulfonate is not metabolized to guaiacol (Refs. 1 and 2).

Many of the submissions to the Panel listed preparations containing potassium guaiacolsulfonate at 80 to 90 mg/5 ml with 1 tablespoonful recommended as the adult dose (240 to 270 mg per dose). One study, however, employed an adult dose of 500 mg (Ref. 4). Based on the scanty evidence, the Panel concludes that there is a wide dose range with no specific optimum level for expectorant activity.

(3) *Proposed dosage.* The Panel is unable to determine a proposed dosage. The Panel concludes that the pharmaceutical industry should consult with the Food and Drug Administration as to a suitable proposed dosage for testing. Otherwise, the Panel recommends that each drug manufacturer evaluate the dosage as labeled on the manufacturer's marketed product(s).

(4) *Labeling.* The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

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k. *Sodium citrate.* The Panel concludes that sodium citrate is safe in the dosage range used as an expectorant but there are insufficient data to permit final classification of its effectiveness for OTC use as an expectorant.

(1) *Safety.* Clinical experience over more than a half a century has confirmed that sodium citrate is safe in the dose ranges used as an expectorant. It is mildly diuretic and, in larger doses, may be laxative. Gastric irritation can be produced if taken undiluted (Ref. 1).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of sodium citrate as an expectorant. Goodman and Gilman (Ref. 1) states that the use of citrates as expectorants is mainly empirical and it is "probable that the water ingested with them is the basis for any beneficial effect." A similar preparation, potassium citrate was found to have very little effect upon the output of respiratory tract fluid in a dose as high as 0.4 gm/kg of body weight (Ref. 2).

(3) *Proposed dosage.* Adult oral dosage is 1.0 to 2.0 gm every 2 to 4 hours taken well diluted with at least ½ glass of water or fruit juice (Ref. 3). Children 6 to under 12 years oral dosage is 0.5 to 1.0 gm every 2 to 4 hours diluted as above with water or fruit juice. Children 2 to under 6 years oral dosage is 250 to 500 mg every 2 to 4 hours diluted as above with water or fruit juice. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Warnings:* (i) *"Caution:* This product must be taken with adequate amounts of fluids (½ to 1 glass) with each dose".

(ii) *"Caution:* Do not take this product if you have heart trouble or kidney disease except under the advice and supervision of a physician".

At smaller amounts, less than the proposed doses above, sodium citrate has been employed in liquid mixtures for its mild saline taste. In these instances, it is not classified as an active ingredient, and no labeling claim should be made for it since it is being used as a flavoring agent.

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

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(2) Boyd, E. M., B. Palmer and B. Pearson, "Is There Any Advantage in Combining Several Expectorant Drugs in a Compound Cough Mixture?" *Canadian Medical Association Journal*, 54:216–220, 1946.

(3) *Remington's Practice of Pharmacy*, 12th Ed., Edited by Martin, E. W., p. 814, 1961.

1. *Terpin hydrate preparations (terpin hydrate, terpin hydrate elixir).* The Panel concludes that terpin hydrate is safe in the dosage ranges used as an expectorant but there are insufficient data to permit final classfication of its effectiveness for OTC use as an expectorant.

(1) *Safety.* Clinical experience has confirmed that terpin hydrate is safe in the dosage ranges used as an expectorant.

A few papers noted gastrointestinal distress from dosages of 340 to 680 mg/24 hours, with nausea and vomiting (Refs. 1 and 2). Elixir terpin hydrate has a high alcoholic content of approximately 42 percent which could be subject to alcohol abuse (Ref. 3). The Panel has recognized the potential for such abuse as stated in a previous section of this document. (See part II. paragraph G. above—Drug Misuse and Abuse.) Based on the available data and its long history of use, the Panel concludes that terpin hydrate is safe for OTC use in the dosages discussed below. However, because of the high alcohol content required to formulate and manufacture elixir terpin hydrate, the Panel recommends that elixir terpin hydrate not be used in children younger than 12 years.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of terpin hydrate as an expectorant. The majority of papers in the literature question the effectiveness of terpin hydrate and indicate that it is probably harmless and useless (Refs. 2 through 5). Two papers indicate that at a dose of 300 mg 4 times daily, it had a "loosening effect," but these were subjective evaluations (Refs. 6 and 7). The Panel concludes that the information available is not sufficient to determine that terpin hydrate is effective as an expectorant.

(3) *Proposed dosage.* Adult oral dosage is 200 mg every 4 hours not to exceed 1200 mg in 24 hours. The elixir should not be given to children under 12 years of age but terpin hydrate by itself or in a nonalcoholic mixture can be used. Children 6 to under 12 years oral dosage is 100 mg every 4 hours not to exceed 600 mg in 24 hours. Children 2 to under 6 years oral dosage is 50 mg every 4 hours not to exceed 300 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Warnings.* (i) "May produce nausea and vomiting".

(ii) For elixir products containing 42 percent alcohol: *"Caution:* This product contains 42 percent alcohol and should not be given to children under 12 years except under the advice and supervision of a physician".

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

REFERENCES

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(2) Hirsch, S. R., "The Use of Expectorants," *Wisconsin Medical Journal*, 70:153–156, 1971.

(3) Anonymous, "Cough Remedies," *The Medical Letter on Drugs and Therapeutics*, 13:9–11, 1971.

(4) Richerson, H. B., "Expectorants," *Journal of the Iowa Medical Society*, 58:875–876, 1968.

(5) Grzybowski, S., "Cough Medicines," *Canadian Medical Association Journal*, 92: 619–620, 1965.

(6) Rose, I., "The Ineffectiveness of Expectorants," *Canadian Medical Association Journal*, 69:494–495, 1953.

(7) Boyd, E. M., "Expectorants and Respiratory Tract Fluid," *Pharmacological Reviews*, 6:521–542, 1954.

m. *Tolu preparations (tolu, tolu balsam, tolu balsam tincture).* The Panel concludes that tolu balsam is safe in the dosage range used as an expectorant but there are insufficient data to permit final classification of its effectiveness for OTC use as an expectorant.

(1) *Safety.* Clinical experience has confirmed that tolu preparations are safe in the dosage ranges used as expectorants. Tolu balsam can be considered safe in the dosages used for expectorant activity when administered orally or by inhalation.

There is no documentation as to toxicity at the dose levels in general usage in man. One report (Ref. 1) states that huge doses, "1,000 times that recommended," when given by inhalation produced an acute inflammation of the tracheal lining in rabbits.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of tolu preparations as expectorants. There is no evidence that tolu balsam possesses expectorant activity.

Several reports by Boyd and his coworkers (Refs. 2 through 4) are conflicting and consist for the most part of statements rather than data from studies, i.e., "Syrup of Tolu did have an expectorant action." Certain volatile oils (Friar's balsam) stimulate the output of respiratory tract fluids (RTF) or bronchial secretions (Ref. 3). In another paper (Ref. 4), the author states that inhalation by animals of therapeutic doses of certain volatile oils (Friar's balsam) has no effect upon respiratory tract fluids. A standard text states that tolu balsam syrup is "widely employed as a vehicle for expectorant drugs but has no specific virtue for this purpose" (Ref. 5). The Panel takes cognizance of the fact that tolu balsam has been used for many decades as an ingredient in steam inhalations and in oral expectorant mixtures but concludes that there are insufficient data to determine the effectiveness of tolu balsam as an expectorant.

(3) *Proposed dosage.* Adult oral dosage is 50 mg every 2 to 3 hours. Children 6 to under 12 years oral dosage is 25 mg every 2 to 3 hours. Children 2 to under 6 years oral dosage is 12.5 mg every 2 to 3 hours. For children under 2 years, there is no recommended dose except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

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(2) Boyd, E. M., "Expectorants and Respiratory Tract Fluid," *Pharmacological Reviews*, 6:521–542, 1954.

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n. *Turpentine oil (spirits of turpentine) (topical/inhalant).* The Panel concludes that turpentine oil is safe in the dose ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as an expectorant.

(1) *Safety.* Clinical experience has confirmed that turpentine oil is safe when applied topically or used as an inhalant in the dose ranges used as an expectorant. The Panel concludes that oil of turpentine is safe when applied externally or vaporized in boiling water as a steam inhalant. However, the Panel has determined elsewhere in this document that it is not safe for OTC use when used orally as an expectorant. (See part IV. paragraph B.2.f. above—Turpentine oil (spirits of turpentine) (oral).)

Oil of turpentine is a volatile oil consisting of a mixture of pinenes derived from the oleoresin obtained from Pinus palustrus. Nelson et al. (Ref. 1) found exposure to a vapor of 420 to 560 mcg/l acceptable to most of their human subjects. The threshold for industrial exposure for 8 hours has been set at 560 mcg/l. The maximum concentration obtainable with a currently marketed OTC preparation is 36 mcg/l (Refs. 2 and 3). No histological evidence of pulmonary lesions were seen in mice and rats exposed to lethal concentrations of turpentine vapors (Ref. 4). Inhalation of 300 mcg/l of turpentine vapor by mice for 15 minutes did not influence the electrocardiogram, respiratory minute volume, pulmonary airway, resistance or compliance (Ref. 5). One study in mice using a mixture of volatile oils, one of which was turpentine, showed a decrease in pulmonary antibacterial activity (Ref. 6). Two other studies showed no change when the mixture was used (Refs. 7 and 8).

In several studies in children and infants suffering from minor breathing discomforts associated with the "common cold," no side effects that were drug related were observed when a medicated steam was administered (Refs. 9 through 13). Turpentine has been widely used as a part of a mixture of volatile oils for many years, with approximately two complaints per million packages purchased (Ref. 14).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of turpentine oil as an expectorant when applied externally or vaporized in boiling water as a steam inhalant due to a lack of objective measurement studies of the substance by itself.

(3) *Proposed dosage.* Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 4.0 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help

the vapor rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use a 5.5 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl, or washbasin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

For children under 2 years, there is no recommended topical or inhalant dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for expectorant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: *Warning:* "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: *Warning:* "For steam inhalation only. Do not take by mouth".

(5) *Evaluation.* The Panel made the following recommendations: (i) For topical ointment use: Data to demonstrate effectiveness will be required from only one additional well-controlled cough-counting objective study in patients with coughs due to respiratory disease in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing expectorant drugs. (See part IV. paragraph C. below—Data Required for Evaluation.)

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(14) OTC Volume 040279.

Category III Labeling

The Panel concludes that substantiation by additional data is required before statements regarding duration of action, e.g., "all day", "all night", "for hours" will be acceptable. Such statements must specify in the labeling the number of hours of relief claimed. The statements must be verified by appropriate documentation.

C. DATA REQUIRED FOR EVALUATION

The Panel has agreed that the protocols recommended in this document for the studies required to bring a Category III drug into Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved methodology in the future.

1. *Principles in the design of an experimental protocol for testing expectorant drugs.* a. *General principles.* The effectiveness of an expectorant preparation is based on its ability to facilitate the removal of sputum from the respiratory passageways and thus clear the airway of retained secretions. By aiding in the removal of these secretions and through a soothing effect on irritated mucous membranes, it will indirectly ease the act of coughing. While the ease in raising secretions may seem simple to measure and assess, there are, at present, no suitable objective methods for evaluating this. This difficulty stems, in part, from a lack of basic knowledge concerning the biochemical and physiochemical nature of respiratory tract secretion in various respiratory diseases, as well as the changes produced by expectorant drugs, and the lack of evidence as to which property of sputum correlates best with ease of expectoration. Because of this, the subjective evaluation of the patient must be relied upon the assessment of the drug's expectorant activity.

b. Selection of patients. Based upon the method of study to be used, two types of patients may be selected. One patient type who would be chosen for a crossover study could include subjects with chronic cough due to chronic pulmonary disease such as chronic bronchitis, pulmonary emphysema, inactive pulmonary tuberculosis, etc., and whose condition is relatively stable with no evidence of intercurrent infection that would affect cough or character of the sputum. A second patient type could include subjects with an acute upper respiratory infection, such as an acute bronchitis or tracheobronchitis, in which a dry nonproductive cough is a prominent feature. Because the production of respiratory secretions may be influenced by other systems, such as the circulation, patients with congestive heart failure or significant renal or hepatic disease must be excluded. Furthermore, every effort must be made to maintain the same relative state of hydration and activity, and drugs must be prohibited that may affect sputum, such as the anticholinergics and antihistamines. While nonsmokers would be preferable as subjects, the smoking habits of patients must be carefully documented and maintained at the same level throughout the clinical trials. No smoking would be permitted during the actual recording sessions. While impractical to control, the effect of environmental factors such as temperature, humidity, and degree of air pollution should be recognized.

c. *Methods of study* (1) *Double-blind crossover design in patients with chronic lung disease.* A suitable period for baseline studies must be performed prior to the administration of the test drugs. During this period, the following subjective indices will be noted: Ease of expectoration; character of the cough (whether productive or not); frequency of coughing; and breathing comfort, i.e., heavy, noisy, rattling, etc. Additional help in evaluating effectiveness may be provided by some objective indices such as: The volume and dry weight of sputum collections over a given time (12 to 24 hours); the character and color of the sputum raised; and some measure of its flow properties, such as viscosity or consistency. If a cough suppression claim is to be substantiated, an objective cough-counting study must be done as discussed under antitussives. (See part III. paragraph C. above—Data Required for Evaluation.) Following baseline studies, similar observations are obtained during the administration of the drug and placebo which must be indistinguishable from each other, randomized, and provided at a dose and time sequence recommended for OTC use. This type of study would require approximately 3 weeks, 1 week on each preparation and 1 week for the baseline data.

(2) *A randomized double-blind design in patients with acute upper respiratory infections.* Groups of patients would receive either a placebo or the drug under study in a similar dose and time interval as recommended for OTC use over a period of 3 to 5 days. Similar observations, as discussed above, would be obtained where possible to evaluate effectiveness, but no prior baseline period would be obtainable with this model and most of the data would be limited to the subjective indices. Patient diaries would be kept in which the type of symptoms, their duration and severity as well as adverse reactions would be recorded daily.

d. *Interpretation of data.* Evidence of drug effectiveness is required from a minimum of three positive studies based on the results of three different investigators or laboratories. At least one of the three studies must be in patients with chronic pulmonary disease. Approximately 20 to 30 patients will be required for the crossover study described above. Because of the marked variability in cough and sputum production in acute respiratory disease from day to day together with the spontaneous waning of

symptoms as part of its natural history, a much larger number of patients, possible 75 or more, must be studied for this group. The subjective indices to be evaluated can be scored for statistical analysis, with a p value of 0.05 or less (95 percent confidence level) being acceptable as evidence of a drug effect when compared with placebo.

All data submitted to the Food and Drug Administration must present both favorable and any unfavorable results.

e. *Evaluation of safety.* Tests for safety of expectorant ingredients not reviewed by this Panel should involve the usual animal studies and observations in man relevant to various organs and system, i.e., cardiovascular, respiratory, renal, hepatic, cerebral, and hematologic. Of special note insofar as expectorant drugs may be concerned are such factors as carcinogenicity, effect on clotting mechanisms, thyroid function, electrolyte and acid-base balance, in addition to the general areas mentioned above.

V. Bronchodilators

A. General Discussion

Bronchodilators are agents used for the symptomatic treatment of the wheezing and shortness of breath associated with asthma. These agents are used to overcome the spasm that causes narrowing of the bronchial air tubes. These drugs are also used but are much less effective in relieving the shortness of breath of chronic bronchitis and emphysema. The drugs most commonly used as bronchodilators are some sympathomimetics (sympathomimetic amines), theophylline, and theophylline salts. The Panel has classified these two major forms of bronchodilators, i.e., sympathomimetic amines and theophyllines, as distinct pharmacologic groups. The sympathomimetic amines and theophyllines work well when given together, but it is preferable that the dose of each should be individualized for each patient (Ref. 1).

The sympathomimetics may be given orally (ephedrine and methoxyphenamine), by aerosol inhalation (epinephrine solution), by rectal installation, by injections under the skin or into the muscle of the upper arm or buttocks, and in some situations under medical supervision sympathomimetics may be used under the tongue.

Theophyllines are usually given by oral administration but they may also be given, under medical supervision, by the rectal route or by intravenous injection. The oral preparations of theophylline are not affected by food in the stomach (Ref. 2). Excessive doses result in high blood levels which cause nausea and vomiting. Individuals metabolize these drugs at different rates. Therefore, some patients require only a relatively small dose of the drug while others require quite large doses for a satisfactory effect. Occurrence of nausea or vomiting will indicate when the dose of drug is excessive. Only one of the theophyllines and only one route of administration should be used at a time because of the additive effects of these drugs.

Adverse reactions associated with the sympathomimetic bronchodilators consist primarily of those affecting the cardiovascular and central nervous systems. These drugs may cause arrhythmias, hypertension, dizziness, tremor, nervousness, and sleeplessness. They may also cause a rise in blood sugar concentration and in older men they may cause slowing or even obstruction to the urinary stream. Because of these possible reactions, the drugs should be used with caution in individuals with cardiac disease, hypertension, hyperthyroidism, diabetes, or prostatic enlargement.

The theophyllines given orally or rectally may produce nausea and vomiting which, in extreme cases, may result in dehydration and shock.

Theoretically a combination product containing a theophylline drug and a sympathomimetic to be taken by mouth, for example, as a tablet, should be very effective and convenient. However, to obtain the most effective bronchodilation, the dose of theophylline should be individualized because of individual variation in the metabolic breakdown of theophyllines (Ref. 3).

The Panel is concerned that in a patient who is a rapid metabolizer of theophylline, a fixed-dose of a theophylline and a sympathomimetic in an oral combination product might have reduced effectiveness because of a low theophylline dose. If the number of dosage units, e.g., combination tablets taken, is increased to provide an effective theophylline dose, the dose of sympathomimetic might be excessive and cause side effects. Conversely, in a patient who is a slow metabolizer of theophylline, the standard dose of an oral combination product of theophylline and a sympathomimetic might produce theophylline toxic effects. If the number of combination tablets is decreased to avoid these side effects, then the dose of sympathomimetic might be so low as to have a low effectiveness.

Therefore, it would appear that single ingredient preparations containing either a theophylline or a sympathomimetic would be both more effective and have increased safety as compared to combination products.

Although the bronchodilators are generally safe for OTC use at recommended dosage and are effective in relieving the shortness of breath caused by bronchospasm, the Panel emphasizes that these preparations should not be used unless a diagnosis of asthma has been made by a physician and a dosage schedule of OTC medicine has been established by a physician.

Patients with asthma may also require prescription drugs which may have serious dangers and side effects and there is, then, an added need for continued medical supervision.

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B. Categorization of Data

1. Category I conditions under which bronchodilator ingredients are generally recognized as safe and effective and are not misbranded.

Category I Active Ingredients

The Panel has classified the following bronchodilator active ingredients as generally recognized as safe and effective and are not misbranded:

Sympathomimetic amines

Ephedrine preparations: Ephedrine, Ephedrine hydrochloride, Ephedrine sulfate, Racephedrine hydrochloride

Epinephrine preparations (inhalant): Epinephrine, Epinephrine bitartrate, Epinephrine hydrochloride (racemic)

Methoxyphenamine hydrochloride

Theophyllines

Theopyhiline preparations: Aminophylline, Theophylline anhydrous, Theophylline calcium salicylate, Theophylline sodium glycinate

a. *Ephedrine preparations (ephedrine, ephedrine hydrochloride, ephedrine sulfate, racephedrine hydrochloride).* The Panel concludes that ephedrine preparations are safe and effective for OTC use as bronchodilators as specified in the dosage section discussed below.

(1) *Safety.* Ephedrine, when absorbed systemically, has effects both on the brain (central) and on nerve endings (peripheral) (Ref. 1). In clinical usage, the central effects are stimulatory and include tenseness, nervousness, tremor and sleeplessness. Peripheral effects include bronchodilatation, and possibly shrinkage of mucous membranes (decongestion), although this has not been documented. Other peripheral effects include awarness of heartbeat and rapid heart beat accompanied usually by some elevation of blood pressure. However, a study by Dulfano and Glass on 26 asthmatics between the ages of 28 and 61 years showed that a single dose of 25 mg had no significant effect on either heart rate or blood pressure (Ref. 2). Another recent study of the cardiovascular effects of 25 mg ephedrine in 20 asthmatics showed there was only a modest increase in heart rate up to 11 beats per minute as a maximum, and the systolic and diastolic blood pressure showed no significant change (Ref. 3). In spite of these findings, the cardiovascular and central effects appear to set limits on dosage, limits which vary widely among patients as judged by clinical experience. Loss of appetite and nausea also occur in some patients. Difficulty in urination may occur in older males who might have enlarged prostate glands. The drug, under these circumstances, exacerbates obstruction to urine flow by causing spasm of the outlet of the bladder. Overdosage results in exaggeration of the side effects which patients describe as disagreeable and can usually be depended upon to prevent overuse or abuse. Ordinary doses may cause marked and potentially dangerous increases in blood pres-

sure in patients taking drugs containing monoamine oxidase (MAO) inhibitors.

(2) *Effectiveness.* The bronchodilator effects of ephedrine taken by mouth are slow in onset, probably 15 to 25 minutes, and probably persist for 2 to 3 hours, based on the Panel's clinical observations. The drug is less effective as a bronchodilator than epinephrine, and its usefulness is limited to the milder forms of asthma.

A dose of 25 mg by mouth given to asthmatic patients prevented the bronchospasm induced by various chemicals (Ref. 4). The fall in vital capacity induced by histamine was prevented to the extent of 40 percent and that by methacholine to the extent of 32 percent (Ref. 4). Although based on objective measurements, this study does not seem to have been rigorously planned or executed as judged by today's standards.

In a double-blind comparison of 24 mg ephedrine and a combination of 24 mg ephedrine and 130 mg theophylline, measurements including specific airway resistance, vital capacity, and FEV_1 (forced expiratory volume in one second—a measurement related to airway obstruction, the higher the figure the better the airflow and the less the obstruction in the air tubes) showed that ephedrine significantly decreased the first and increased the last two over a period of 2 hours, an effect that was enhanced and prolonged by the presence of theophylline (Ref. 5). Each preparation also contained 8 mg of phenobarbital. Although a placebo was not included, these findings carried out with sophisticated objective measurements, strongly support a bronchodilator effect for ephedrine.

In a study comparing ephedrine and terbutaline in 26 asthmatics, it was shown that 25 mg ephedrine resulted in a maximal change of FVC 11 percent, FEV_1 18 percent, MVV 17 percent, MMF 25 percent, and MEFR 24 percent over the controlled figures. The improvement in the pulmonary function tests were statistically significant between 120 and 240 minutes after taking a single dose. The results were similar to 2.5 mg terbutaline but were less than the effect of 5.0 mg terbutaline (Ref. 2).

In a recent study of 20 patients with asthma, 25 mg ephedrine showed effective bronchodilation for up to 4 hours (the respiratory function tests of FVC, FEV_1 and airway resistance were used) (Ref. 3).

(3) *Dosage.* Adult oral dosage is 12.5 to 25 mg not more often than every 4 hours not to exceed 150 mg in 24 hours. Children 2 to under 12 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician. There is insufficient information as to the possible toxic effect of ephedrine in this age group.

The Panel strongly recommends that ephedrine be available as scored tablets containing 12.5 mg and 25 mg ephedrine per tablet to permit flexibility in dosage.

(4) *Labeling.* The Panel recommends the Category I labeling for bronchodilator active ingredients. (See part V. paragraph B.1. below—Category I Labeling.) In addition the Panel recommends the following specific labeling: *Warnings.* (i) "*Caution:* Do not continue to take this product but seek medical assistance immediately if symptoms are not relieved within 1 hour or become worse".

(ii) "Nervousness, tremor, sleeplessness, nausea and loss of appetite may occur".

(iii) "Do not take this product if you have heart disease, high blood pressure, thyroid disease, diabetes, or difficulty in urination due to enlargement of the prostate gland".

(iv) *Drug Interaction Precaution.* "Do not take this product if you are presently taking a prescription antihypertensive or antidepressant drug containing a monoamine oxidase inhibitor".

(v) "Do not give this product to children under 12 years except under the advice and supervision of a physician".

(vi) *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 6 to under 12 years oral dosage is 6.25 to 12.5 mg not more often than every 4 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is 0.3 to 0.5 mg/kg of body weight not more often than every 4 hours not to exceed 2 mg/kg of body weight in 24 hours.

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b. *Epinephrine preparations (epinephrine, epinephrine bitartrate, epinephrine hydrochloride (racemic)) (inhalant).* The Panel concludes that epinephrine is safe and effective for OTC use as a bronchodilator as specified in the dosage section discussed below.

(1) *Safety.* Wide use of epinephrine aerosols for temporary relief of spasm that causes narrowing of air tubes has been attended by few and mild side effects. However, one early report by Benson and Perlman (Ref. 1) raised the possibility that excessive use of epinephrine aerosols caused serious harm to the lining of the air tubes, resulting in an increase in air tube secretions which in turn predisposes to infection and collapse of small areas of the lungs. Alternative causes for these changes were not seriously considered. The report was retrospective and it found that a greater number of deaths occurred in users of epinephrine aerosols, 48 of 648 (7.4 percent) as compared with 22 of 1,588 nonusers (1.4 percent). The possibility that the users might have had a more severe illness than nonusers was not considered and might well explain the findings.

In a study of 86 patients with various types of cardiac involvement and 16 patients with uncontrolled diabetes who inhaled aqueous epinephrine from a nebulizer (Ref. 2), no untoward effects developed following administration of many times the dose considered to be effective in asthma, nor were there significant changes in pulse rate, blood pressure, electrocardiogram, or blood sugar level. The authors conclude that the presence of cardiovascular disease or diabetes is not a contraindication to the use of d,l-epinephrine (racemic) or l-epinephrine (levorotatory) by inhalation.

Epinephrine aerosol was used for many years before its safety was seriously questioned. The question arose because of an increase in the number of deaths among those using a chemically related drug, isoproterenol, a prescription drug, which also caused aggravation of the airway obstruction in some patients.

The reports of an increase in deaths from isoproterenol had their origin in England (Ref. 3). A possible explanation was that the preparation used there had a concentration of isoproterenol 5 times greater than that used in Sweden, Australia, and the United States, where no such increase in deaths had been noted (Ref. 4). It was inferred that the high concentration of isoproterenol accounted for the increased deaths. Deaths decreased when a lower concentration of isoproterenol was used.

Aggravation of the obstructive abnormality clearly occurs in some patients with asthma following administration of isoproterenol (Ref. 5). This may be due to some fraction of absorbed isoproterenol being converted to a metabolite which could predispose to causing spasm of air tubes (Ref. 6).

It has been further observed (Ref. 7) that isoproterenol by inhalation, while producing bronchodilation, may simultaneously cause a small and usually clinically insignificant fall in blood oxygen level. That this has not been observed with epinephrine by inhalation may merely reflect the small amount of interest in this drug in the years since techniques for making the necessary measurements have become readily available, but the tests have not been done.

It is unlikely that these observations of toxicity concerning isoproterenol are relevant in judging the safety of epinephrine by inhalation. Epinephrine stimulates both alpha and beta receptors (Ref. 8) and would be expected to have a local constrictor effect on blood vessels in the lungs as it does in subcutaneous tissue, an effect expected to limit systemic absorption of the administered

drug. Isoproterenol is predominantly a stimulator of beta receptors (Ref. 8) and would be expected to cause vascular dilatation and systemic absorption of the administered drug. The relative therapeutic advantage or disadvantage of this difference between the two drugs is unknown and needs further study.

Since the isoproterenol adverse reactions are not known to bear on the safety of epinephrine by inhalation and since these postulated hazards would appear to be avoidable by using low concentrations and by instructing the patient by appropriate labeling, epinephrine by inhalation is judged by the Panel to be a safe preparation for OTC use.

One additional difficulty may arise which applies to all sympathomimetic drugs self-administered by inhalation for relief of asthma. A patient with severe and worsening obstructive pulmonary disease may obtain very temporary relief and this relief may give a false sense of security. Under such circumstances the patient may postpone calling a physician or going to a hospital until his disease has reached life-threatening severity and the suggested labeling in this document takes this possibility into account. The safety of propellants used in these preparations has not been reviewed by this Panel because they are considered to be pharmaceutical necessities which should be reviewed independently by the Food and Drug Administration. The side effects of sympathomimetics are worsened by monoamine oxidase inhibitors which prevent the breakdown of these drugs.

(2) *Effectiveness.* A number of letters from experts in the field of respiratory and allergic disease attest to the safety and effectiveness of inhaled aerosolized epinephrine (Ref. 9). In a double-blind study in asthmatics the timed vital capacity ($FEV_{0.5}$) was compared after metered inhalations of 0.125 mg epinephrine delivered per inhalation, 0.06 mg isoproterenol delivered per inhalation and a placebo (Ref. 10). The means taken to maintain experimental control are not described. Both epinephrine and isoproterenol gave significant increase within 15 minutes accompanied by symptomatic relief whereas the placebo gave little change. Side effects were not mentioned.

In a comparative study of several bronchodilator preparations including epinephrine but lacking a placebo (Ref. 11), epinephrine and the other preparations gave improved bronchial air flow in 12 asthmatic subjects. A specific bronchodilator effect for the preparations given seems highly probable but remains unestablished because of the lack of experimental control and the failure to include a placebo. In an uncontrolled study of the capacity of sympathomimetic drugs to prevent the fall in vital capacity and expiratory flow rate induced by methacholine and histamine (Ref. 12), inhaled epinephrine was effective.

(3) *Dosage.* Adults and children 4 years and above inhalation dosage is 1 to 3 inhalations of a 1 percent aqueous solution of l-epinephrine or the equivalent in a pressurized preparation not more often than every 3 hours, except under the advice and supervision of a physician. For children under 4 years, there is no recommended dosage except under the advice and supervision of a physician.

Children and adolescents should not have unsupervised access to this inhaler. There is the possibility of abuse of this material and possible adverse effects on the heart if excessively used.

(4) *Labeling.* The Panel recommends the Category I labeling for bronchodilator active ingredients. (See part V. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling for preparations of epinephrine used by inhalation: *Warnings.* (i) "Do not take this product at higher than recommended doses except under the advice and supervision of a physician for it may cause nervousness and rapid heart beat".

(ii) *"Caution:* Do not continue to take this product but seek medical assistance immediately if symptoms are not relieved within 20 minutes or become worse".

(iii) "Do not take this product if you have heart disease or high blood pressure except under the advice and supervision of a physician".

(iv) *"Drug Interaction Precaution.* Do not take this product if you are presently taking a prescription antihypertensive or antidepressant drug containing a monoamine oxidase inhibitor".

(v) "Keep this product out of reach of children and adolescents because unsupervised access may cause abuse or possible adverse effects on the heart if excessively used".

(vi) "Do not give this product to children under 4 years except under the advice and supervision of a physician".

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c. *Methoxyphenamine hydrochloride.* The Panel concludes that methoxyphenamine hydrochloride is safe and effective for OTC use as a bronchodilator as specified in the dosage section discussed below.

(1) *Safety.* In a crossover study in 12 asthmatics, comparing 100 mg methoxyphenamine orally against 30 mg ephedrine sulfate, the types of side effects noted were similar although the frequency of complaints of side effects were only about one-half as frequent with methoxyphenamine. Other studies in asthmatic patients have also reported a lower incidence of side effects, particularly blood pressure changes and central nervous system stimulation, with comparable bronchodilator doses of methoxyphenamine and ephedrine (Refs. 1 through 4). Patients with a history of ephedrine intolerance were often able to tolerate 100 to 200 mg methoxyphenamine without experiencing the usual ephedrine-like side effects of nervousness, insomnia, tremor, and headache (Refs. 2 and 5). The most common side effects of methoxyphenamine appear to be dryness of mouth and mild anorexia (Ref. 4).

(2) *Effectiveness.* In asthmatic patients, oral methoxyphenamine 200 mg and ephedrine sulfate 30 mg offered comparable protection against decreased vital capacity and asthma-like symptoms due to parenterally administered histamine or methacholine (Refs. 1 and 6). Objective measurement studies in asthmatic patients have revealed an increase in vital capacity, up to 20 percent over a 4-hour period, following oral methoxyphenamine 100 to 200 mg (Refs. 2, 4, and 7). Of 61 asthmatic patients who took 100 mg every 4 hours, 37 obtained subjective relief of breathing difficulty. Six of the remaining 24 gained relief with a 200 mg dose every 4 hours (Ref. 2).

No data on the use of methoxyphenamine in children under 12 years are available and there has been little clinical experience with this drug in children. The Panel concludes that methoxyphenamine should not be used in children under 12 years until such time as satisfactory evidence of safety and effectiveness is available.

(3) *Dosage.* Adult oral dosage is 100 mg every 4 to 6 hours not to exceed 600 mg in 24 hours. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for bronchodilator active ingredients. (See part V. paragraph B.1 below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Warnings.* (i)

"*Caution:* Do not continue to take this product but seek medical assistance immediately if symptoms are not relieved within 1 hour or become worse."

(ii) "Nervousness, tremor, sleeplessness, nausea and loss of appetite may occur".

(iii) "Do not take this product if you have heart disease, high blood pressure, thyroid disease, diabetes or difficulty in urination due to enlargement of the prostate gland".

(iv) "'*Drug Interaction Precaution.* Do not take this product if you are presently taking a prescription antihypertensive or antidepressant drug containing a monoamine oxidase inhibitor".

(v) "Do not give this product to children under 12 years except under the advice and supervision of a physician".

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d. *Theophylline preparations (aminophylline, theophylline anyhydrous, theophylline calcium salicylate, theophylline sodium glycinate).* The Panel concludes that the theophylline preparations are safe and effective for OTC use as bronchodilators as specified in the dosage section discussed below when the dosage is based on the anhydrous theophylline equivalent.

(1) *Safety.* The most commonly encountered adverse effects of theophylline—anorexia, nausea, and vomiting—are apparently centrally mediated. Whether administered orally as uncoated tablets, by injection, or rectally, gastrointestinal symptoms in adults and children are usually negligible if whole blood levels of theophylline do not exceed 8 μg/ml (equivalent to plasma levels of 15 μg/ml). The corresponding plasma level is greater because theophylline does not enter the red blood cells (Refs. 1 through 7). Gastrointestinal symptoms were associated with orally administered aminophylline (theophylline ethlenediamine) when whole blood levels of theophylline exceeded 11 μg/ml (equivalent to plasma levels of 20 μg/ml) (Ref. 1).

Aminophylline administered as an uncoated tablet or theophylline as an alcoholic elixir is quite rapidly and reproducibly absorbed within 1 hour from an empty stomach. Thus, oral absorption and tissue response to a given concentration of theophylline as well as rate of renal excretion are fairly uniform from patient to patient. However, administration with meals or as an enteric coated tablet markedly contributes to slowing and variability in extent of absorption (Refs. 5 and 7). However, recent studies showed that food makes little difference in the absorption of theophylline provided the tablet has a satisfactory dissolution time (Refs. 8 and 9). Studies of theophylline indicate that variations between patients in their maintenance dose requirements are attributable to remarkable differences in the rate at which theophylline is metabolized. In one study of 83 patients, oral aminophylline dosage ranged from 400 to 3,200 mg/24 hours in order to maintain therapeutic blood levels. About 10 percent of patients receiving 300 mg every 4 hours for at least 48 hours experienced loss of. appetite, nausea, and vomiting. Despite apparent variations in rate of theophylline metabolism between patients, each individual is internally quite stable in terms of rate of handling this drug so that it is possible to individualize a safe and effective dose for continued therapy (Ref. 1).

In children, oral doses of aminophylline of 4 to 5 mg/kg every 8 hours (80 percent of this dose for theophylline calculated as the free base) is recommended as generally devoid of undesirable side effects (Refs. 8 and 9). Severe toxicity in children may include vomiting with blood in the vomitus and dehydration, central nervous system stimulation leading to convulsions and coma, and cardiovascular collapse. The majority of literature reports of theophylline and aminophylline toxicity in children, and particularly those resulting in death, have been associated with use of aminophylline suppositories. Administered dosage of suppositories in reported toxicity cases ranged from a normal dosage of 10 mg/kg/24 hours to 75 mg/kg/36 hours (Refs. 8 and 10 through 29). Analysis of the cases of toxicity with recommended dosage of suppositories reveal the concurrent oral or parenteral administration of a theophylline preparation. Because of the toxicity potential from overdose unless the dose is individualized to the needs of a child on a mg/kg basis, the Panel believes that such OTC products should not contain labeling with a recommended dosage for children.

Aminophylline, due to its ethylenediamine content, may produce a contact-type dermatitis upon systematic administration to individuals previously sensitized to the topical application of ethylenediamine (Ref. 30).

(2) *Effectiveness.* Following intravenous aminophylline in a variety of patients with narrowing of the air tubes caused by spasm, the degree of objectively measured bronchodilation using measurements of air flow and airway resistance was correlated with whole blood levels of theophylline between 2 μg/ml up to a maximum effect at 8 μg/ml (equivalent to plasma levels of 3.6 to 14.5 μg/ml). A study of airway resistance changes in adult asthmatics following single oral doses of aminophylline demonstrated minimum whole blood levels of theophylline for maximal bronchodilator effect to range from 4.5 to 11 μg/ml (equivalent to plasma levels of 8 to 21 μg/ml). Because of patient variability in metabolism of aminophylline, the authors found that doses of 400 to 3,200 mg/24 hours, averaging 1,200 mg/24 hours, were needed to maintain therapeutically effective "trough" levels (middosing blood levels) of theophylline in the 5.5 to 11 μg/ml range. These authors recommend 300 mg aminophylline (240 mg anhydrous theophylline every 6 hours, 4 times daily (Ref. 1). Following 130 mg doses, blood levels at best reach 4.3 μg/ml (equivalent to plasma levels of 7.6 μg/ml) (Refs. 1, 3, and 31 through 33). Since the blood level attained and maintained in a given patient is dependent on drug metabolism rate, which varies among individuals, an OTC dose recommendation of 100 to 200 mg of anhydrous theophylline equivalent should help patients individualize the dose for optimal response yet minimize side effects.

The Panel recommends that scored compressed tablets in dosage units of 50 mg, 100 mg and 200 mg of anhydrous theophylline equivalent be made available for OTC use. The Panel is concerned that theophylline tablets be readily absorbed when ingested. All tablets must pass a satisfactory dissolution test. The Panel recommends that each tablet formulation be tested according to the procedures described in the United States Pharmacopeia XIX (Ref. 34). The tablets shall be considered satisfactory for OTC use if the quantity of theophylline dissolved within 15 minutes is not less than 50 percent of the labeled amount (based on anhydrous theophylline equivalent content) and the quantity of theophylline dissolved within 30 minutes is not less than 90 percent of the labeled amount of theophylline (based on anhydrous theophylline equivalent content) for any of the tablets tested. The resulting data should be submitted to the Food and Drug Administration prior to marketing.

A double-blind controlled study in 300 asthmatic children, ages 6 to 12, receiving 150 mg theophylline by mouth in plain capsules correlated with significant improvement as measured by pulmonary function tests with theophylline blood levels greater than 3.2 μg/ml (equivalent to plasma levels of 6 μg/ml) (Ref. 3).

A review of oral theophylline drugs lists the anhydrous theophylline equivalents in various proprietary preparations (Ref. 29). For purposes of standardization, the dosage recommendations of the Panel are based on anhydrous theophylline equivalent content.

(3) *Dosage.* Adult oral dosage based on the anhydrous theophylline equivalent is 100 to 200 mg every 6 hours not to exceed 800 mg in 24 hours. Children 2 to under 12 years oral dosage is identified in the labeling section discussed below under professional labeling. For children

under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

The Panel recommends that scored compressed tablets in dosage units of 50 mg, 100 mg and 200 mg of anhydrous theophylline equivalent be made available for OTC use.

(4) *Labeling.* The Panel recommends the Category I labeling for bronchodilator active ingredients. (See part V. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Warnings.* (i) "Do not exceed recommended dosage except under the advice and supervision of a physician".

(ii) "Do not take this product if nausea, vomiting or restlessness occurs".

(iii) *"Caution:* Do not continue to take this product but seek medical assistance immediately if symptoms are not relieved within 1 hour or become worse".

(iv) "Do not take this product if you are presently taking a drug or suppository containing any form of theophylline except under the advice and supervision of a physician".

(v) "Do not give this product to children under 12 years except under the advice and supervision of a physician. Excessive use may cause toxic effects and even death in children".

(vi) *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 12 years oral dosage based on the anhydrous theophylline equivalent is 3.33 mg/kg of body weight 3 times daily every 8 hours not to exceed 10 mg/kg in 24 hours.

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Category I Labeling

The Panel recommends the following Category I labeling for bronchodilator active ingredients to be generally recognized as safe and effective and not misbranded as well as the specific labeling discussed in the individual ingredient statements.

a. *Indications.* (1) "For temporary relief of bronchial asthma".

(2) "For symptomatic control of bronchial asthma".

(3) "Provides temporary relief from acute symptoms of bronchial asthma".

(4) "Relaxes tense bronchial muscles to ease breathing for asthma patients".

(5) "For temporary relief of wheezing (attacks and distress) of bronchial asthma".

(6) For products to be taken by inhalation: statements as to onset of action, e.g., "fast" or "quick", must be substantiated and accompanied by a specific time, e.g., "within 5 minutes".

b. *Warnings.* (1) *"Caution:* Do not take this product unless a diagnosis of asthma has been made by a physician".

2. *Category II conditions under which bronchodilator ingredients are not generally recognized as safe and effective or are misbranded.* The use of bronchodilators under the following conditions is unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel concludes that the following ingredients and labeling should be removed from the market until scientific testing supports their use.

Category II Active Ingredients

The Panel has classified the following bronchodilator active ingredients as not generally recognized as safe and effective or as misbranded:

Belladonna alkaloids

Pseudoephedrine preparations: Pseudoephedrine hydrochloride, Pseudoephedrine sulfate

a. *Belladonna alkaloids by inhalation (as contained in Atropa belladonna and Datura stramonia).* The Panel concludes that belladonna alkaloids by inhalation are not safe and effective for OTC use in the treatment of asthma. The effectiveness of this preparation is unproven and it has great potential for drug abuse and toxicity. In view of the availability of other safer and effective OTC drugs for the treatment of asthma, the Panel concludes that there is no place for this preparation in the OTC treatment of asthma.

(1) *Safety.* A mixture of stramonium and belladonna is available and is utilized by smoking the cigarettes or pipe mixture or by burning the powder, like incense, and inhaling the smoke. Per unit dose (cigarette, pipeful, etc.), the alkaloid content presumably absorbed systemically is about 0.0125 mg (Refs. 1 and 2). However, the preparation is easily abused for its psychomimetic properties, by excessive use or ingestion of cigarettes, liquid suspensions or capsules filled with the powder (Ref. 2). Intoxication is generally characterized by confusion, delirium, hallucinations, and various anticholinergic effects, such as difficulty in swallowing due to dry mouth, blurred vision, photophobia, difficulty in urination, and constipation. Some deaths have been reported (Ref. 2). The adverse effects of excessive use of the powder have been well described (Ref. 3). There are numerous reports of intoxication us-

ing the powder or ingesting seeds or leaves of stramonium plants (Refs. 4 through 9). Clearly, products containing belladonna alkaloids present a risk to the consumer.

(2) *Effectiveness.* Belladonna alkaloids may be of benefit when given in the form of cigarettes (Ref. 9), but there has been no critical assessment of effectiveness. There are no well-controlled studies or other evidence to support its effectiveness as a bronchodilator when used by inhalation in the treatment of asthma.

(3) *Evaluation.* The Panel concludes that the effectiveness of belladonna alkaloids by inhalation is unproven. In view of the high potential for abuse and toxicity and the availability of other safe and effective drugs, the Panel concludes that belladonna alkaloids by inhalation are not safe and effective for OTC use in the treatment of asthma.

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(7) DeYoung and E. G. Cross, "Stramonium Psychodelia," *Canadian Anaesthetists' Society Journal*, 16:429–432, 1969.

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b. *Pseudoephedrine preparations (pseudoephdrine hydrochloride, pseudoephedrine sulfate).* The Panel concludes that pseudoephedrine preparations are safe but not effective for OTC use as a bronchodilator.

(1) *Safety.* In a study of cardiovascular effects of pseudoephedrine, dose response in four subjects showed that 210 to 240 mg (3.05 to 4.0 mg/kg) were required to raise diastolic blood pressure to 90 mm Hg or above (Ref. 1). However, a serious rise in blood pressure may occur if the drug is taken concurrently with monoamine oxidase (MAO) inhibitors (Refs. 2 and 3). Skin reactions both of long and short duration may be associated with taking the drug but these are rare (Refs. 4 and 5). Six of 21 patients who took 60 mg orally had mild side effects of drowsiness, nausea, insomnia, and headache (Ref. 6).

(2) *Effectiveness.* In a careful double-blind study using 210 mg pseudoephedrine hydrochloride orally in nine subjects with reversible obstruction to air flow, measurements were made of vital capacity and forced expiratory volume in 1 second (FEV_1), which is a measurement related to airway obstruction, the higher the figure the better the air flow and the less the obstruction in the air tubes (Ref. 1).

This high dose of pseudoephedrine increased FEV_1 to less than half that produced by ephedrine. The maximum mean percentage increased in FEV_1 was only 11 percent after pseudoephedrine and this is within the variation of the technique and not considered a significant change. Ephedrine was used in the same study and caused a 27 percent improvement in FEV_1. In another double-blind placebo-controlled study, 100 to 200 mg pseudoephedrine was given intravenously and was ineffective in 12 human subjects as a bronchodilator as judged by changes in forced vital capacity (FVC) and forced expired volume (FEV_1) (Ref. 7).

(3) *Evaluation.* Based on the two studies reviewed (Refs. 1 and 7), the Panel concludes that pseudoephedrine is ineffective for use as a bronchodilator and therefore cannot be generally recognized as effective in the treatment of asthma.

REFERENCES

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(2) Elis, J. et al., "Modification by Monoamine Oxidase Inhibitors of the Effect of Some Sympathomimetics on Blood Pressure," *British Medical Journal*, 2:75–78, 1967.

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(4) Brownstein, M. H., "Fixed Eruptions Due to an Ephedrine Isomer," *Archives of Dermatology*, 97:115–119, 1968.

(5) Abramowitz, E. W. and M. H. Noun, "Ephedrine Dermatoses: Clinical and Experimental Study of a Personal Case, with a Review of the Literature," *The British Journal of Dermatology and Syphilis*, 45:225–237, 1933.

(6) Arbesman, C. E. and R. J. Ehrenreich, "New Drugs in the Treatment of Allergies," *New York State Journal of Medicine*, 61:219–229, 1961.

(7) Levy, D., S. Permutt and W. F. Russell, Jr., "An Evaluation of Three Drugs Alleged to Relieve Airway Obstruction in Asthmatic Patients," *Current Therapeutic Research* 3: 174–184, 1961.

Category II Labeling

All claims that state or imply a therapeutic action or safety property peculiar to the preparation that cannot be demonstrated in controlled studies are not acceptable. The Panel has previously discussed such labeling (See part II. paragraph O. above—CCABA Product Labeling Claims Not Supported by Scientific Evidence.). However, labeling that is descriptive of the product such as its taste or appearance are acceptable.

The Panel concludes that the following labeling is misleading and contains unacceptable claims for preparations used for the treatment of asthma. The Panel assumes that preparations under consideration will contain only a sympathomimetic of the bronchodilator type and/or theophylline ingredients. The Panel believes that the language expressed in the following misleading claims is excessive and claims either too much or claims effects which do not occur. For example, most asthma preparations have no effect on hay fever, the nose, the "common cold", or on congestion. The following apply regardless of whether the preparation is given by inhalation or by mouth:

a. *Unacceptable labeling because these claimed effects do not occur with bronchodilators.* (1) "Relief of hay fever".

(2) Claims for any effects "on nasal passages".

(3) Statements related to "congestion of air tubes or lungs".

(4) "Decongests swollen membranes, acts to loosen congestion, relief of general respiratory congestion".

(5) "Relief of bronchitis or 'the common cold' ".

(6) "Relief of fear, anxiety, nervous tension".

(7) "Cleans bronchial passages".

(8) "Contains anti-allergen ingredient".

(9) "Eases irritation of bronchial and nasal mucous membranes, and itchy, watery eyes".

(10) "Relief of other respiratory conditions".

(11) "Phlegm broken up and one is able to expel the phlegm with little effort".

(12) "Nagging cough is reduced to a minimum and as a result sleep is much deeper and uninterrupted".

b. *Unacceptable labeling because of the difficulty to substantiate and the implication that high use rate is evidence of the particular effectiveness of the ingredients.* "Most prescribed or recommended by doctors in medical practice".

c. *Unacceptable labeling because the claim suggests it is particularly effective.* "Proved highly effective in medical practice". The Panel notes that effectiveness must already be established to be classified as Category I.

d. *Unacceptable labeling because the claim is excessive and difficult to substantiate.* "Effective when all other available means have failed".

e. *Unacceptable labeling because excessive claims are made in emotional terms.*

(1) "Relieves gasping for air".

(2) "Free breathing restored".

(3) "Breathes a sigh of relief".

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel concludes that adequate and reliable scientific evidence is not available at this time to permit final classification of the claimed ingredient and conditions listed below. The Panel believes it is reasonable to provide 3 years for the development and review of such evidence. Marketing need not cease during this time if adequate testing is undertaken. If adequate effectiveness data are not obtained within 3 years, however, the ingredient and conditions listed in this category should no longer be marketed in over-the-counter products. Effectiveness as a bronchodilator must be demon-

strated by controlled objective studies. Subjective data alone are unacceptable because of the marked variability in the subjective awareness of the wheezing and shortness of breath associated with asthma.

Category III Active Ingredient

The Panel concludes that the available data are insufficient to permit final classification of the following claimed bronchodilator active ingredient.

The Panel concludes that there is insufficient evidence that euphorbia pilulifera is effective as a bronchodilator.

a. *Safety.* Clinical experience has confirmed that euphorbia pilulifera is safe in the dosage ranges used as a bronchodilator. In large dosage, it is said to be an irritant to the gastric mucous membrane (Ref. 1). There is some disagreement as to its effect on the skin. In one reference it is said not to irritate the skin (Ref. 1), but in others it is said to produce vesication (Refs. 2 and 3). It produces an increase in bronchial secretion, and large doses cause vomiting and diarrhea. Limited animal experiments showed no serious side effects (Ref. 4). Marketing experience of a capsule product has resulted in no serious complaints (Ref. 4).

b. *Effectiveness.* There are no well-controlled studies documenting the effectiveness of euphorbia pilulifera as a bronchodilator. The drug has been used in the treatment of asthma and bronchitis but "its value is not apparent" (Ref. 5). In Pharmacotherapeutics, 1928, (Ref. 2) it stated: "It finds some use as a bronchodilator in spasmodic asthma and in chronic bronchitis." It has been employed as a constituent of cough mixtures containing more active drugs and it has occasionally been employed in small dose in the treatment of the "common cold" and hay fever (Ref. 2). It has been marketed in a dosage of 0.715 gm in combination with aspirin and caffeine as a capsule, and many patients have claimed relief from asthma, sinusitis, bronchitis, hay fever, and rhinitis as well as good results in colds (Ref. 4). However, there is no evidence from the references that the drug has ever had any type of scientific testing.

c. *Proposed dosage.* The Panel is unable to determine a proposed dosage. Euphorbia pilulifera has been used as an elixir, fluidextract, tincture, in capsule and powder form, and as leaves to be smoked. The dosages are as follows: Elixir euphorbiae compositum (National Formulary) 4 to 46 mg followed by 92 mg twice daily for not more than a total of 3 doses daily; 8 ml fluidextractum euphorbiae (National Formulary) 1 to 3 ml; and tinctura euphorbiae (unofficial) 0.6 to 1.8 ml; powder 0.6 to 4 gm; and capsule (no dose could be determined). These dosages are recommended in the literature (Refs. 2 and 6). There are no details regarding frequency of dosage.

The Panel concludes that the pharmaceutical industry should consult with the Food and Drug Administration as to a suitable proposed dosage for testing. Otherwise, the Panel recommends that each drug manufacturer evaluate the dosage as labeled on the manufacturer's marketed product(s).

d. *Labeling.* The Panel recommends the Category I labeling for bronchodilator active ingredients. (See part V. paragraph C. below—Category I Labeling.)

e. *Evaluation.* Data to demonstrate effectiveness as a bronchodilator will be required in accordance with the guidelines set forth below for testing bronchodilator drugs. (See part V. paragraph C. below—Data Required For Evaluation.)

REFERENCES

(1) "The Dispensatory of the United States of America," 25th Ed., Edited by Osol, A. and G. E. Farrar, J. B. Lippincott Co., Philadelphia, p. 1688, 1960.

(2) Solis-Cohen, S. and T. S. Githens, "Pharmacotherapeutics, Materia Medica and Drug Action," D. Appleton and Co., New York, p. 1391, 1928.

(3) Culbreth, D. M. R., "A Manual of Materia Medica and Pharmacology," 7th Ed., Lea and Febiger, Philadelphia, p. 372, 1927.

(4) OTC Volume 040211.

(5) Hellerman, R. C. and L. W. Hazelton, "The Antispasmodic Action of Euphorbia Pilulifera," *Journal of the American Pharmaceutical Association (Scientific Edition)*, 39:142–146, 1950.

(6) "The Merck Index," 5th Ed., Merck and Co., Inc., Rahway, New Jersey, p. 232, 1940.

Category III Labeling

The Panel concludes that the available data are insufficient to permit final classification of the labeling claim identified below for bronchodilators. Additional data are required to support the following bronchodilator claim: "For temporary relief of cough caused by the 'common cold' or 'bronchitis'". The Panel concludes that the effect of bronchodilators on cough (other than due to asthma) is uncertain.

C. DATA REQUIRED FOR EVALUATION

The Panel has agreed that the protocols recommended in this document for the studies required to substantiate Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved methodology in the future.

1. *Principles in the design of an experimental protocol for testing bronchodilator drugs.* a. *General principles.* The effectiveness of a bronchodilator drug is determined by its ability to reverse the airway obstruction of patients with asthma. Although clinical improvement may be reported, it is essential to have objective measurements of pulmonary function to substantiate improvement. Tests of bronchodilator drugs should be double-blind and crossover studies. Pulmonary function tests should be performed before and after the drug or placebo is given. Objective testing should be done for a sufficient time to show the duration of action of the drug. For OTC drugs a single dose should be shown to be effective. Continual taking of the drug over days or weeks to show improvement is not acceptable for OTC products. The patient needs to get quick and obvious relief from a single dose. The drugs used should be tested in the same dosage as the purchaser might be expected to take, i.e., the recommended dosage on the label.

To show effectiveness it is necessary for two studies by two different investigators to indicate that there is definite improvement in pulmonary function following single doses of the drug under test as described under Interpretation of data, below.

b. *Selection of patients.* Selection of patients for testing should be based on the diagnosis of asthma. There should be generalized airway obstruction whose severity varies greatly over short periods of time, and this should be demonstrated by pulmonary function tests improving significantly after the use of an accepted bronchodilator drug.

c. *Methods of study.* For large series of patients, the forced vital capacity, forced expiratory volume (one second), and maximal midexpiratory flow rate are the simplest and most available tests. However, measurements of flow from flow-volume curves at 50 percent and 75 percent of the vital capacity, measurements of airway resistance and specific conductance using a body plethysmograph are recommended when the complex equipment is available.

The precise number of patients to be tested cannot be stated. However, if the drug is effective, approximately 20 patients should be sufficient for satisfactory statistical analysis of data.

d. *Interpretation of data.* Ideally, the response should be interpreted according to the recognized variability in the laboratory in which the test is being performed. Where such variability is not precisely defined, improvement of 15 to 25 percent may be considered a slight reversibility; a change of 26 to 50 percent is moderate reversibility; and greater than 50 percent is marked reversibility. However, for the purposes of an experimental protocol, statistical analysis and significance is essential.

Evidence of drug effectiveness is required from a minimum of two positive studies based on the results of two different investigators or laboratories.

All data submitted to the Food and Drug Administration must present both favorable and any unfavorable results.

e. *Evaluation of safety.* Tests of safety should involve the usual tests for toxicity to the respiratory system and be relevant to the known possible adverse effects of the drugs under testing. Tests should be done in the form of dose response curves up to maximum therapeutic effectiveness.

REFERENCE

(1) Woolf, C. R., R. Kory and J. Ross, "Criteria for the Assessment of Reversibility in Airway Obstruction," *Chest*, 65:552–553, 1974.

VI. ANTICHOLINERGICS

A. GENERAL DISCUSSION

Anticholinergics are drugs used in the symptomatic relief of excessive secretions of the nose (rhinorrhea) and eyes commonly associated with hay fever, allergy, rhinitis and the "common cold." The tissues responsible for these secretions, the glands of the nasal mucosa and

the lacrimal glands, are supplied by nerves known as cholinergic or parasympathetic nerves. These nerves release a neurohumoral substance, acetylcholine (ACh), which acts on receptors in these tissues apparently causing the excessive secretions. The anticholinergic drugs, by competing with ACh for these receptors, reduce or prevent the secretions.

There are other tissues having receptors acted on by ACh, and the anticholinergic drugs are able to prevent the response usually caused by ACh at these sites as well. These other tissues are the sweat, salivary and bronchial glands, the muscles for visual accommodation (adaptation of the eye for distinct vision at different distances), the heart, the gastrointestinal tract, and the urinary bladder. The cholinergic nerves which innervate these tissues are compositely known as the parasympathetic nervous system. All these tissues are not equally sensitive to the anticholinergic agents and the responses are dose related. Small doses depress salivary bronchial and sweat secretions. Larger doses are required to inhibit visual accommodation or increase the heart rate. Still larger doses are required to inhibit the parasympathetic control of the gastrointestinal tract or the urinary bladder.

The naturally occurring anticholinergic drugs, the alkaloids of the belladonna plants, are widely distributed in nature especially among the Solanaceae. The active drugs derived from these plants are atropine (dl-hyoscyamine) and scopolamine (l-hyoscine) depending upon which plant is the source. The official preparations of belladonna act chiefly by virtue of their atropine content.

Atropine is the classical representative of this group of anticholinergic drugs. It is dl-hyoscyamine, the stereoisomers being present in equal amounts but the activity residing in the l-form. The drying effect on the respiratory tract may be useful in the symptomatic relief of excessive secretions of the nose (rhinorrhea) and eyes commonly associated with hay fever, allergy, rhinitis and the "common cold." The effect of atropine is most noticeable if there are excessive secretions. There is no evidence that the course of the illness is altered by these drugs. At higher doses, the bronchi and bronchioles (large and small airways) are relaxed. This relaxation is most pronounced if the bronchi and bronchioles are contracted by histamine or increased parasympathetic activity and the atropine is administered by inhalation.

These drugs reduce the volume of secretions as well as making them less fluid. The less fluid secretions are more difficult to remove from the respiratory passages and may lead to obstruction. This predisposes the patient to infection. In a person with bronchial asthma or chronic obstructive pulmonary disease, this may be extremely hazardous.

The belladonna alkaloids will have little effect on the intraocular pressure of the normal eye. However, in the glaucomatous eye, when the intraocular pressure is initially above normal, they are likely to increase the intraocular pressure and damage the eye, especially in narrow angle glaucoma.

The toxic or side effects of the anticholinergic drugs are an extension of the pharmacologic effects of the drugs. These effects are dry mouth, anhydrosis, tachycardia, dilatation of the pupil and blurred vision, photophobia, restlessness, confusion and difficulty in urination. Very large doses may cause elevated body temperature and respiratory depression. Elderly men with enlargement of the prostate gland may develop urinary obstruction with less than toxic doses. There are numerous synthetic anticholinergic compounds, none of which differ significantly in pharmacologic effects or toxic effects from the naturally occurring drugs. Antihistaminics in varying degrees also have an anticholinergic effect. Antihistamines are discussed in another section of this document. (See part VII. below—Antihistamines.) Given together with an anticholinergic in the same preparation or at the same time, an antihistaminic drug will have at least an additive anticholinergic effect. With this in mind, the dose of each should be adjusted accordingly.

REFERENCES

(1) Innes, I. R. and M. Nickerson, "Drugs Inhibiting the Action of Acetylcholine on Structures Innervated by Postganglionic Parasympathetic Nerves (Antimuscarinic or Atropinic Drugs)," *in* "The Pharmacological Basis of Therapeutics," 4th Ed., Edited by Goodman, L. A. and A. Gilman, MacMillan Co., New York, pp. 524–548, 1970.

(2) "Drill's Pharmacology in Medicine," 4th Ed., Edited by DiPalma, J. R., McGraw-Hill, pp. 608–626, 1971.

B. CATEGORIZATION OF DATA

1. *Category I conditions under which anticholinergic ingredients are generally recognized as safe and effective and are not misbranded.*

Category I Active Ingredients

The Panel was unable to classify a claimed anticholinergic active ingredient as generally recognized as safe and effective and not misbranded.

Category I Labeling

The Panel recommends the following Category I labeling for anticholinergic active ingredients to be generally recognized as safe and effective and not misbranded:

a. *Indications.* (1) "For temporary relief of watery nasal discharge and watering eyes as may occur in certain allergic conditions and infections of the upper respiratory tract".

(2) "Temporarily suppresses watery nasal discharge".

(3) "Temporary relief from excessive nasal secretions".

(4) "Temporary relief from running nose".

(5) "Temporarily suppresses watering of eyes".

b. *Warnings.* (1) "Do not exceed recommended dosage except under the advice and supervision of a physician".

(2) "Do not continue to take this product if constipation, excessive dryness of the mouth, insomnia, excitement, confusion, rapid pulse, or blurring of vision occur".

(3) "*Caution:* Do not take this product if you have asthma, glaucoma or have difficulty in urination due to enlargement of the prostate gland except under the advice and supervision of a physician".

(4) "Do not give this product to children under 12 years except under the advice and supervision of a physician".

2. *Category II conditions under which anticholinergic ingredients are not generally recognized as safe and effective or are misbranded.* The use of anticholinergics under the following conditions is unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel concludes that the following ingredients and labeling should be removed from the market until scientific testing supports their use.

Category II Active Ingredients

The Panel has classified the following anticholinergic active ingredient as not generally recognized as safe and effective or as misbranded:

The Panel concludes that belladonna alkaloids (as contained in Atropa belladonna and Datura stramonia) when used by inhalation are not safe and effective for OTC use in asthma. The effectiveness of this preparation is unproven and it has great potential for drug abuse and toxicity. In view of the availability of other, safer, effective OTC drugs for the treatment of asthma, the Panel concludes that there is no place for this preparation in the OTC treatment of asthma.

a. *Safety.* The Panel has discussed the safety of belladonna alkaloids by inhalation in reference to the treatment of asthma with bronchodilators. (See part V. paragraph B.2.a. above—Belladonna alkaloids by inhalation (as contained in Atropa belladonna and Datura stramonia).)

b. *Effectiveness.* The Panel has discussed the effectiveness of belladonna alkaloids by inhalation in reference to the treatment of asthma with bronchodilators. (See part V. paragraph B.2.a. above—Belladonna alkaloids by inhalation (as contained in Atropa belladonna and Datura stramonia).)

c. *Evaluation.* The Panel concludes that the effectiveness of belladonna alkaloids by inhalation is unproven. In view of the high potential for abuse and toxicity and the availability of other drugs, the Panel concludes that belladonna alkaloids by inhalation are not safe and effective for OTC use as an anticholinergic.

Category II Labeling

The Panel concludes that the use of certain labeling claims related to the safety and/or effectiveness of the product are unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel has previously discussed such labeling. (See part II. paragraph O. above—CCABA Product Labeling Claims Not Supported by Scientific Evidence.) However, labeling that is descriptive of the product such as its taste or appearance is acceptable.

The Panel concludes that the following claims are misleading and are unacceptable for preparations used as anticholinergics:

a. *Claims not supported by scientific data.* "Clears nasal passages, open airways".

b. *All claims which state or imply a therapeutic action or safety property peculiar to the preparation that cannot be demonstrated in controlled studies.* These include claims such as "specially formulated", "scientifically improved or selected", "natural", "extra strength", "teamed components", "superior to ordinary", also claims implying a physiological effect which either has no foundation or meaning or will be meaningless or misleading to the public such as "antiallergic", "gets at the roots of", "fights", "wakes up", "recommended by doctors", and "travels through the blood stream".

c. *Claims for relief where time is indeterminate, and not supported by scientific data.* These include claims such as "all day", "all night", "for hours", "fast", and "prompt".

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel concludes that adequate and reliable scientific evidence is not available at this time to permit final classification of the claimed ingredients and conditions listed below. The Panel believes it reasonable to provide 3 years for the development and review of such evidence. Marketing need not cease during this time if adequate testing is undertaken. If adequate effectiveness data are not obtained within 3 years, however, the ingredients listed in this category should no longer be marketed as over-the-counter products. Effectiveness as an anticholinergic must be demonstrated by the ability to reduce rhinorrhea in patients with acute or chronic rhinitis. The evaluation must be a subjective study since the Panel is unaware of any technique for objective measurements.

Category III Active Ingredients

The Panel concludes that the available data are insufficient to permit final classification of the following claimed anticholinergic active ingredients: Atropine sulfate, Belladonna alkaloids.

a. *Atropine sulfate.* The Panel concludes that atropine sulfate is probably safe in the dosage range currently used (0.2 mg to 0.3 mg) as an anticholinergic but there are insufficient data to permit final classification of its effectiveness for OTC use as an anticholinergic. Although atropine at a higher dose, 0.6 mg, may be effective in relieving excessive secretions of the nose, there is no evidence that smaller doses as used in OTC preparations will do this. However, the Panel recommends that atropine not be made available for OTC use at a 0.6 mg dosage until suitable studies have been completed to show safety.

(1) *Safety.* Clinical experience has confirmed that atropine sulfate is probably safe in adults when taken orally as an anticholinergic in the currently marketed OTC dose of 0.03 mg to 0.2 mg total belladonna alkaloids. Dryness of the mouth appears first at about 0.5 mg (Ref. 1). No adverse effect was found in patients with open angle glaucoma taking 0.6 mg 3 times daily for 7 days (Ref. 2). Suppression of salivation occurred in children at the following oral doses: 1 to 12 months, 0.016 mg/kg; 12 to 36 months 0.014 mg/kg; 3 to 6 years, 0.022 mg/kg; and 6 to 12 years, 0.02 mg/kg (Ref. 3). A 7-week infant took more than 40 mg in 24 hours and recovered (Ref. 4). Ingestion of 450 mg in an adult has been followed by recovery (Ref. 5). There is a lack of data to support the use of anticholinergic active ingredients in children under the age of 12. The Pediatric Consultant Panel recommended that no dosage be marketed for children until further studies were completed. (See part II. paragraph H. above—Pediatric dosage.)

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of atropine sulfate as an anticholinergic. In the treatment of excessive secretions of the nose associated with the "common cold," atropine appears to be ineffective, but only one study is available (Ref. 6). The study indicated that a dose of 0.6 mg given early may transiently reduce the nasal secretions associated with the "common cold" giving some temporary comfort. However, there is no evidence that the very small doses of belladonna alkaloids per dosage unit in currently marketed OTC preparations, i.e., 0.03 to 0.2 mg total alkaloids, are effective.

(3) *Proposed dosage.* The Panel is unable to determine a proposed dosage. Although 0.6 mg atropine sulfate may be effective, the Panel concludes that such a dosage should not be available for OTC use until studies demonstrate safety. The Panel concludes that the pharmaceutical industry should consult with the Food and Drug Administration as to a suitable proposed dosage. Otherwise, the Panel recommends that each drug manufacturer evaluate the dosage as labeled on the manufacturer's marketed product. In such a case, the Panel concludes that for children under 12 years, there be no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for anticholinergic active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing anticholinergic drugs. (See part VI. paragraph C. below—Data Required for Evaluation.)

REFERENCES

(1) Gowdy, J. M., "Stramonium Intoxication," *Journal of the American Medical Association*, 221:585–587, 1972.

(2) Lazenby, G. W., J. W. Reed and W. M. Grant, "Anticholinergic Medication in Open-Angle Glaucoma," *Archives of Ophthalmology*, 84:719–723, 1970.

(3) Unna, K. R., K. Glaser, E. Lipton and P. R. Patterson, "Dosage of Drugs in Infants and Children: I. Atropine," *Pediatrics*, 6:197–207, 1950.

(4) Joos, H. A., "Atropine Intoxication in Infancy," *American Journal of Diseases of Children*, 79:855–861, 1950.

(5) Comroe, B. I., "Atropine Poisoning: Recovery After 7½ Grains of Atropine Sulfate by Mouth," *Journal of the American Medical Association*, 101:446–447, 1933.

(6) Personnel of the U.S. Naval Medical Research Unit No. 4, "The Prophylaxis and Treatment of Acute Respiratory Diseases with Antihistaminic Drugs," *Journal of Laboratory and Clinical Medicine*, 36:555–569, 1951.

b. *Belladonna alkaloids.* The Panel concludes that the belladonna alkaloids are probably safe in the dosage range used as anticholinergics but there are insufficient data to permit final classification of their effectiveness for OTC use as anticholinergics.

(1) *Safety.* Clinical experience has confirmed that belladonna alkaloids are safe in the dosage ranges used as anticholinerics. The belladonna alkaloids contain atropine (d, dl hyoscyamine) and scopolamine (l-hyoscine) and are present in official preparations, e.g., belladonna tincture United States Pharmacopoeia (USP) and belladonna extract National Formulary (NF). These preparations act by virtue of their atropine content. Scopolamine is approximately 10 percent of the total alkaloid content and has the same pharmacological effect and toxicity as atropine, but is slightly more potent. The Panel has discussed the safety of atropine elsewhere in this document. (See part VI. paragraph B.3.a. above—Atropine sulfate.)

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of belladonna alkaloids as anticholinergics. Atropine and other belladonna alkaloids and substitutes reduce secretion in both the upper and the lower respiratory tract, and they are common constituents of proprietary "cold" tablets (Ref. 1). This effect in the nasopharynx may provide some symptomatic relief of acute rhinitis associated with conditions such as coryza or hay fever. However, there are no controlled studies to support this hypothesis.

The belladonna alkaloids can induce bronchial dilatation. This is particularly marked when they are administered by inhalation, but it is still less than can be achieved by other types of medication.

All antimuscarinic agents reduce the volume of bronchial secretion which results in decreased fluidity and inspissation of the residual secretion. This viscid material is difficult to remove from the respiratory tree, and its presence can dangerously obstruct airflow and predispose to infection. Because of the effect on bronchial secretion, repeated administration of any antimuscarinic to a patient with chronic lung disease must be considered as potentially hazardous.

(3) *Proposed dosage.* Adult oral dosage is 0.2 mg 2 times daily. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for anticholinergic active ingredients. (See part VI. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for anticholinergic drugs. (See part VI. paragraph C. below—Data Required for Evaluation.)

REFERENCE

(1) Innes, I. R. and M. Nickerson, "Drugs Inhibiting the Action of Acetylcholine on Structures Innervated by Postganglionic Parasympathetic Nerves (Antimuscarinic or Atropinic Drugs)," *in* "The Pharmacological Basis of Therapeutics," 4th Ed., Edited by Goodman, L. S. and A. Gilman, The MacMillan Co., New York, p. 542, 1970.

Category III Labeling

The Panel concludes that the available data are insufficient to permit final classification of the labeling claim identified below for anticholinergics. Additional data are required to support the following anticholinergic claim: a. "Prolongs relief by helping to prevent further swelling and irritation."

b. The Panel concludes that claims relating to duration of action, e.g. "all day", "all night", "for hours", will require documentation.

c. *Claims that sleep will be facilitated.* These include claims such as "helps you fall asleep" and "for restful sleep".

C. DATA REQUIRED FOR EVALUATION

The Panel has agreed that the protocols recommended in this document for the studies required to bring a Category III drug into Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved methodology in the future.

1. *Principles in the design of an experimental protocol for testing anticholinergic drugs.* a. *General principles.* The effectiveness of an anticholinergic drug should be determined by the ability to reduce rhinorrhea (excessive watery nasal secretions) in patients with acute or chronic rhinitis. Tests should involve double-blind placebo controlled assessment of the ability of the drug to decrease watery nasal secretions and/or tearing when administered orally and increase the comfort of the patient. This evaluation must be a subjective one since there is no technique for objective measurements. The dosage, intervals of administration and conditions for the trials should be identical to the labeled recommendations.

b. *Selection of patients.* Selection of patients for treatment should be based on the diagnosis of rhinitis with rhinorrhea. Patients with chronic allergic or vasomotor rhinitis may present more stable symptoms but in most patients rhinorrhea is a variable and inconstant symptom. Because of this, a large number of suitable patients, e.g., approximately 50 subjects depending upon the protocol, must be used and assigned in a random fashion to placebo or drug groups. Further, these groups should be matched by age and sex, and if possible, by severity of symptom. It is also highly desirable to control conditions of temperature and humidity.

c. *Methods of study.* There is nothing in the literature concerning techniques for testing rhinorrhea and it is possible that a subjective method could be developed. It might be possible to semiquantitate the degree of rhinorrhea by weighing tissues or handkerchiefs; the wet weight minus the dry weight would be a rough index of the amount of secretions per unit of time. The subjects should be evaluated on the basis of the severity of the rhinorrhea and the subject's appraisal of his discomfort. Numerical values should be assigned indicating increasing severity. A double-blind technique is used for patients with acute rhinitis and in chronic rhinitis with rhinorrhea a double-blind crossover design. Observation should be carried out for 3 to 5 days to determine the extent of possible side effects.

d. *Interpretation of data.* The data should be subjected to statistical analysis and a p value of 0.05 or less would be acceptable as evidence of drug action.

Evidence of drug effectiveness is required from a minimum of three positive studies based on the results of three different investigators or laboratories.

All data submitted to the Food and Drug Administration must present both favorable and any unfavorable results.

e. *Evaluation of safety.* Tests of safety should involve the usual tests for toxicity relevant to the known possible adverse effects of the drugs under testing. Tests should be done in the form of dose-response curves up to maximum therapeutic effectiveness.

VII. ANTIHISTAMINES

A. GENERAL DISCUSSION

1. *Development.* The antihistamines were developed in France from a series of compounds with pronounced antihistaminic activity in the laboratory but which were too toxic for clinical use. One of these antihistaminic drugs, Antergan, was used for the first time clinically in 1942 in France. This was promptly followed by pyrilamine maleate. There then followed in 1946 the appearance in the United States of diphenhydramine and tripelennamine (Ref. 1). Many active antihistamine drugs appeared soon thereafter and the total number currently marketed is probably now close to fifty.

REFERENCE

(1) Loew, E. R., "Pharmacology of Antihistamine Compounds," *Physiological Reviews*, 27:542–573, 1947.

2. *Mechanism of action.* The antihistamines are useful primarily for the symptomatic relief of certain allergic disorders (Refs. 2 through 5). They suppress symptoms presumably caused by the release of histamine and possibly other chemical mediators from mast cells in mucous membranes (Refs. 1, 2, 5, and 6). Histamine attaches to specific receptor sites at the surface of cells in the nose, eyes, lungs, and skin and causes characteristic "allergic" symptoms. The antihistamines appear to act by competing with histamine for the receptor sites. If the antihistamine reaches the receptor site first, histamine is blocked from initiating a response. In this manner, antihistamines effectively block most smooth muscle responses to histamine.

The antihistaminic drugs are well tolerated by laboratory animals and produce recognizable effects on blood pressure, heart rate or respiration when given in large oral doses. These effects are more pronounced if the drugs are given intravenously (Refs. 2 and 5).

In man, the involvement of renal (kidney), hepatic (liver), hematologic (blood) or other major body systems in adverse reactions appears to be remarkably uncommon (Refs. 5 and 7).

In the skin of man, antihistamines inhibit the wheal, flare and itch reaction that occurs within a few minutes after the injection of histamine intracutaneously (into the skin). The antihistaminic drugs also inhibit similar reactions mediated by antibodies belonging to the IgE class of immunoglobulins (antibodies), but to a somewhat lesser degree. The Panel has previously discussed the role of antibodies in allergy earlier in this document. (See part II. paragraph B.1. above—Allergy.) Examples of reactions mediated by antibodies of the IgE class are those produced by skin testing with pollen extracts in which histamine release is involved. In addition to histamine, there are other chemical mediators released in IgE mediated reactions, and the antihistaminic drugs antagonize these much less effectively if at all. It is probably for this reason that these drugs are more active in protecting against the effects of injected histamine than in protecting against anaphylaxis in animals or allergic symptoms in man.

REFERENCES

(1) Loew, E. R., "Pharmacology of Antihistamine Compounds," *Physiological Reviews*, 27:542–573, 1947.

(2) Douglas, W. W., "Histamine and Antihistamines; 5-Hydroxytryptamine and Antagonists," *in* "The Pharmacological Basis of Therapeutics," 4th Ed., Edited by Goodman, L. S. and A. Gilman, The MacMillan Co., New York, pp. 635–642, 1970.

(3) "AMA Drug Evaluations," 2d Ed., Publishing Sciences Group, Incorporated, Action, Massachusetts, pp. 491–492, 1973.

(4) "Antihistamine Drugs," *in* "American Hospital Formulary Service," The American Society of Hospital Pharmacists, Washington, D.C., 4:00, 1975.

(5) Beckman, H., "Pharmacology; The Nature, Action and Use of Drugs," 2d Ed., The W. B. Saunders Co., Philadelphia, 1961.

(6) Roth, F. E. and I. I. A. Tabachnick, "Histamine and Antihistamines," *in* "Drill's Pharmacology in Medicine," 4th Ed., Edited by Dipalma, McGraw Hill Co., New York, pp. 995–1020, 1971.

(7) Wyngaarden, J. B. and M. H. Seevers, "The Toxic Effects of Antihistamine Drugs," *Journal of the American Medical Association*, 145:277–282, 1951.

3. *Preclinical studies.* As a group the antihistamines have the capacity to decrease or suppress effects produced by histamine in animals (Refs. 1 through 4). Animal "models" are therefore useful in determining drugs which will have antihistamine activity. An animal commonly used is the guinea pig. Guinea pigs can be protected by an antihistaminic drug from the often fatal narrowing of the air passages in the lung (bronchoconstriction) produced by histamine which causes death by asphyxia. Likewise, contraction of isolated tissues

of the guinea pig intestine (ileum) and of the airways of the trachea and bronchus produced by histamine is prevented by antihistamines in in vitro studies. These effects are most easily demonstrated in the guinea pig because of the animal's intense sensitivity to histamine but the antihistaminic drugs also act in a similar manner in some other laboratory animals and in man (Refs. 1 through 3).

The antihistaminic drugs are somewhat protective in experimental allergic reactions (anaphylaxis) but their action here is not so intense as their action against histamine. Apparently in man, some allergic reactions (hay fever and hives) are caused entirely or in large part by histamine release whereas other reactions, for example asthma, are not. The capacity to block the symptom-producing effects of histamine presumably explains why antihistamines are effective in relieving the symptoms of hay fever and hives (consisting of rashes associated with itching wheals) in which release of histamine appears to be the main cause of the symptoms (Refs. 2 and 3).

In concentrations that are effective against the spasmogenic activity of histamine, antihistamines have little or no capacity to counter the spasmogenic activity of other drugs such as acetylcholine, nicotine or barium.

Gastric ulcers with perforation have occurred in guinea pigs receiving both histamine and antihistamine under highly artificial conditions (Ref. 3). The experiment depends on the fact that antihistamine drugs can protect against histamine-induced bronchospasm and asphyxia although the antihistaminic drugs do not prevent another action of histamine which is to stimulate the production of acid within the stomach. Under the conditions of the experiment, increased acid production is induced in the guinea pig by giving large doses of histamine. The antihistamine protects the guinea pig from bronchospasm and fatal asphyxia which the histamine would otherwise cause. The Panel finds, therefore, that the antihistaminic drugs play no ulcer-producing role in this type of experiment and there are no other data which would implicate the antihistaminic drugs in promoting acid production in the stomach or ulcer.

In view of the chemical heterogeneity of the antihistamines, there is a surprising unanimity among the statements of critical investigators and authorities in describing their antihistaminic actions. The antihistamines under consideration are described as being intense antagonists of histamine, are of low acute (Ref. 1) and chronic (Ref. 2) toxicity and most are effective in suppressing the symptoms of allergic rhinitis (Refs. 1, 2, 3, 5, and 6). It is because these attributes are shared by most or all of the antihistamine drugs that individual drugs are not often singled out for special attention in the texts reviewed.

REFERENCES

(1) Roth, F. E. and I. I. A. Tabachnick, "Histamine and Antihistamines," *in* "Drill's Pharmacology in Medicine," 4th Ed., Edited by Dipalma, J., McGraw-Hill Co., New York, pp. 995–1020, 1971.

(2) Beckman, H., "Pharmacology; The Nature, Action and Use of Drugs," 2d Ed., The W. B. Saunders Co., Philadelphia, 1961.

(3) Douglas, W. W., "Histamine and Antihistamines; 5-Hydroxytryptamine and Antagonists," *in* "The Pharmacological Basis of Therapeutics," 4th Ed., Edited by Goodman, L. S. and A. Gilman, The MacMillan Co., New York, pp. 635–642, 1970.

(4) Loew, E. R., "Pharmacology of Antihistamine Compounds," *Physiological Reviews*, 27:542–573, 1947.

(5) "AMA Drug Evaluations," 2d Ed., Publishing Sciences Group, Incorporated, Acton, Massachusetts, pp. 491–492, 1973.

(6) "Antihistamine Drugs," *in* "American Hospital Formulary Service," The American Society of Hospital Pharmacists, Washington, D.C., 4:00, 1975.

4. *Common side effects.* Among the antihistamines, there are minor differences in the nature and frequency of side effects and toxicity which are related to chemical class (Refs. 1 through 3). With the exception of phenindamine, all the antihistamines considered by the Panel cause central nervous system depression, often recognized as drowsiness (sedation). Drowsiness is most marked among the antihistamines from the chemical class known as the ethanolamines, e.g., diphenhydramine, doxylamine and phenyltoloxamine, and least marked among the alkylamines, e.g., chlorpheniramine, brompheniramine and pheniramine. The ethylenediamines, e.g., methapyrilene, pyrilamine maleate, thenyldiamine and thonzylamine, are intermediate in this respect.

There is a wide range of susceptibility to actions of the antihistaminic drugs especially as regards the central nervous system. The chief danger from overdosage of antihistamines is central nervous system depression. The ethanolamines, (e.g., diphenhydramine and doxylamine) and the ethylenediamines, (e.g., methapyrilene) are also used as mild sleep inducers, and the ethanolamines, (e.g., diphenhydramine and dimenhydrinate) and the ethylenediamines, (e.g., methazine) as antiemetics for the treatment of the symptoms of motion sickness. Some are useful in treating paralysis agitans and petit mal seizures. No exact explanation for these actions is available.

Stimulation of the central nervous system has been observed in patients with focal cortical lesions in whom small doses of antihistamines may cause electroencephalographic activity and even frank seizures (Ref. 4). However, the precise basis for this stimulation is not fully understood. Excessive doses in any patient may cause restlessness, excitation, delirium, tremors, and even convulsions (Refs. 1 through 3). Phenindamine causes stimulation rather than depression as a common side effect and is unique in this respect among the antihistamines under consideration. The Panel has discussed this side effect observed with phenindamine later in this document. (See part VII. paragraph B.1.f. below—Phenindamine tartrate.)

Dryness of the mouth is also a common side effect of the antihistaminic drugs. Other side effects which are not as common as drowsiness have been reported in scientific texts but are poorly documented and often cannot be definitely ascribed to antihistamines. These include gastrointestinal effects such as anorexia (appetite loss), nausea, vomiting, epigastric distress, constipation or diarrhea (Ref. 1).

Also reported are cardiovascular symptoms which may include palpitations, hypotension, headache or tightness of the chest (Ref. 1). In the genitourinary system, an effect on the frequency of urination and/or dysuria may be encountered (Ref. 1). Cutaneous side effects such as urticarial, eczematous, bullous, or petechial rashes and photosensitivity may occur (Ref. 5). Hematologic complications that have been reported have included rare occurrences of pancytopenia, thrombocytopenia, hemolytic anemia and agranulocytosis (Ref. 5).

The Panel concludes that serious side effects produced by the antihistaminic drugs in the dosages recommended for OTC use are rare and the more common side effects are rarely serious.

REFERENCES

(1) Douglas, W. W., "Histamine and Antihistamine; 5-Hydroxytryptamine and Antagonists," *in* "The Pharmacological Basis of Therapeutics," 4th Ed., Edited by Goodman, L. S. and A. Gilman, The MacMillan Co., New York, pp. 635–642, 1970.

(2) Beckman, H. "Pharmacology; The Nature, Action and Use of Drugs," 2d Ed., The W. B. Saunders Co., Philadelphia, 1961.

(3) Roth, F. E. and I. I. A. Tabachnick, "Histamine and Antihistamines," *in* "Drill's Pharmacology in Medicine," 4th Ed., Edited by Dipalma, J., McGraw-Hill Co., New York, pp. 995–1020, 1971.

(4) King, G. and S. D. Weeks, "Pyribenzamine Activation of the Encephalogram, EEG," *Clinical Neurophysiology*, 18:503, 1965.

(5) "AMA Drug Evaluations," 2d Ed., Publishing Sciences Group, Incorporated, Acton, Massachusetts, pp. 491–492, 1973.

5. *Reduction of nasal secretions.* A common but variable action of the antihistaminic drugs is their anticholinergic effect of reducing nasal secretions. Some patients describe this as a disagreeable drying effect. In the recommended dosage, the drying effect of most antihistamines is less intense than that of atropine. This action appears to be entirely palliative and does not alter or shorten the course of the illness. The Panel is aware that a controversy exists concerning the use of antihistamines in patients with bronchial asthma where a "drying action" is undesirable. Many physicians consider this effect to be disadvantageous in patients with bronchial asthma and some maintain that the antihistaminic drugs are contraindicated in patients with this disease.

It is the view of the Panel that in the presence of allergic rhinitis and in the "common cold," secretions are often excessive and a "drying" agent may then be appropriate. However, the Panel finds, as do other investigators, that effectiveness of antihistamines widely used in the "common cold" has not been demonstrated in controlled studies (Ref. 1). In

addition, the Panel concludes that there is no evidence that release of histamine is either the cause of symptoms in the "common cold" nor is histamine release a significant factor in the "common cold." This will be discussed more fully below. (See part VII. paragraph C.2. below—Principles in the design of an experimental protocol for testing antihistamine drugs in the "common cold.")

REFERENCE

(1) West, S., B. Brandon, P. Stolley and R. Rumrill, "A Review of Antihistamines and the Common Cold," *Pediatrics*, 56:100–107, 1975.

6. *Human toxicity.* Unlike other classes of drugs, the extensive clinical experience with antihistamines has fairly well identified virtually all of the central nervous system manifestations of toxicity. The Panel has extensively reviewed these known toxic symptoms. While many of the more severe symptoms of antihistamines are relatively rare or are due to large doses or accidental overdose, the Panel has included them in the interest of completeness of this review.

Although rare, fatal or near fatal doses cause fixed, dilated pupils; muscular twitching followed by convulsions, sometimes with opisthotonos; coma; circulatory collapse; and respiratory failure. Convulsions may persist for 24 hours, coma for several days. Death rarely occurs later than 24 hours after ingestion unless due to infection associated with agranulocytosis (Ref. 1).

Because of the unique nature and wide use of antihistaminic drugs and because of the lack of extensive well-controlled clinical studies, the Panel has reviewed adverse reaction reporting systems to obtain a better understanding of the safety of antihistamines. Two major sources of data are the adverse reaction files of the Food and Drug Administration and the latest Poison Control Studies of the National Clearinghouse for Poison Control Centers. Since antihistamines have been extensively marketed for nearly 30 years, the Panel believes that a review of adverse reactions reports will serve as an indication of their safety.

It should be emphasized that these information sources are not entirely accurate nor do they necessarily give a valid picture of the incidence or prevalence of particular side effects. However, these reporting mechanisms do highlight the types of adverse reactions that can be expected. Where massive overdoses are ingested, such as in suicide attempts, these reports give a clearer picture of an ingredient's toxicological profile, significant elements of which include morbidity levels, toxic reactions which occur at varying dosage levels as well as dosage levels at which reversibility of an ingredient's toxic effects may occur.

The latest "Poison Control Statistics," published by the National Clearinghouse for Poison Control Centers provides the latest published data now available and covers the period from January to December, 1973 (Ref. 2). This publication presents collective toxicity data on household products and medicines from the Nation's 580 Poison Control Centers. This information reflects the treatment or response to each telephone inquiry to the Poison Control Centers concerning a poisoning or accidental ingestion and usually is not verified for accuracy except for the more obvious incongruities. Although only 1973 statistics were reviewed in detail by the Panel, that particular year is considered representative of all the years for which this type data was compiled.

Unlike the Poison Control Center data the adverse reaction data compiled by the Food and Drug Administration are cumulative and represent the total number of reported cases since the reporting system was implemented in 1968. Adverse reactions are reported to the agency in a variety of ways and at various levels of sophistication. These sources include hospitals, physicians, pharmaceutical manufacturers, consumers, or Food and Drug Administration personnel who often obtained these reports from consumers and physicians. While some of the data are verified for accuracy, they are often incomplete. Data are reported as having one of four causal relationships: directly related, probably related, possibly related and remotely related. For the Panel's purposes, only the adverse reactions which are directly or probably related to drug ingestion are discussed. The Panel recognizes that the statistics generated by the Poison Control Center and the Food and Drug Administration can be misleading and must be carefully used in determining the potential health threat of ingredients to consumers because the extenuating circumstances of each individual case are not represented.

A review of these two sources reveals several variables in the collection and comprehensiveness of the data which must be taken into consideration for a realistic view of the statistics compiled. For example, in the Poison Control Center data, few of the ingestions were of a single chemical entity. Most ingestions were of multi-ingredient products identified by brand name or conversly were ingestion of multiple products. Thus, it is improper to clearly attribute the symptom(s) reported to any one ingredient contained in a product. Further, in some cases no clear delineation of the quantity or number of units of an agent ingested is given. These data were often incomplete and left blank or "unknown" on the document. Of those listing a quantity, several were found to be at normal or subnormal dosage levels with no symptoms exhibited. These cases are included in the Poison Control Statistics as a reported "poisoning" when in fact no "poisoning" occurred. In addition, reported cases of hospitalization allude to symptoms serious enough to require treatment in a hospital, but give no indication whether the patient was seen only at the emergency room or actually admitted for treatment. Many of these same weaknesses and inconsistencies in data collection and assimilation also appear in the compilations from the Food and Drug Administration.

The Panel concludes that summaries of the Poison Control Statistics and the data from the Food and Drug Administration can only be used as an indication of the potential threat posed by OTC products because ingestions of both prescription and OTC products are combined in such statistics.

REFERENCES

(1) Loew, E. R., "Pharmacology of Benadryl and the Specificity of Antihistamine Drugs," *Annals of the New York Academy of Sciences*, 50:1142, 1950.

(2) "Poison Control Statistics, 1973," National Clearinghouse for Poison Control Centers, Bethesda, 1973.

7. *Criteria for classification of antihistamines as Category I.* In evaluating the antihistamines submitted for review, the Panel established the following criteria for classification of an ingredient as safe and effective and not misbranded for use as an antihistamine:

a. *Antihistamine activity.* If an ingredient has been tested in animal models and demonstrated to have antihistamine activity, i.e., in vitro test and in vivo tests (animal challenge with histamine and animal anaphylaxis protection), the findings were used to support a Category I determination.

b. *Animal toxicity.* If an ingredient has been tested in animals and found to have a low order of toxicity, the findings were used to support a Category I determination.

c. *Clinical studies.* If an ingredient has been tested clinically and the studies were determined to be controlled double-blind studies of an adequate design that included an appropriate dosing interval for each age group of patients, the findings were used to support a Category I determination. The Panel has discussed adequate design for clinical testing later in this document. (See part VII. paragraph C. below—Data Required for Evaluation.)

d. *Clinical experience.* If an ingredient has been subjected to uncontrolled clinical trials and has been shown to have sufficiently broad acceptable clinical use, i.e., general use and recognition by the medical community of safety and effectiveness for the treatment of allergic rhinitis, the findings were used to support a Category I determination. The Panel has determined that such clinical use may have been acquired while the ingredient was marketed and available only by prescription but only when used for the treatment of allergic rhinitis similar to that to be encountered with OTC use.

e. *Acceptable side effects.* If an ingredient is shown to have side effects in man for which appropriate labeling can be established, i.e., adequate directions for use and warnings against unsafe use such as "May cause drowsiness", the findings were used to support a Category I determination. In considering the acceptability of these side effects, the Panel questioned whether warnings were sufficient or whether the degree of side effects, and possibility of abuse or misuse under ordinary conditions of use, could be compensated for with adequate labeling. The Panel finds that this is an

especially important consideration for recommended dosages of ingredients higher than those currently available for OTC use, e.g., chlorpheniramine 4 mg or for ingredients previously not available for OTC use, e.g., diphenhydramine.

The Panel has summarized the findings in the following table:

Active ingredients	Antihistamine activity [1]	Animal toxicity [2]	Clinical studies [3]	Clinical experience [4]	Acceptable side effects [5]
Brompheniramine maleate	+	+	+	+	+
Chlorpheniramine Maleate	+	+	+	+	+
Diphenhydramine hydrochloride	+	+	0	+	++
Doxylamine succinate	+	+	+	+	++
Methapyrilene fumarate and hydrochloride.	+	+	0	+	++
Phenindamine tartrate	+	+	0	+	+−
Pheniramine maleate	+	+	0	+	++
Phenyltoloxamine citrate	+	+	0	0	+
Promethazine hydrochloride	+	+	0	+	++
Pyrilamine maleate	+	+	0	+	+
Thenyldiamine hydrochloride	+	+	0	0	0
Thonzylamine hydrochloride	+	+	0	+	+

[1] The (+) symbol indicates that the ingredient showed antihistamine activity in animals.
[2] The (+) symbol indicates that animal studies are available and show low toxicity.
[3] The (+) symbol indicates that controlled double-blind clinical studies of adequate design are available. The (0) symbol indicates that no data are available.
[4] The (+) symbol indicates that adequate clinical experience with the ingredient exists. The (0) symbol indicates that no data are available.
[5] The (+) symbol indicates a positive finding of "drowsiness." The (++) symbol indicates a positive finding of "marked drowsiness." The (+−) symbol indicates a positive finding of either "drowsiness" or "nervousness and insomnia." The (0) symbol indicates that no data are available.

The Panel has determined that if four of the five criteria are satisfied (antihistamine activity, animal toxicity, clinical experience and acceptable side effects), the ingredient may be classified as Category I. The Panel has further determined that the availability of clinical studies is not always required for each ingredient. The Panel has fully discussed these ingredients in the appropriate sections below. (See part VII. paragraph B. below—Categorization of Data.)

8. *Summary.* The antihistamine ingredients as a group are strikingly antihistaminic in animal models. This is their main pharmacologic action and appears to be closely related to their clinical effectiveness. The Panel has found that three of these ingredients, chlorpheniramine, brompheniramine, and doxylamine, have been subjected to controlled clinical studies which support their clinical effectiveness. For most of the remaining ingredients marketed OTC, extensive clinical use over a period exceeding 20 years indicates that these antihistaminic drugs are also effective in treating allergic rhinitis. As a group the antihistamines possess a low order of toxicity which the Panel feels is essential for the use of any ingredient in the OTC market.

B. CATEGORIZATION OF DATA

1. *Category I conditions under which antihistamine ingredients are generally recognized as safe and effective and are not misbranded.*

Category I Active Ingredients

The Panel has classified the following antihistamine active ingredients as generally recognized as safe and effective and not misbranded:

Brompheniramine maleate
Chlorpheniramine maleate
Diphenhydramine hydrochloride
Doxylamine succinate
Methapyrilene preparations: Methapyrilene fumarate, Methapyrilene hydrochloride
Phenindamine tartrate
Pheniramine maleate
Promethazine hydrochloride
Pyrilamine maleate
Thonzylamine hydrochloride

a. *Brompheniramine maleate.* The Panel concludes that brompheniramine maleate is safe and effective for OTC use as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) *Safety.* Studies in animals indicate that brompheniramine maleate has low toxicity (Ref. 1). The chief side effect of brompheniramine is sedation which occurs in about 20 percent or less of patients taking clinically effective doses (Refs. 2 and 3). Also observed is an atropine-like effect (anticholinergic action), which is not pronounced, but might have an adverse effect in patients with narrow angle glaucoma. The drying effect due to atropine-like action has been considered to be disadvantageous in patients with asthma because drying of secretions interferes with their removal from the airway. However, the Panel is unable to find evidence that these possible adverse effects are of clinical significance (Ref. 4).

Recovery from accidental overdosage with brompheniramine indicates that this drug has a wide margin of safety (Ref. 5). An injection of 100 mg caused only dry mouth 8 hours later in a hospitalized patient (Ref. 5). Observations in children indicate a relatively low degree of toxicity for brompheniramine (Ref. 2).

A 6-year-old boy tolerated 8 mg/lb/24 hours orally. A 2-year-old boy received a single oral dose of 60 mg without side effects and a 4-year-old boy received 96 mg in a single dose and subsequently had mild drowsiness. A 2½-year-old boy ingested an estimated twenty-five 12 mg tablets in whom hyperactivity and convulsions occurred followed by gastric lavage 2½ hours later with final recovery (Refs. 1 and 6).

The Panel is aware of a reported case of agranulocytosis following therapy with two antihistaminic drugs, thenalidine tartrate and parabromdylamine maleate (Ref. 7). The incident occurred during 1958 in which a 64-year-old female had taken both drugs. The drug manufacturer of thenalidine tartrate discontinued marketing the ingredient within months of its reported association in the medical literature with agranulocytosis. The other drug, parabromdylamine maleate, is also known as brompheniramine maleate. The patient had taken 4 mg brompheniramine maleate orally 4 times daily concurrently with an antibiotic ointment for the treatment of a pruritic rash. The patient received a total dose of 568 mg brompheniramine maleate over a period of approximately 60 days. The symptoms persisted and the drug was discontinued at which time 25 mg thenalidine tartrate was given orally 4 times daily for an additional period of approximately 60 days for a total dose of 1,850 mg thenalidine maleate prior to hospitalization. The author reporting the case noted that previous investigators had reported three cases of agranulocytosis associated with thenalidine tartrate therapy (Ref. 8). The Panel concludes that the data do not adequately substantiate that brompheniramine maleate was the causative factor in producing the blood dyscrasia. The drug has been extensively marketed and available by prescription for over 15 years with no documented cases of agranulocytosis occurring.

The Panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which a minimum of 600 million dosage units of brompheniramine maleate were sold. (See part VII. paragraph A.6. above—Human toxicity.) Of the 568 reported cases of suspected poisonings for brompheniramine maleate, 17.1 percent exhibited some symptoms and 5.5 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There was one fatality reported with the drug identified as a contributing cause of death but it was not possible to determine whether the ingestion was accidental or suicidal.

The Panel's review of the data supplied by the Food and Drug Administration showed a total of 47 adverse reaction reports on three marketed products containing brompheniramine since 1968 (Ref. 9). Of the 47, no adverse reactions were listed as being definitely related to ingestion of brompheniramine, 43 were listed as probably caused by ingestion of the drug and 4 were listed as possibly related to its ingestion.

The only other serious adverse reaction, aplastic anemia, was listed as possibly related to brompheniramine ingestion. A review of the source document disclosed few details of the case except that several other drugs were also ingested. The Panel was unable to conclude from the sketchy data whether there was any relationship between ingestion of brompheniramine and the aplastic anemia.

It should be noted that while brompheniramine is currently available only by prescription, the dosage levels are comparable to those that would be available in OTC use. Therefore, the safety considerations presented to the Panel for prescription marketing have given a reasonably accurate picture of what to expect from OTC use of this ingredient.

The Panel concludes that brompheniramine maleate is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) *Effectiveness.* Studies in animals have shown brompheniramine to have intense antihistaminic activity and to protect against anaphylaxis (Refs. 1 and 6). In addition to its demonstrated effectiveness as an antihistamine and protection against anaphylaxis in animals, brompheniramine has been shown in double-blind studies in humans to be effective in suppressing the symptoms of allergic rhinitis in doses of 4 mg or more given at 4 to 6 hour intervals (Refs. 10 through 12).

Available evidence indicates that brompheniramine has about the same effectiveness on a mg for mg basis as chlorpheniramine (Ref. 13).

In studies of the treatment of perennial rhinitis, efficacy was reported in 23 children ages 2 months to 2 years at a dosage of 0.2 mg to 0.5 mg/lb in 24 hours divided into 3 doses (Ref. 2). Likewise, 0.2 mg/lb in 24 hours was reported as effective in 28 children ages 2 to 6 years and 0.15 mg/lb in 24 hours in 16 children ages 6 to 14 years. Most of these patients had received other antihistamines without benefit. In addition to treatment with brompheniramine, all had been instructed in environmental control measures and many were receiving injections of allergenic extracts. The contribution made by these measures to the reported benefit cannot be assessed. There were no controlled groups although the statement is made that the patients were selected by "alternate allocation," the meaning of which is unclear. The statement that over three-fourths of the patients had failed to obtain benefit from "various other antihistaminic agents" is surprising in the light of what is known today about the efficacy of the antihistaminic drugs in rhinitis. Therefore, the Panel concludes that evidence of effectiveness for children is insufficient.

The Panel concludes that brompheniramine maleate 4 mg is the minimum effective OTC dosage for the relief of the symptoms of allergic rhinitis.

(3) *Dosage.* Adult oral dosage is 4 mg every 4 to 6 hours not to exceed 24 mg in 24 hours. Children 6 to under 12 years oral dosage is 2 mg every 4 to 6 hours not to exceed 12 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistamine active ingredients. (See part VII. paragraph B.1. below—Catagory I Labeling.) In addition, the Panel recommends the following specific labeling: *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 1 mg every 4 to 6 hours not to exceed 6 mg in 24 hours.

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b. *Chlorpheniramine maleate.* The Panel concludes that chlorpheniramine maleate is safe and effective for OTC use as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) *Safety.* The chief side effect of chlorpheniramine is sedation which occurs in about 10 to 20 percent of persons taking clinically effective doses. The drug also has a mild atropine-like effect (anticholinergic action) in some patients. This effect might have an adverse effect in patients with narrow angle glaucoma. Likewise, a drying effect has been considered to be a disadvantage in patients with asthma because drying of secretions interferes with their removal from the airways. Data supporting these potentially adverse effects in glaucoma and asthma are not available. Overdosage with chlorpheniramine has been relatively well tolerated. Adults receiving 1.5 gm orally in 69 hours and 200 mg in a single intramuscular dose recovered from the induced side effects without incident (Ref. 1) as did a 4-year-old boy who received 175 mg orally in 3½ hours (Ref. 2).

The Panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which a minimum of 2 billion dosage units of chlorpheniramine maleate were sold. (See part VII. paragraph A.6. above—Human toxicity.) Of the 1,609 reported suspected poisonings for chlorpheniramine maleate 15.8 percent exhibited some symptoms and 5.3 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There were no fatalities reported with the drug.

The Panel's review of the data supplied by the Food and Drug Administration disclosed a total of 14 adverse reaction reports on chlorpheniramine since 1968 (Ref. 3). Of the 14 reports, no adverse reactions were listed as being definitely related to ingestion of chlorpheniramine, three were listed as probably caused by this drug's ingestion, five were listed as possibly related to its ingestion and six were listed as remotely related to ingestion of this drug.

It should be noted that chlorpheniramine is available by prescription at the 4 mg dosage level and OTC at the 2 mg dosage level. However, the safety picture presented by the prescription dosage level has given the Panel a reasonably accurate idea of what to expect from OTC marketing of the 4 mg dosage level.

The Panel concludes that chlorpheniramine maleate is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) *Effectiveness.* Chlorpheniramine has been demonstrated to be effective in animal challenge tests with histamine in anaphylaxis protection (Ref. 4). In addition, its effectiveness in doses of 4 to 8 mg 4 times daily in the treatment of allergic rhinitis is described in a number of articles and uncontrolled studies and is supported by controlled studies (Refs. 5 through 8).

In a double-blind controlled study of the effectiveness of doxylamine succinate, chlorpheniramine was included as a standard of effectiveness. In this study 7.5 mg and 12.5 mg doxylamine were compared with chlorpheniramine 4 mg and a placebo, all given 4 times daily. Each group contained approximately 40 patients and the study extended for 1½ days. Chlorpheniramine and both dosages of doxylamine gave relief of pollen-induced symptoms of allergic rhinitis as compared with the placebo. The effectiveness of chlorpheniramine 4 mg was not significantly different from 7.5 or 12.5 mg doxylamine. In this study measurements of resistance to nasal air flow were made and failed to show any effect of the antihistamine preparations as compared with the placebo (Ref. 9). Other studies corroborate this finding. Using measurements of resistance to airflow in the nose, a well-controlled study

to determine the effect of chlorpheniramine given in an oral dose of 4 mg on relief of nasal obstruction gave no objective evidence of any effect over a period of 4 hours (Ref. 10). There was a significant decrease in resistance to flow when pseudoephedrine was given in a dose of 30 mg, indicating that the method was capable of revealing therapeutic effect. Likewise, a study submitted in an OTC Volume showed increased nasal obstruction in patients with nonallergic acute rhinitis after 8 mg chlorpheniramine in sustained action form (Ref. 11). Both of these studies were done in patients without evidence of allergy. These studies indicate that chlorpheniramine does not relieve and indeed, may aggravate nasal obstruction.

Only one study (Ref. 5) appears to have been done using a 2 mg dose, which is commonly used in OTC preparations, demonstrating effectiveness. The Panel concludes that chlorpheniramine maleate has not been shown to be effective for adults at a dose less than 4 mg.

The Panel concludes that chlorpheniramine maleate 4 mg is the minimum effective OTC dosage for adults for the relief of the symptoms of allergic rhinitis.

(3) *Dosage.* Adult oral dosage is 4 mg every 4 to 6 hours not to exceed 24 mg in 24 hours. Children 6 to under 12 years oral dosage is 2 mg every 4 to 6 hours not to exceed 12 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistamine active ingredients. (See part VII. paragraph B.1. below—Category I Labeling.) In addition the Panel recommends the following specific labeling: *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 1 mg every 4 to 6 hours not to exceed 6 mg in 24 hours.

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c. *Diphenhydramine hydrochloride.* The Panel concludes that diphenhydramine hydrochloride is safe and effective for OTC use as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) *Safety.* Diphenhydramine has a low order of toxicity in laboratory animals (Ref. 1). Its first clinical use was in 1946. Since then it has been used widely for treatment of such common conditions as allergic rhinitis, sundry rashes, the "common cold", and has also been used as a sedative. With the exception of sedation, adverse effects have been rare and the drug is considered safe. The Panel has also reviewed the side effects and toxicity of diphenhydramine when used as an antitussive and finds it to be safe when used at the same dosage level and regimen. That safety discussion is included elsewhere in this document. See part III. paragraph B.1.c. above—Diphenhydramine hydrochloride.)

In a double-blind study in 20 males (Ref. 2) there was no evidence of interference with tests for memory, rotary pursuit, or reaction time at a dose of 12.5 mg or 25 mg. These doses are below that recommended for adults on the treatment of allergic rhinitis. Clinical experience indicates that about 50 percent of persons have drowsiness as a side effect when 50 mg is given (Refs. 3 and 4). In some individuals, this occurs to a degree which would probably impair competence in driving a car or operating machinery. An atropine-like effect is also frequently described by patients as a drying sensation of the mouth and nose.

Many toxicologic studies have been carried out on diphenhydramine hydrochloride. Unpublished animal studies performed with mice demonstrated the LD_{50} to be 145 mg/kg and 263.0 mg/kg (Refs. 5 through 7). In rats, the LD_{50} was found to be 520 mg/kg and 549.5 mg/kg. The results of these studies are very similar when different animal strains, times when the studies were run, and variations inherent under different laboratory conditions are considered (Ref. 5). Diphenhydramine hydrochloride was demonstrated to have low toxicity in all three studies. Based upon these studies the usual adult human oral dosage level of 50 mg or 0.7 mg/kg 3 to 4 times daily is $\frac{1}{200}$th of the oral LD_{50} of diphenhydramine hydrochloride in mice (the LD_{50} is equivalent to at least 200 times the therapeutic dose in man) and $\frac{1}{700}$th the LD_{50} in rats (the LD_{50} is equivalent to at least 700 times the therapeutic dose in man) (Ref. 5).

In chronic toxicity studies dogs were given diphenhydramine hydrochloride at dosage levels of 10, 25, 40 and 60 mg/kg/day for periods up to 6 months. There were no gross microscopic pathologic changes attributable to diphenhydramine hydrochloride (Ref. 5).

Toxic psychoses from overdoses of diphenhydramine have occurred. A case of schizophrenic-like behavior was described by Nigro (Ref. 8). Possibly the earliest suicide was that reported by Duerfeldt in 1947 (Ref. 9).

Wyngaarden and Seevers also found that very high doses of diphenhydramine in infants may cause excitement and convulsions. They reviewed three cases in children under 3 years of age (2½, 1⅔, and 1½ years of age) who had taken 850 mg, 800 mg and 150 to 250 mg of diphenhydramine respectively with all doses resulting in convulsions (Ref. 10). In another case, a 32-month-old baby swallowed 9 capsules (450 mg) of diphenhydramine, after which a state of excitation was observed. Phenobarbital was prescribed, and the next day, the baby was normal (Ref. 10).

They also reviewed a group of adults ranging from 18 to 72 years, who sustained nonfatal convulsions, excitation, toxic psychosis, coma, petit mal, or somnolence (Ref. 10).

One case involved a 72-year-old asthmatic man, weighing 145 pounds who ingested 2,500 mg (50 capsules) of diphenhydramine hydrochloride. He fell into a deep sleep. Approximately 16 hours later, he awoke, feeling well. He had received no medication for this somnolence. In other cases dealing with adult fatalities, Wyngaarden and Seevers found that the ability to withstand large overdoses appears to increase with age, and the older the patient, the more the toxic manifestation shifts from that of central nervous system stimulation to that of depression. But it was also seen that a 47-year-old severely asthmatic woman died in depression after ingesting only 200 mg of diphenhydramine hydrochloride. However, the death cannot be unequivocally attributed to diphenhydramine since the shock-like state observed could well have been a complication of the disease itself and could easily have been influenced by other depressant medicaments that were given (Ref. 9).

The Panel considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which a minimum of 187.4 million dosage units of diphenhydramine hydrochloride were sold. (See part VII. paragraph A.6. above—Human toxicity.) Of the 334 reported suspected poisonings for diphenhydramine hydrochloride, 37.4 percent exhibited some symptoms and 16.5 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There were two fatalities reported with the drug identified as a contributing cause of death.

The Panel's review of the data supplied by the Food and Drug Administration disclosed a total of 178 adverse reaction reports on diphenhydramine since 1968 (Ref. 11). Of those 178 reports, nine were listed as definitely related to diphenhydramine ingestion, 95 were listed as probably caused by the drug's ingestion, 58 were listed as possibly related to its ingestion and 16 were listed as remotely related to diphenhydramine ingestion.

A 69-year-old female who had a history of serious medical problems and

drug ingestion was diagnosed to have agranulocytosis. Three days after termination of pentazocine lactate by injection and 1 day after termination of diphenhydramine therapy, her white blood cell count progressively climbed to normal values (Ref. 11).

The Panel is aware that recently there was some concern expressed about the potential for misuse and abuse of diphenhydramine. This concern was contained in the statement of the Commissioner of Food and Drugs, which was included in the preamble to the report of the OTC Advisory Panel on Sedatives, Tranquilizers and Sleep Aid Drug Products and published in the FEDERAL REGISTER of December 8, 1975 (40 FR 57292). This Panel will not attempt to comment on the findings of the other Panel or on the societal impact or abuse potential of diphenhydramine when used as an OTC nighttime sleep-aid. However, after a review of all the available data, the Panel concluded that diphenhydramine, as well as the other antihistamines reviewed, have a very low abuse potential and that there is little if any evidence of tolerance or habituation. However, the Panel does recognize that doses of diphenhydramine higher than those recommended for OTC use are likely to result in some side effects but that these side effects are sufficient to discourage abuse or misuse. In addition, the two pharmacologic groups for which this Panel is recommending diphenhydramine for OTC use, i.e., as an antitussive and as an antihistamine, are not recognized as being abusable by the drug abusing subculture. It should also be noted that diphenhydramine is available without a prescription for use as an antihistamine in Canada, the United Kingdom, and many other industrialized countries of the world. The Panel was unable to determine that significant abuse of this ingredient was a problem in any of these countries.

The Panel notes that the dosage levels of diphenhydramine currently available by prescription are comparable to those that would be available for OTC use. Therefore, the safety considerations presented to the Panel for prescription marketing have given a reasonably accurate picture of what to expect from OTC use of this ingredient.

The Panel concludes that diphenhydramine hydrochloride is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) *Effectiveness.* In animal tests, diphenhydramine has an intense antihistamine action both in vitro (Refs. 1 and 12) and in vivo (Refs. 1 and 13). The drug gives protection to guinea pigs against anaphylactic shock (Ref. 13).

Diphenhydramine is also effective for the symptomatic treatment of allergic rhinitis. Although no studies with a double-blind control were found, the Panel's opinion concerning effectiveness in the treatment of allergic rhinitis rests on wide usage over a period of 30 years.

A number of uncontrolled clinical studies indicate that the drug is effective in relieving the symptoms of allergic rhinitis (Refs. 14 through 16) and one study also describes reduction of whealing in the skin induced by intracutaneous injection of both histamine and allergic extracts in patients with hay fever (Ref. 17). The Panel has also found the drug to be effective for use as an antitussive, which is discussed elsewhere in this document. (See part III. paragraph B.1.c. above—Diphenhydramine hydrochloride.)

The Panel concludes that diphenhydramine hydrochloride 25 to 50 mg is an effective OTC dosage range for the relief of the symptoms of allergic rhinitis.

(3) *Dosage.* Adult oral dosage is 25 to 50 mg every 4 to 6 hours not to exceed 300 mg in 24 hours. Children 6 to under 12 years oral dosage is 12.5 to 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistaminic active ingredients. (See part VII. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) *Warning.* "May cause marked drowsiness."

(ii) *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 6.25 to 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours.

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d. *Doxylamine Succinate.* The Panel concludes that doxylamine succinate is safe and effective for OTC use as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) *Safety.* Doxylamine has a low oral toxicity in laboratory animals (LD_{50}: mice 470 mg/kg; rabbits 250 mg/kg) at doses which greatly exceed those required to demonstrate antihistaminic effects (Ref. 1). Brown and Werner found the intravenous LD_{50} to be 49 and 62 mg/kg for rabbits and mice, respectively (Ref. 1). The subcutaneous dose in mice was about 87 percent less toxic than when given intravenously. The oral dose was about 80 percent less toxic than when given in rabbits. The administration of doses of doxylamine succinate as high as 45 mg/kg twice daily for a period of 38 days had no significant effect in rats. Repeated administration of increasing doses from 50 to 150 mg/kg also had no gross effects. However, an increase to 200 mg/kg resulted in a decreased rate of growth in some animals, and an increase up to 400 mg/kg caused lack of appetite and death in one case. Thus, repeated doses resulted in toxicity only when the doses approached acutely lethal ones (Ref. 1). Daily administration of doxylamine to dogs, rats and monkeys in doses of 3 to 7.5 mg/kg for 2 months gave no evidence of accumulation and the drug was well tolerated (Ref. 2).

Clinical experience indicates that the primary side effect in humans is central nervous system depression. Standard scientific tests state that there is a high incidence of sedation at the usual therapeutic dosage of 12.5 to 25 mg up to 4 times daily (Refs. 3 through 7). In one double-blind, placebo controlled study, the hypnotic effectiveness of doxylamine, 25 to 50 mg, was greater than that of 100 mg secobarbital (Ref. 8). Dizziness and nervousness occur less frequently than sedation (Ref. 3).

One study reports that of 118 patients being treated for allergy with doses of

12.5 to 50 mg of doxylamine succinate, side effects were observed in 39 (Ref. 9). Sedation or sleepiness was seen in 36 of these 39 patients or 92 percent. Nervousness was noted in four patients, and vertigo in four others. No serious toxic effects were noted after use of the drug for 6 months. Sheldon et al. (Ref. 10) gave allergic patients 12.5 to 50 mg of doxylamine succinate and found that 57 percent complained of drowsiness. However, there was no apparent correlation, they stated, between the dosage of the drug and drowsiness. Palpitation, irritability, and diarrhea were noted in three patients. There was no evidence of any hepatic, renal or vascular changes. In the study by Ferguson there was no change in pulse, respiration, temperature or blood pressure with high doses of up to 1,600 mg of doxylamine succinate daily by mouth for up to 6 months (Ref. 11). Blood chemistry and organ function tests remained normal. In addition, Ferguson found that there has been no habituation to doxylamine, but he noted a mild degree of tolerance (Ref. 11).

Selzer and Waldman gave chronic psychotic patients doses of doxylamine (unspecified salt) up to 900 mg/day for 3 months in which side effects were virtually nonexistent (Ref. 12).

In a review of antihistaminic drugs, it is reported that 36 percent of 56 patients receiving the drug for treatment of allergic rhinitis had side effects, chiefly drowsiness (Ref. 13).

It appears from some studies that 50 mg and above of doxylamine succinate produces the side effect of sedation which is characteristic of antihistamines (Refs. 9 and 13). However, as stated above, Ferguson (Ref. 11) and Selzer and Waldman (Ref. 12) gave doses up to 900 mg daily in three divided doses with little evidence of drowsiness in the schizophrenic patients. Such apparently contradictory results have not yet been explained.

The Panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which a minimum of 60 million dosage units of doxylamine succinate were sold. (See part VII. paragraph A.6. above—Human toxicity.) Of the 100 suspected poisonings reported for doxylamine succinate, 32 percent exhibited some symptoms and 5 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There were no fatalities reported with the drug.

The Panel has reviewed and concurs with the statement in the report of the Advisory Review Panel on OTC Sedatives, Tranquilizers and Sleep-Aid Drug Products published in the FEDERAL REGISTER of December 8, 1975 (40 FR 57292) "that no literature was found by the Panel concerning poisoning or doses which cause death in humans."

The Panel's review of the data supplied by the Food and Drug Administration disclosed a total of 10 adverse reaction reports on doxylamine succinate since 1968 (Ref. 14). Of the 10 reports none was listed as directly related to ingestion of doxylamine succinate, five were listed as probably caused by this drug's ingestion, three were listed as possibly related to its ingestion and two were listed as remotely related to ingestion of doxylamine succinate.

The Panel concludes that doxylamine succinate is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) *Effectiveness.* Doxylamine is highly active in the protection of guinea pigs against the intravenous injection of histamine (Ref. 1). Using ileum strips in vitro, marked antihistaminic action was also demonstrated. The drug was also effective in protecting guinea pigs against anaphylaxis (Ref. 1).

Clinical experience and standard scientific textbooks indicate that doxylamine is an effective antihistamine in dosages of 12.5 to 25 mg up to 4 times daily (Refs. 3, 7, and 15).

Two double-blind clinical trials have demonstrated the effectiveness of doxylamine in a dosage of 12.5 and 25 mg up to 4 times daily in the treatment of hay fever (Refs. 15 and 16). In these studies, subjective evaluations by patients and physicians were logged and analyzed.

In a third well-designed study, doxylamine was given in a dose of 7.5 mg to one group and in a dose of 12.5 mg to a second group and a placebo to a third group, all with allergic rhinitis caused by pollen. The preparations were administered 4 times a day as required for 6 days with double-blind control. There were 40 to 45 patients in each group. Both the 7.5 mg and 12.5 mg dosages gave significant relief of symptoms as compared with the placebo, with the effectiveness of 12.5 mg exceeding that of 7.5 mg (Ref. 17). The incidence of drowsiness in both the 7.5 mg and 12.5 mg groups was not different from placebo.

In a fourth well-designed study with double-blind control, 7.5 and 12.5 mg doxylamine were compared with chlorpheniramine 4 mg and a placebo, all given 4 times daily. Each group contained approximately 40 patients and the study extended for 1½ days. Chlorpheniramine and both dosages of doxylamine gave relief of pollen-induced symptoms of allergic rhinitis as compared with the placebo. The effectiveness of chlorpheniramine 4 mg was not significantly different from either 7.5 or 12.5 mg doxylamine. In this study, measurements of resistance to nasal air flow were made and failed to show any effect of the antihistamine preparations as compared with the placebo (Ref. 17). One study ranked doxylamine 8th in a series of 13 antihistamines tested for antihistamine activity in man (histamine wheal test) (Ref. 18). Doxylamine has also been described as being slightly "less potent" than promethazine but having a longer duration of action (Ref. 5). An effective dosage for children 6 to 12 years of age is 6.25 mg 2 to 4 times daily (Ref. 3) or 2 mg/kg/24 hours of 60 mg/m²/24 hours divided in 4 to 6 doses (Ref. 19).

The Panel concludes that doxylamine succinate 7.5 mg is the minimum effective OTC dosage for the relief of the symptoms of allergic rhinitis.

(3) *Dosage.* Adult oral dosage is 7.5 to 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours. Children 6 to under 12 years oral dosage is 3.75 to 6.25 mg every 4 to 6 hours not to exceed 37.5 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistamine active ingredients. (See part VII. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) *Warning.* "May cause marked drowsiness."

(ii) *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 1.9 to 3.125 mg every 4 to 6 hours not to exceed 18.75 mg in 24 hours.

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e. *Methapyrilene preparations (methapyrilene fumarate, methapyrilene hydrochloride).* The Panel concludes that methapyrilene fumarate and methapyriline hydrochloride are safe and effective for OTC use as antihistamines in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) *Safety.* In animal studies, methapyrilene appears to have a low order of toxicity in laboratory animals as compared with other common antihistaminics (Refs. 1 and 2). From the results of human studies, methapyrilene appears to be safe at the recommended dosage (Ref. 3). Specifically, in the Friedlaender and Friedlaender study (Ref. 4) of 117 patients, one or more side effects, usually mild in nature, were encountered in approximately 25 percent of the patients receiving methapyrilene hydrochloride. These occurred most often when doses of 100 mg were administered but usually abated after the initial treatment and seldom affected the continued use of the drug. In most instances, a reduction in dosage to 50 mg obviated the side effects while not modifying the effectiveness. Drowsiness, the most common side effect, occurred in 13 patients. Vertigo, headache, nausea and vomiting, diarrhea and excessive dryness of mouth were next in order of frequency. No serious toxic effect was observed in any patients in this group receiving a daily dose of 200 to 300 mg (50 mg every 4 to 6 hours) (Ref. 4).

In another study, Peirce and Mothersill studied 77 patients and reported that five patients who had been treated with methapyrilene hydrochloride in daily amounts of 100 to 200 mg showed minor side effects but no toxic symptoms (Ref. 5). Rarely did side effects interfere with the patient's ability to continue the administration of the drug. In some cases, lowering the dosage obviated the side effects without significantly altering the therapeutic effectiveness of the drug. Peirce and Mothersill concluded that, ordinarily, 200 mg could be taken daily with "no discomfort" (Ref. 5).

Douglas stated that methapyrilene hydrochloride has been found to have low to intermediate activity for sedation, and its action is less pronounced than that of other antihistamines in therapeutic doses, particularly diphenhydramine (Ref. 3). Occasionally, the anticholinergic action of antihistamines generally may predominate and methapyrilene may cause excitation that results in insomnia, tremors, nervousness, irritability, and palpitation. Dryness of mouth, blurred vision, urinary retention, tachycardia, and constipation may also occur, but these reactions are rare unless large doses are used (Ref. 3). This same view of the toxicity of methapyrilene also appears in several other standard scientific texts (AMA Drug Evaluation, and New and Nonofficial Drugs) (Refs. 6 and 7). However, AMA Drug Evaluation also states that convulsions have been reported in patients with focal lesions of the cerebral cortex and in individuals who have ingested toxic doses (Refs. 6 and 7).

In a study of three patients receiving 400 mg a day for 8 to 10 weeks, no change in blood or urine constituents was observed (Ref. 4). An accidental overdose of 800 mg methapyrilene in a 20-month-old infant resulted in cyanosis, loss of consciousness, convulsions, and cardiorespiratory depression with eventual recovery (Ref. 8). An unusual case of fever, rigor, vomiting, and general malaise with recovery after 3 days is also described (Ref. 9). The symptoms recurred after challenge with methapyrilene 2 weeks after the initial attack. An 18-year-old man who became stuporous after ingestion of an unknown quantity of methapyrilene recovered (Ref. 10).

Methapyrilene fatalities have included a 16-month-old girl who developed hyperpyrexia, cerebral edema, upper nephron nephrosis and uremia (Ref. 11), an adult suicide who died in convulsions after ingestion of methapyrilene (Ref. 12), and two other adults who were found dead (Refs. 13 and 14). Nonfatal cases include two adults (Ref. 15) manifesting convulsions, and two other adults in coma (Ref. 16).

The panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which 543 million dosage units of methapyrilene were sold. (See part VII. paragraph A.6. above—Human toxicity.) Of the 168 suspected poisonings reported for methapyrilene fumarate or methapyrilene hydrochloride, 11.9 percent exhibited some symptoms and 5.9 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There were no fatalities reported with the drug.

The Panel's review of the data supplied by the Food and Drug Administration showed a total of one adverse reaction report on methapyrilene since 1968 (Ref. 17).

The Panel concludes that methapyrilene fumerate and methapyrilene hydrochloride are safe for OTC use as antihistamines in the dosage ranges described below.

(2) *Effectiveness.* Tests in animal models have demonstrated methapyrilene's specific antihistamine activity. Methapyrilene prevents histamine-induced contraction of the guinea pig ileum and protects sensitized guinea pigs from anaphylactic shock when challenged with an antigen (Refs. 2 and 18).

No double-blind human studies using methapyrilene alone were found. Uncontrolled studies of methapyrilene reported that 63 to 79 percent of patients suffering from hives or hay fever were relieved following administration of the drug (Refs. 4, 5, 15, 18, and 19). In the Friedlaender study, approximately 75 percent of the 40 patients suffering from acute seasonal hay fever obtained some benefit from methapyrilene fumarate or methapyrilene hydrochloride, although the relief of the symptoms was seldom complete. This study utilized 100 mg doses in adults, administered 4 times daily, after meals and at bedtime (Ref. 20).

The Peirce and Mothersill study found that 75 patients received methapyrilene hydrochloride for periods varying from 1 day to 3 months (Ref. 5). The medication exhibited its greatest effectiveness in acute skin rash due to drug and food allergy, watery eyes and runny nose due to pollen sensitivity, and histamine induced headaches. They found that the effective dosage ranged from 50 to 400 mg daily. The average maintenance dose for all cases was between 150 to 200 mg daily (Ref. 5).

In the Feinberg and Bernstein study of 112 patients with allergic rhinitis (seasonal as well as that due to the pollen of trees, grasses and weeds, and to the spores of molds), 79 patients or 70 percent benefited from methapyrilene hydrochloride. Of 95 patients with vasomotor rhinitis (nonseasonal hay fever) 44 patients or 46 percent received some measure of relief (Ref. 19). The symptoms of asthma were not appreciably altered in 30 patients although the preasthmatic, spasmodic cough was decidedly helped in 6 out of 9 patients. The subjective symptoms of skin rash were helped in 4 of 12 patients. In 13 patients with atopic dermatitis (skin rash), 8 obtained considerable relief from itching. The average dose of methapyrilene hydrochloride in the Feinberg-Bernstein study was 50 mg orally, 1 to 4 times daily (Ref. 19). A controlled study of 236 patients receiving methapyrilene and 203 receiving powdered starch presented no evidence that methapyrilene aborted or ameliorated colds (Ref. 20).

The Panel concludes that methapyrilene fumarate 50 mg and methapyrilene hydrochloride 50 mg are the minimum effective OTC dosages for the relief of the symptoms of allergic rhinitis.

(3) *Dosage.* Adult oral dosage is 50 mg every 4 to 6 hours not to exceed 300 mg in 24 hours. Children 6 to under 12 years oral dosage is 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistamine active ingredients. (See part VII. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) *Warning.* "May cause marked drowsiness."

(ii) *Professional labeling.* The Panel recommends that labeling provided to health professionals, but not to the general public may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours.

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f. Phenindamine tartrate. The Panel concludes that phenindamine tartrate is safe and effective for OTC use as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) *Safety.* Acute toxicity studies in guinea pigs indicated an LD_{50} value of 125 mg intraperitoneally which is approximately the same as the intraperitoneal LD_{50} value for diphenhydramine. Daily doses of 100 mg for 5 months or of 200 mg for 6 months were reported to have no adverse effects on the weight, blood formation, blood glucose and non protein nitrogen of dogs. No histopathological changes were found (Refs. 1 and 2).

In 136 healthy subjects ingesting 75 to 600 mg phenindamine daily for 7 to 31 days, toxicity studies revealed no abnormality of hemoglobin, red cell count or white cell count, urinalysis, blood pressure, electrocardiogram, gastric acidity, glucose tolerance, pulse rate, basal metabolic rate or blood chemistry (Ref. 3). In 15 healthy volunteers receiving 50 mg or more daily for 6 months, the blood and urine remained normal (Ref. 4).

In 280 patients receiving 25 to 150 mg daily (adults averaging 75 mg; children 30 mg daily), there were side effects in 27 percent (Ref. 1). In more than 1,000 subjects side effects were frequent but mild and were directly related to dosage. At 75 mg daily, 15 percent of the subjects developed side effects. At 150 mg daily, 25 percent of 380 patients developed side effects. At 300 mg daily, 50 percent of the patients suffered side reactions, and many discontinued the drug. Receiving a dose of 600 mg daily for 7 days, 75 percent of the patients developed side effects (Refs. 3 and 5). Side effects included insomnia, stimulation, nervousness, dryness of mouth, and drowsiness (Refs. 1 through 6).

The Panel recognizes that phenindamine may produce stimulation in some persons and drowsiness in others (Ref. 7). In one study, stimulation is reported to have occurred in 35 percent of patients (Ref. 4). In a review of clinical studies (Ref. 7) comprising 250 patients with allergic rhinitis, it was reported that 3 percent had drowsiness and 12 percent had stimulation. However, data that would establish the frequency of stimulation or drowsiness among those taking the drug in recommended dosages are inadequate and cannot be used for making phenindamine an exception with respect to a warning regarding the occurrence of drowsiness as a side effect.

The Panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which a minimum of 14 million dosage units were sold. (See part VII. paragraph A.6. above—Human toxicity.) Of the 118 reported suspected poisonings for phenidamine tartrate, 21.2 percent exhibited some symptoms and 10.2 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There were no fatalities reported with the drug.

The Panel's review of the data supplied by the Food and Drug Administration disclosed no adverse reaction reports on phenindamine tartrate since 1968 (Ref. 8).

The Panel concludes that phenindamine tartrate is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) *Effectiveness.* The Panel concludes on the basis of clinical reports that phenindamine tartrate is effective for OTC use in the treatment of the symptoms of allergic rhinitis (Refs. 2, 3 and 6).

Phenindamine tartrate demonstrated antihistaminic activity in animals. It could protect guinea pigs against lethal doses of histamine. The histamine-induced contraction of guinea pig intestinal strips in vitro was inhibited by phenindamine. The drug also had a protective action in guinea pigs against fatal anaphylactic shock produced by horse serum sensitization (Refs. 1 and 2).

Clinical trials have also shown the effectiveness of phenindamine tartrate as an antihistamine in man. A dose of 200 mg of phenindamine inhibited the wheals and flares produced in ragweed-sensitive patients after they were skin-tested with ragweed or histamine (Ref. 2).

In a subjective, uncontrolled clinical evaluation of phenindamine in 389 patients with allergic conditions such as hay fever, allergic perennial rhinitis, bronchial asthma, atopic dermatitis, contact dermatitis, urticaria and angioneurotic edema, and migraine, a dose of 25 mg every 4 hours was given orally (Ref. 2). Of the 180 patients in the study with hay fever who took the drug during the hay fever season, 44 percent reported complete relief, 32 percent reported moderate relief, 14 percent had slight relief and 10 percent reported no relief. In the 71 patients with allergic perennial rhinitis, 35 percent had complete relief, 39 percent moderate relief, 9 percent slight relief and 17 percent had no relief. The relief from a dose of 25 mg lasted approximately 2 to 5 hours. Of the 389 patients, 23 percent had side reactions such as nervousness, palpitations, nausea, vomiting, insomnia, drowsiness, headache, constipation, etc. No appreciable change was seen in blood pressure or electrocardiogram.

In another report, 78.2 percent of 197 patients with hay fever who were given a daily dose of 25 to 150 mg of phenindamine for an average of 17 days reported fair to excellent relief (Ref. 1). The drug was of benefit to 76.1 percent of the 71 patients with nonseasonal vasomotor rhinitis in this study.

The symptomatic relief of allergic rhinitis by daily doses of 25 to 200 mg of phenindamine was studied in 131 patients. Seventy-five to 100 percent relief was reported by 105 of these patients whose ages ranged from 2 to 70 years. Only 27 of the patients complained of side effects (Ref. 6). In a study of 40 patients with hay fever, a daily dose of 25 to 75 mg gave marked relief to 52.5 percent, moderate relief to 25 percent, slight relief to 15 percent and 7.5 percent had no relief (Ref. 4). Daily doses of 75 to 120 mg phenindamine for 15 to 120 days to 66 hay fever subjects gave complete

relief to 18 percent, partial relief to 62 percent and 20 percent were not helped (Ref. 3). Daily doses of 75 to 250 mg to 25 patients with vasomotor rhinitis brought no relief for 44 percent and complete relief for 20 percent. At 75 mg daily, approximately 15 percent of the patients showed side effects.

Experience has also indicated that the duration of effect of one 25 mg dose is 2 to 10 hours averaging 4 to 5 hours. The onset of action is rapid, occurring within 15 minutes of ingestion (Ref. 1). In one study, 86 percent of 66 patients with hay fever received moderate to complete relief receiving a dosage of 75 to 150 mg daily. In a review of the antihistamine drugs (Ref. 7), 76 percent of 912 patients with allergic rhinitis were benefited.

In one study, moderate to marked relief of hay fever occurred in 78 percent of 40 patients taking 50 mg daily (Ref. 4).

Seventy-eight percent of patients with hay fever noted fair to excellent relief (Ref. 1). A placebo failed to provide relief of the symptoms in these patients.

The Panel concludes that phenindamine tartrate 25 mg is the minimum effective OTC dosage for the relief of the symptoms of allergic rhinitis.

(3) *Dosage.* Adult oral dosage is 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours. Children 6 to under 12 years oral dosage is 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistamine active ingredients (See Part VII. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) *Warning.* "*Caution:* May cause nervousness and insomnia in some individuals."

(ii) *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 6.25 mg every 4 to 6 hours not to exceed 37.5 mg in 24 hours.

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g. *Pheniramine maleate.* The Panel concludes that pheniramine maleate is safe and effective for OTC use as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) *Safety.* Pheniramine maleate has been shown in animal experiments to possess a high degree of antihistaminic activity and a low order of toxicity (Refs. 1 and 2). Clinical experience has confirmed that pheniramine maleate is safe in the dosage ranges used as an antihistamine. The chief side effect of pheniramine appears to be sedation. It also appears to have a mild atropine-like effect. Since most of the studies have been done with other drugs combined with pheniramine, the action of this drug alone cannot be described with certainty. In one study in which pheniramine alone was given, drowsiness and dryness of the mouth (atropine-like effect) occurred in 11 percent of the subjects (Ref. 3). In a review of clinical studies with the antihistamine drugs (Ref. 4) 29 percent of 49 patients receiving pheniramine maleate 25 mg for allergic rhinitis had side effects, chiefly drowsiness. Among 184 subjects receiving 10 mg pheniramine 4 times daily in the course of a double-blind study of the "common cold," side effects, chiefly drowsiness, did not significantly exceed the side effects in an equal number of subjects receiving a placebo (Ref. 5). There appear to be no reports of accidental overdose. A single case was described in which acute psychosis occurred following treatment for 2 months with pheniramine 25 mg 3 times daily (Ref. 6). Following withdrawal of pheniramine, recovery occurred in 8 days. No definite conclusion could be drawn in this case as to the role played by pheniramine. An atropine-like effect suggests a potential hazard in patients with enlargement of the prostate gland and also narrow angle glaucoma and this effect has also been considered to be disadvantageous in patients with asthma although data supporting this potentially adverse effect are not available.

The Panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which a minimum of 291 million dosage units were sold. (See part VII. paragraph A.6. above—Human toxicity.) Of the 358 suspected poisonings reported for pheniramine maleate, 20 percent exhibited some symptoms and 1.7 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There were no fatalities reported with the drug identified as a contributing cause of death.

The Panel's review of the data supplied by the Food and Drug Administration disclosed no adverse reaction reports on pheniramine maleate since 1968 (Ref. 7).

The Panel concludes that pheniramine maleate is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) *Effectiveness.* Pheniramine maleate has been shown in animal experiments to possess a high degree of antihistaminic activity (Refs. 1 and 2).

There are no well-controlled studies documenting the effectiveness of pheniramine maleate as an antihistamine. In a review of several reports of clinical experience, pheniramine in a dose of 25 mg gave relief of allergic rhinitis in 81 percent of 442 patients (Ref. 4). Likewise the drug gave relief in 66 percent of patients with nonallergic rhinitis (vasomotor rhinitis).

The Panel concludes that pheniramine maleate 12.5 mg is the minimum effective OTC dosage for the relief of the symptoms of allergic rhinitis.

(3) *Dosage.* Adult oral dosage is 12.5 to 25 mg every 4 or 6 hours not to exceed 150 mg in 24 hours. Children 6 to under 12 years oral dosage is 6.25 to 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistamine active ingredients (See part VII. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) *Warning.* "May cause marked drowsiness".

(ii) *Professional labeling.* The Panel recommends that labeling provided to health professionals, (but not to the general public), may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 3.125 to 6.25 mg every 4 to 6 hours not to exceed 37.5 mg in 24 hours.

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h. *Promethazine hydrochloride.* The Panel concludes that promethazine hydrochloride is safe and effective for OTC use as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) *Safety.* Promethazine is well-tolerated by laboratory animals; doses which greatly exceed those giving protection against histamine are well tolerated by guinea pigs (Ref. 1). Like other antihistamine drugs, promethazine may cause drowsiness when taken in clinically effective doses. In a study in which up to 1 gm was administered therapeutically 4 times daily to psychiatric patients, drowsiness occurred as the most important and frequent side effect (Ref. 2). In a suicide attempt a 35-year-old female survived an estimated dose of 1.5 gm, developing coma and clonic contractions (Ref. 3). Another such case had a similar course after the patient consumed 500 mg of promethazine (Ref. 4). Children may be less tolerant of this drug. Seven to 10 hours after a 12-year-old boy ingested 200 mg, he was hospitalized with many symptoms including restlessness, excitation, stupor, fright and hallucinations. Recovery followed in 3 days (Ref. 5).

The Panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which a minimum of 385 million dosage units were sold. (See part VII. paragraph A.6. above—Human toxicity.) Of the 56 reported suspected poisonings for promethazine, 28.6 percent exhibited some symptoms and 14.3 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There were no fatalities reported with the drug. This relative incidence of adverse reactions is remarkably low in light of the substantial and long use of the drug (4½ billion oral doses have been used since 1951 (Ref. 6)).

The Panel's review of the data supplied by the Food and Drug Administration showed a total of 169 adverse reactions involving marketed products containing promethazine (Ref. 7). Of the 169, 4 adverse reactions were listed as being definitely related to the oral ingestion or injection of promethazine, 105 were listed as probably caused by the drug's use, 49 were listed as possibly related to its use and 11 were listed as remotely related to promethazine.

Of particular concern are blood dyscrasias which have been reportedly associated with the drug. A total of five adverse experience reports have remotely related blood dyscrasias to promethazine. Analysis of the experience reports indicates that these dyscrasias are not attributable to promethazine. One case of agranulocytosis is reported to have occurred in a patient who was receiving promethazine and methaqualone. The patient's white blood cell count and the neutrophils began to increase and returned to normal 3 days after methaqualone was discontinued. Agranulocytosis was reported in another patient receiving large doses of two antibiotics intravenously who was also receiving oral promethazine. Additional drugs in the regimen included a thyroid derivative and tetracycline prior to the other medications. This blood dyscrasia may well be attributed to the two antibiotics, methacillin and/or cephalothin, both of which are known to cause agranulocytosis. A case of thromocytopenia was reported in a 2-year-old child who developed symptoms of an upper respiratory infection with fever and cough. The patient was treated with aspirin, a product containing triprolidine hydrochloride and pseudoephedrine, and promethazine syrup with dextromethorphan. The attending physician believed that the thromocytopenia was caused by the basic disease process and not by the medications. Leukopenia and thrombocytopenia was reported in a patient receiving promethazine but there are no data provided on the patient's disease state or concomitant drug therapy. On the basis of this limited data it is not possible to determine the cause and effect relationship between promethazine and the blood dyscrasias. Another patient, an 88-year-old male, with an upper respiratory infection who was receiving promethazine, tetracycline and propoxyphene reportedly had hypoplastic anemia secondary to drug reaction. Again, no information on drug dosages or final diagnosis was available and promethazine cannot be determined to cause the hypoplastic anemia.

A further review of adverse reaction reports from the Boston Collaborative Drug Surveillance Program and the University of Florida adverse reaction study shows a low incidence (5.2 percent and 7.1 percent, respectively) of adverse reactions (Ref. 8). The most frequently occurring reactions were drowsiness and confusion or disorientation. In contrast to other phenothiazine derivatives, promethazine showed few incidences of extrapyramidal syndrome (1 of 2,468 patients followed in the studies who received promethazine) and hypotension (3 of 2,468 patients followed in the studies who received promethazine).

Clinical studies (Refs. 1, 9, 10, and 11) indicate that the drug is safe in a dosage effective in allergic rhinitis and authorities in the field of clinical allergy concur (Refs. 12 and 13).

The Panel is aware of the current package insert labeling for promethazine which warns against various possible adverse reactions. These adverse effects are those usually associated with phenothiazine derivatives and clinical experience generally supports their occurrence with most other phenothiazine compounds. According to one authority, jaundice, excessive hypotension or hematopoietic damage have not been reported (Ref. 13). After analysis of published research studies and adverse experience reports on promethazine, however, the Panel concluded that promethazine does not cause the wide range of serious or potentially toxic effects characterizing other members of the chemical class of phenothiazines.

It should be noted that while promethazine is currently available only by prescription, the dosage levels are comparable to those that would be available in OTC use. Therefore, the safety considerations presented to the Panel for prescription marketing have given a reasonably accurate picture of what to expect from OTC use of this ingredient.

The Panel concludes that promethazine hydrochloride is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) *Effectiveness.* In animal studies, promethazine is highly effective in protecting guinea pigs against histamine and the drug is also effective in protecting guinea pigs against anaphylaxis (Ref. 13). Promethazine appears to share with other antihistamine drugs the capacity to suppress rhinorrhea, sneezing and itching but differs from most other antihistamine drugs under consideration in having a longer duration of action. However, no controlled clinical trials appear to have been done to test the effectiveness of promethazine in allergic rhinitis nor in the "common cold". A number of uncontrolled studies indicate that promethazine is effective in the treatment of allergic rhinitis in a dose of 12.5 to 25 mg (Refs. 1, 7, 10, and 13). Based on clinical experience and the data available, the Panel concludes that promethazine is effective when taken in the recommended dosage.

The Panel concludes that promethazine hydrochloride 6.25 mg is the minimum effective OTC dosage for the relief of the symptoms of allergic rhinitis.

(3) *Dosage.* Adult oral dosage is 6.25 to 12.5 mg every 8 to 12 hours not to exceed 37.5 mg in 24 hours. Children 6 to under 12 years oral dosage is 3.125 to 6.25 mg every 8 to 12 hours not to exceed 18.75 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistamine active ingredients (See part VII. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) *Warning.* "May cause marked drowsiness."

(ii) *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 1.56 to 3.125 mg every 8 to 12 hours not to exceed 9.375 mg in 24 hours.

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i. *Pyrilamine maleate.* The Panel concludes that pyrilamine maleate is safe and effective for OTC use in suppressing symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) *Safety.* Chronic animal toxicity studies done by Winter et al. showed no evidence of a cumulative effect (Ref. 1). In that study, pyrilamine maleate had been administered to rats, dogs and monkeys for varying lengths of time up to 6 months. The following doses appeared to be entirely safe: in rats 10 mg/kg 5 times weekly for 6 months and up to 200 mg/kg daily for 32 days; in dogs, 20 mg/kg 5 times weekly for 6 months, and in monkeys, 50 mg/kg daily for 35 days. No toxic signs nor any hematological, biochemical or pathological abnormalities were found in the animals on these doses.

In human studies, pyrilamine has a low order of toxicity. Side effects are not infrequent but are usually mild. They include drowsiness, listlessness, irritability, and anorexia (loss of appetite) (Ref. 2). In a study by Gay et al., only 3 percent of the 147 patients showed any sign of drowsiness and the incidence of loss of appetite, nausea and vomiting occurred in 27 percent of the patients (Ref. 3).

Two fatalities were reported with pyrilamine maleate. One was of a 21-month-old child who had ingested 600 mg and died 2¾ hours after ingestion, exhibiting a post-convulsive coma. The other fatality was of a 2-year-old child that had ingested 1,400 mg and died during convulsions 4 hours after ingestion (Ref. 4).

The Panel's review of the data supplied by the Food and Drug Administration disclosed a total of two adverse reaction reports on pyrilamine since 1968 (Ref. 5). Both of the adverse reactions were miner and neither was listed as directly related or probably caused by the ingestion of pyrilamine.

The Panel has also considered the most recent data available from the records compiled from Poison Control Centers. (See part VII. paragraph A.6. above—Human toxicity.) Of the 358 suspected poisonings reported for pyrilamine maleate, 18.7 percent exhibited symptoms and 1.7 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There were no fatalities reported with the drug.

The Panel's review of the data supplied by the Food and Drug Administration showed a total of only two adverse reaction reports on pyrilamine since 1968 (Ref. 5). Of the two reports, no adverse reactions were listed as being definitely related to ingestion of pyrilamine; both were listed as possibly related to its ingestion.

The Panel concludes that pyrilamine maleate is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) *Effectiveness.* In vitro and in vivo animal studies indicate that pyrilamine has an intense antihistamine action (Ref. 6) and that the drug has protective activity against histamine and anaphylaxis in the guinea pig (Ref. 7). Pyrilamine and diphenhydramine were equally effective in protecting against anaphylaxis and in preventing histamine-induced contractions of sensitized guinea pig ileum. Winter found in his animal studies that 0.01 mg/kg of pyrilamine protected 100 percent of 19 guinea pigs against a lethal dose of histamine (0.5 mg/kg) for 2 hours (Ref. 1). Gay et al. used the same dose and 91 percent of the guinea pigs were protected for 2 hours (Ref. 3). In this same study, 80 percent of 10 guinea pigs pretreated with 0.1 mg/kg of pyrilamine survived. The pharmacological effects and the histamine antagonism of pyrilamine are comparable to those of chlorpheniramine and similar to those of the other antihistamines (Refs. 1, 6, and 7).

In an uncontrolled study of several antihistaminic drugs including pyrilamine (Ref. 3), this drug was given to 102 patients with allergic rhinitis of whom 70 percent were improved. Two other comparative uncontrolled studies gave similar findings (Refs. 8 and 9) and in a review of the antihistaminic drugs, 66 percent of 604 patients with allergic rhinitis usually receiving a dose of 50 mg were benefited (Ref. 10).

The Panel concludes that pyrilamine maleate 25 to 50 mg is an effective OTC dosage range for the relief of the symptoms of allergic rhinitis.

(3) *Dosage.* Adult oral dosage is 25 to 50 mg every 6 to 8 hours not to exceed 200 mg in 24 hours. Children 6 to under 12 years oral dosage is 12.5 to 25 mg every 6 to 8 hours not to exceed 100 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistamines. (See part VII. paragraph B.1. below—Category I Labeling). In addition, the Panel recommends the following specific labeling: *Professional labeling:* The Panel recommends that the labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 6.25 to 12.5 mg every 6 to 8 hours not to exceed 50 mg in 24 hours.

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j. *Thonzylamine hydrochloride.* The Panel concludes that thonzylamine hydrochloride is safe and effective for OTC use as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the dosage section discussed below.

(1) *Safety.* Thonzylamine hydrochloride has been shown in animal experiments to possess antihistaminic activity and a low order of toxicity (Ref. 1). Clinical experience has confirmed that thonzylamine hydrochloride is safe in the dosage ranges used as an antihistamine. Although there are no controlled studies using thonzylamine, the incidence and degree of side effects appear to be less than with most other antihistamines (Refs. 2 and 3). In one report in which patients with "allergies" received an average dose of 50 to 100 mg orally 2 to 4 times daily, investigators in seven separate studies concurred that

thonzylamine was the "least toxic" of the antihistamines then in general use (Ref. 4). In other studies, the incidence of side effects was also low (Refs. 5 through 9) but the dosage of thonzylamine was generally not specified. Of the entire series of 874 patients, an average of 10.9 percent reported side effects which consisted of slight nervousness, headache, gastric disturbance, drowsiness, and dizziness. Most of these side effects were not significant, but the drug was discontinued in a small number of patients due to headache or gastric disturbance.

The Panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which 80 million dosage units were sold. (See part VII. paragraph A.6. above—Human toxicity.) There were no reported suspected poisonings for thonzylamine hydrochloride.

The Panel's review of the data supplied by the Food and Drug Administration showed no adverse reaction reports on thonzylamine hydrochloride since 1968 (Ref. 10).

The Panel concludes that thonzylamine hydrochloride is safe for OTC use as an antihistamine at the dosage ranges described below.

(2) *Effectiveness.* Thonzylamine hydrochloride, administered orally, is generally recognized as possessing antihistamine properties and providing symptomatic relief in allergic rhinitis. However, there are only uncontrolled studies documenting the effectiveness of thonzylamine hydrochloride as an antihistamine.

Most textbooks and several studies (Refs. 5, 7, and 9) indicate thonzylamine hydrochloride has antihistamine action. In a series of uncontrolled studies, 64 percent of patients with "allergy" benefited from oral doses of 50 to 100 mg thonzylamine hydrochloride 2 to 4 times daily (Ref. 4) while in the other studies, thonzylamine was found to be about as effective as other antihistamine drugs. In a review of the antihistamines, thonzylamine 50 mg was reported to have given benefit in 54 percent of 384 patients with allergic rhinitis (Ref. 11). The studies cited suggest that a recommended dosage of 50 to 100 mg up to 4 times a day is effective.

The Panel concludes that thonzylamine hydrochloride 50 to 100 mg is an effective OTC dosage range for the relief of the symptoms of allergic rhinitis.

(3) *Dosage.* Adult oral dosage is 50 to 100 mg every 4 to 6 hours not to exceed 600 mg in 24 hours. Children 6 to under 12 years oral dosage is 25 to 50 mg every 4 to 6 hours not to exceed 300 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I Labeling for antihistamine active ingredients. (See part VII. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 2 to under 6 years oral dosage is 12.5 to 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours.

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Category I Labeling

The Panel recommends the following Category I labeling for antihistamine active ingredients to be generally recognized as safe and effective and not misbranded as well as the specific labeling discussed in the individual ingredient statements:

a. *Indications.* (1) "Alleviates, decreases, or for temporary relief of, running nose, sneezing, itching of the nose or throat and itchy and watery eyes as may occur in allergic rhinitis (such as hay fever)".

(2) "Alleviates, decreases, or for temporary relief of, running nose as may occur in allergic rhinitis (such as hay fever)".

(3) "Alleviates, decreases, or for temporary relief of, sneezing as may occur in allergic rhinitis (such as hay fever)".

(4) "Alleviates, decreases, or for temporary relief of, itching of the nose or throat as may occur in allergic rhinitis (such as hay fever)".

(5) "Alleviates, decreases, or for temporary relief of, itchy and watery eyes as may occur in allergic rhinitis (such as hay fever)".

(6) "Dries running nose as may occur in allergic rhinitis (such as hay fever)".

b. *Warnings.* The drowsiness often produced by the antihistaminic drugs is a potential hazard under circumstances in which alertness is important. Therefore the Panel believes that a warning regarding drowsiness should appear on the label for all products containing antihistamine drugs. The Panel believes it is prudent to regard the atropine-like effects of the antihistamines as a possible hazard in patients with glaucoma and as possibly leading to difficulty in urination in those individuals with prostatic hypertrophy. In asthma, the antihistamines may cause drying of bronchial secretions, making expectoration of the secretions more difficult and thereby increasing obstruction of the airway.

Therefore, the Panel recommends that labeling include the following warnings and cautions: (1) For active ingredients not containing the specific warning "May cause marked drowsiness", the statement "May cause drowsiness" should be used.

(2) "May cause excitability especially in children".

(3) "Do not take this product if you have asthma, glaucoma or difficulty in urination due to enlargement of the prostate gland except under the advice and supervision of a physician".

(4) *"Caution.* Avoid driving a motor vehicle or operating heavy machinery".

(5) *"Caution:* Avoid alcoholic beverages while taking this product".

(6) "Do not give this product to children under 6 years except under the advice and supervision of a physician".

There are insufficient data to establish the safety of OTC preparations containing antihistamines in children under 6 years. Individuals vary widely in the degree to which drowsiness, and less commonly, other adverse effects occur when they are given antihistaminic drugs. For this reason, the frequency and severity of side effects cannot be predicted. Respiration may be depressed and this effect can be serious in infections involving the airway. Parents and others may have difficulty assessing the intensity of induced side effects and children cannot be expected to understand their potential hazards. For these reasons, medical supervision is recommended when children under 6 years are given antihistaminic drugs.

2. *Category II conditions under which antihistamine ingredients are not generally recognized as safe and effective or are misbranded.* The use of antihistamines under the following conditions is unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel concludes that the following labeling should be removed from the market until scientific testing supports their use.

Category II Labeling

The Panel concludes that the use of certain labeling claims related to the safety and/or effectiveness of the product are unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel has previously discussed such labeling. (See part II. paragraph O. above—CCABA Product Labeling Claims Not Supported by Scientific Evidence.) However, labeling that is de-

scriptive of the product such as its taste or appearance is acceptable.

Unacceptable claims for antihistamines include statements such as the following:

a. *All claims which state or imply a therapeutic action or safety property peculiar to the preparation that cannot be demonstrated in controlled studies.* These include claims such as "specially formulated", "scientifically improved", or "selected", "natural", "extra strength", "teamed components", "superior to ordinary—".

b. *Claims implying a physiological effect which either have no foundation or meaning or will be meaningless or misleading to the public.* Items include: "gets at the root of—"; "fights"; "wakes up"; "recommended by doctors"; "travels through the blood stream".

c. *Claims for relief where time is indeterminate.* Terms include: "fast"; "prompt".

d. *Claims for relief of nasal symptoms (other than running nose, itchy nose, and sneezing).* Terms include: "decreases nasal obstruction"; "decreases nasal congestion"; "relief of stuffy nose (stopped up nose, nasal stuffiness, clogged up nose)".

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel concludes that adequate and reliable scientific evidence is not available at this time to permit final classification of the claimed active ingredients listed below. The Panel believes it reasonable to provide 3 years for the development and review of such evidence. Marketing need not cease during this time if adequate testing is undertaken. If adequate effectiveness data are not obtained within 3 years, however, the ingredients listed in this category should no longer be marketed as over-the-counter products. Effectiveness as an antihistamine must be demonstrated by controlled, double-blind studies because of the subjective nature of both the symptoms and the effects of any drug-induced changes.

Category III Active Ingredients

The Panel concludes that the available data are insufficient to permit final classification of the following claimed antihistamine active ingredients:

Phenyltoloxamine citrate
Thenyldiamine hydrochloride (oral)

a. *Phenyltoloxamine citrate.* The Panel concludes that phenyltoloxamine citrate is safe for OTC use but there are insufficient data available regarding its effectiveness to permit final classification as an antihistamine in suppressing the symptons of allergic rhinitis as specified in the proposed dosage section discussed below.

(1) *Safety.* Clinical experience has confirmed that phenyltoloxamine citrate is safe in the dose ranges used as an antihistamine. Animal studies have indicated phenyltoloxamine is one of the least toxic antihistamines. As much as 680 mg/kg given orally to rats produced no symptoms. In dogs, 10 mg/kg for 50 days was well tolerated (Ref. 1).

Studies in humans also suggest a low incidence of side effects at a dosage of 100 to 200 mg in 24 hours with moderate drowsiness occurring following dosage in excess of 200 mg in 24 hours (Ref. 2). One reference states that in therapeutic doses, soporific effects occur in less than 7 percent of patients (Ref. 3). A low incidence of side effects, 6.5 percent, was reported in one study in which allergy patients were given 25 or 50 mg 3 or 4 times daily (Ref. 4). In another study (Ref. 5), phenyltoloxamine was given for its "ataraxic" effect in a dosage of 300 mg daily, 100 mg after lunch for daytime sedation and 200 mg at bedtime for nighttime sedation. Side effects were reported to be minimal in this study.

Sainz (Ref. 6) performed a study in 48 patients to determine side effects and toxicity and found that mild drowsiness appeared at oral doses above 200 mg 4 times daily, or with single doses of 400 mg. Ataxia or abnormal reflexes were not noted at oral doses of 400 mg 4 times a day. There were no extrapyramidal symptoms. The EEG was not affected. A slight blood pressure increase was seen and doses higher than 200 mg 4 times daily produced adrenergic stimulation (increased salivation, gastritis, and diarrhea). Heartburn was found in 14 percent of patients taking the drug, and occasionally nausea was seen. No changes were noted in metabolic, nutritional, endocrine, hematologic, urologic or liver function parameters. Sainz concluded that the drug is not only safe but remarkably free from undesirable reactions at oral doses of the dihydrogen citrate salt of phenyltoloxamine at 100 mg (56 mg of the active moiety) 4 times daily.

The Panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which 423 million dosage units were sold. (See part VII. paragraph A.6. above—Human toxicity.) Of the 90 suspected poisonings reported for phenyltoloxamine citrate, 15.6 percent exhibited some symptoms and 5.6 percent exhibited symptoms serious enough to require treatment or observation at a hospital. There were no fatalities reported with the drug.

The Panel's review of data supplied by the Food and Drug Administration showed only one adverse reaction report on phenyltoloxamine citrate since 1968 (Ref. 7). The adverse reaction was listed as possibly related to abnormal kidney function tests.

The Panel concludes that phenyltoloxamine citrate is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of phenyltoloxamine citrate as an antihistamine. Phenyltoloxamine citrate is an antihistamine drug which in animal studies antagonizes most of the pharmacologic actions of histamine (Ref. 1). In clinical use, the drug appears to provide symptomatic relief of allergic symptoms (Refs. 2 and 3), although no controlled studies are available which permit a determination of the minimum effective dosage level.

Cronk and Naumann (Ref. 2) used a dosage of 25 to 50 mg 4 times daily, but reported "relief" only in patients receiving 50 mg 4 times daily. Seyler and Simon (Ref. 4) likewise recommended a dosage of 50 mg 3 or 4 times daily. Thus, clinical experience indicates a daily dosage of 150 to 200 mg.

The Panel concludes that although there are insufficient data to determine that phenyltoloxamine citrate is effective for the relief of the symptoms of allergic rhinitis, 50 mg is the proposed dosage at which this ingredient is most likely effective.

(3) *Proposed dosage.* Adult oral dosage is 50 mg every 4 to 6 hours not to exceed 300 mg in 24 hours. Children 2 to under 12 years oral dosages are identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistamine active ingredients. (See part VII. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 6 to under 12 years oral dosage is 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours; children age 2 to under 6 years oral dosage is 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours.

(5) *Evaluation.* Data to demonstrate effectiveness will be required according to the guidelines set forth below for testing antihistamine drugs. (See part VII. paragraph C. below—Data Required for Evaluation.)

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(7) OTC Volume 040325.

b. *Thenyldiamine hydrochloride (oral).* The Panel concludes that thenyldiamine hydrochloride (oral) is safe for OTC use but there are insufficient data available regarding effectiveness to permit final

classification as an antihistamine in suppressing the symptoms of allergic rhinitis as specified in the proposed dosage section discussed below.

(1) *Safety.* Clinical experience has confirmed that thenyldiamine hydrochloride (oral) is safe in the dosage ranges used as an antihistamine. The Panel has discussed the topical use of this drug as a nasal decongestant elsewhere in this document. (See part VIII. paragraph B.3.k. below—Thenyldiamine hydrochloride (topical).)

This drug was selected from among several related compounds because of marked antihistaminic and anti-anaphylactic properties and its low toxicity in animals (Refs. 1 and 2). Thenyldiamine is relatively nontoxic in animals. The oral LD_{50} for mice is about 190 mg/kg and for the guinea pig 240 mg/kg. There are no human safety data on the use of thenyldiamine administered orally alone. Data in uncontrolled studies with a combination product containing phenylephrine, acetaminophen and caffeine in addition to thenyldiamine in a dose of 25 to 150 mg daily revealed no significant changes in pulse rate or blood pressure (Refs. 3 and 4). Tabulations of side effects in patients receiving thenyldiamine hydrochloride alone and those receiving the combination formulation are difficult to interpret. The chief side effect appears to be sedation or drowsiness. Dizziness, dryness of the throat, headache, perspiration, and nausea have also been reported (Ref. 1).

The Panel has considered the most recent data available from the records compiled from Poison Control Centers during 1973 in which 2.5 million dosage units were sold. (See part VII. paragraph A.6. above—Human toxicity.) In the one suspected poisoning reported for thenyldiamine hydrochloride, no symptoms were exhibited.

The Panel's review of the data supplied by the Food and Drug Administration showed no adverse reaction reports on thenyldiamine hydrochloride since 1968 (Ref. 5).

The Panel concludes that thenyldiamine hydrochloride is safe for OTC use as an antihistamine in the dosage ranges described below.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of thenyldiamine hydrochloride (oral) as an antihistamine and reports of clinical experience are lacking. Thenyldiamine hydrochloride was official in U.S.P. XII. The dose was 15 mg orally. The frequency of treatment was not stated. A secondary reference source indicates the dosage to be 15 to 30 mg (Ref. 6). It appears that effective adult dosage may not be attained by using the commercially available OTC combination products which contain 2.5 to 7.5 mg per dosage unit.

In vitro studies of 0.03 gamma thenyldiamine in a 20 ml bath gave 75 percent inhibition of a standardized contraction produced by 0.3 gamma histamine. The drug compared well with diphenhydramine and pyrilamine as measured by histamine shock in the guinea pig where 1 mg/kg gave complete protection against the LD_{100}. The drug also gave marked protection against anaphylaxis in the guinea pig.

The Panel concludes that although there are insufficient data to determine that thenyldiamine hydrochloride (oral) is effective for the relief of the symptoms of allergic rhinitis, 15 to 30 mg are the proposed dosage at which this ingredient is most likely effective.

(3) *Proposed dosage.* Adult oral dosage is 15 to 30 mg every 4 to 6 hours not to exceed 180 mg in 24 hours. Children 2 to under 12 years oral dosages are identified in the labeling section discussed below under professional labeling. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for antihistamine active ingredients. (See part VII. paragraph B.1. above—Category I Labeling.) However, the Panel recommends that the Category I warning pertaining to use in children be revised from 6 years to 12 years with the following specific labeling: (i) *Warning.* "Do not give this product to children under 12 years except under the advice and supervision of a physician". (ii) *Professional labeling.* The Panel recommends that labeling provided to health professionals (but not to the general public) may contain the following additional dosage information: Children 6 to under 12 years oral dosage is 7.5 to 15 mg every 4 to 6 hours not to exceed 90 mg in 24 hours; children 2 to under 6 years oral dosage is 3.75 to 7.5 mg every 4 to 6 hours not to exceed 45 mg in 24 hours.

(5) *Evaluation.* Data to demonstrate effectiveness will be required according to the guidelines set forth below for testing antihistamine drugs. (See part VII. paragraph C. below—Data Required for Evaluation.)

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Category III Labeling

The Panel concludes that the available data are insufficient to permit final classification of the labeling claims identified below for antihistamines. Additional data are required to substantiate these claims for OTC antihistamine use: a. The following statements of duration are unacceptable unless documentation can specify the number of hours: "provides hours of relief" "all day" "all night".

b. "Alleviates, decreases or for temporary relief of running nose, sneezing, itching of the nose or throat and itchy and watery eyes as may occur in the common cold".

c. "Alleviates, decreases or for temporary relief of running nose as may occur in the common cold."

d. "Alleviates, decreases or for temporary relief of sneezing as may occur in the common cold".

e. "Alleviates, decreases or for temporary relief of itching of the nose or throat as may occur in the common cold".

f. "Alleviates, decreases or for temporary relief of itchy and watery eyes as may occur in the common cold".

g. "Dries running nose as may occur in the common cold".

h. *Claims that sleep will be facilitated.* Terms include "promotes restful sleep".

C. DATA REQUIRED FOR EVALUATION

The Panel has agreed that the protocols recommended in this document for the studies required to bring a category III drug into Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved technology in the future.

1. *Principles in the design of an experimental protocol for testing antihistamine drugs in allergic rhinitis.* a. *General principles.* The antihistaminic drugs are indicated for the symptomatic relief of IgE mediated allergic reactions. (See part II paragraph B.1.—Allergy.) When such reactions occur in the upper airway, the symptoms include sneezing, nasal discharge, nasal obstruction and itching of the nose, eyes, throat and ears. Such symptoms may or may not be accompanied by objective manifestations and for this reason, the patients' subjective sensations must be relied upon in the assessment of drug action. However, observations on the degree of edema of the nasal mucus membrane, the quantity of nasal discharge and the degree of injection of the sclerae may be helpful. The action of this group of drugs is limited to a few hours so that reepated doses at regular intervals are required for a sustained effect. All the antihistamines have side effects which again are subjective and have virtually no objective counterpart. Because of the subjective nature of both the symptoms and the effect of any drug-induced change, double-blind experimental control is especially important in the assessment of antihistaminic drugs.

Considerable experience in assessing therapy for allergic rhinitis caused by pollen (hay fever) has accumulated in the past 15 or more years in the course of efforts to determine the effectiveness of injection therapy (immunotherapy). Hitherto unrecognized problems in the selection of cases, the recording and scoring of symptoms, the tally of medication other than preparation(s) under test and the maintenance of experimental control became apparent (Ref. 1).

b. *Selection of patients.* The selection of patients should be limited of those

giving a clear history of having had allergic symptoms (hay fever) in at least two consecutive annual pollen seasons, who are free from symptoms at other times of the year, who react intensely to prick or scratch test with an extract of the appropriate pollen and who are otherwise in good general health. Patients who are not undergoing treatment with injections of allergenic extracts are preferred in the study.

The diagnosis of allergic rhinitis depends on both a history of the symptoms occurring at the times of allergenic exposure and their absence at other times, and the presence of intense relevant immunologic reactivity commonly determined by skin test. The patient's statements as to the time of year when symptoms occur may be in error. Therefore, documentation of the occurrence of symptoms at the time of exposure and the absence of symptoms at other times by observation of the patient is preferable to the history. Patients who react intensively by skin test to one pollen usually react to several other pollens also. Some of the reactions obtained by skin test may be irrelevant, a positive skin test being a necessary but not sufficient basis for identifying the cause of the symptoms. Thus the limitations of the history and the skin test need to be taken into account.

c. *Methods of study.* Assessment of therapy is based on a subjective response. Therefore, some means of quantitating symptoms must be adopted. Experience has indicated that this can be done satisfactorily by maintaining a daily tally of symptoms specifying type, e.g., sneezing, rhinorrhea, etc., duration in hours per day and intensity. Most patients have little difficulty in describing intensity numerically if they are given an intensity scale wherein points on the scale are defined by statements indicating the degree of discomfort (Refs. 2 and 3). Assignment of a numerical value to the degree of discomfort is space saving and greatly facilitates analysis of the data. However, account should be taken of the burden that a diary imposes on the patient. If too detailed and complicated, patients lose interest and record their symptoms in a perfunctory manner with the result that the data may be worthless. Some compromise between what is ideal and what is practicable must be reached. A satisfactory compromise was one in which the patient was given a symptom score card covering 1 week of study, to be filled out at the end of each day. The patient returned with the card at the end of each week at which time the patient was interviewed and the card rechecked for comprehensibility (Ref. 2). A new card was then supplied.

In a double-blind study which includes a placebo, some patients will suffer severe symptoms and the patient's continuation in the study will thereby be jeopardized. If the design of the study does not permit withdrawal from the study because of severe symptoms as an endpoint, then the investigator will be under great pressure to prescribe or permit use of medication other than the preparations under test or the patient will take medication without reporting having done so. Such medications, if taken, should be recorded accurately on the weekly diary form. Before the study is started, each such drug should be assigned a numerical value per dose based on anticipated efficacy in relieving symptoms of allergic rhinitis. The data may then be incorporated into the analysis at the end of the study.

A placebo identical in appearance and closely similar or identical in taste to the preparation(s) under test must be included in any assessment of drugs for the treatment of allergic rhinitis. Assignment of subjects to the drug(s) under test and the placebo must be random and the code identifying the preparations administered must not be broken until the study is complete.

Patients should be seen throughout the season not less often than every week. Patient diaries should be maintained in which the type, frequency and severity of symptoms and side effects are recorded daily as well as the medication taken. A crossover double-blind design with 30 or more patients is recommended in which each patient takes the test drug or the placebo on alternate weeks. If two dose levels of the test drug are tested, twice the number of patients will be needed.

d. *Interpretation of data.* Results should be subjected to statistical analysis, a p value of 0.05 or less (95 percent confidence or more) being acceptable as evidence of a drug effect. Evidence of drug effectiveness is required from a minimum of three positive studies based on results from three different investigators or laboratories.

All data submitted to the Food and Drug Administration must present both favorable and any unfavorable results.

(5) *Evaluation of safety.* The effect of the drug on the hepatic, renal and other systems should be monitored with particular emphasis on systems expected to be influenced by the drug. In the case of the antihistamines the central nervous system is often affected as indicated by such side effects as drowsiness and fatigue. These should not be induced by the drug at a frequency and intensity which might pose a hazard to the patient in the performance of a daily routine.

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2. *Principles in the design of an experimental protocol for testing antihistamine drugs in the "common cold."* a. *Assessment of the use of antihistaminic drugs for the "common cold."* The antihistaminic drugs have been widely used for the treatment of the symptoms of the "common cold." These drugs are usually marketed in combination products with nasal decongestant drugs. It is the Panel's view that this use of the antihistaminic drugs has been based predominantly on clinical impressions and uncontrolled clinical trials, the first of which was published by Brewster in 1947 (Ref. 1). On the other hand, a number of trials have been conducted with double-blind experimental controls but have failed for the most part to substantiate claims for effectiveness. These negative results indicate that if the antihistaminic drugs indeed have a favorable effect on the symptoms of the "common cold," this effect must be of a relatively low order. The subject has been recently reviewed (Ref. 2). The Panel concurs with the authors who stated:

> Many of the reports favoring antihistamine use were published some years ago when a well-controlled, randomized, double-blind clinical trial was not generally recognized as important in the evaluation of therapy. However, results supporting antihistamine use should be interpreted with caution when the research goals are imprecise and the study design permits biases. On the other hand, the findings of the less favorable reports that antihistamines appear not to prevent, abort, or relieve the symptoms of a cold, are supported by only a slightly greater specificity of definition and increased rigor of research methodology. Of all the reports, only two combined precision in definitions and controlled design; their conclusions did not support the use of antihistamines to prevent or relieve the symptoms of a cold. The general lack of specificity in defining disease and research goals and lack of rigor in research design in the majority of all studies is noteworthy. In short, there appears to be little valid evidence that antihistamines have any effect on the common cold.

Studies on the efficacy of the antihistaminic drugs in the treatment of the "common cold" may be misleading if the means of selection do not minimize inadvertent inclusion of subjects with allergic rhinitis, the symptoms of which are similar to those of the "common cold." Relief of symptoms will then be erroneously ascribed to favorable effect of the antihistaminic drugs on the symptoms of the "common cold" when indeed the observed benefit may be attributable to the known efficacy of the antihistaminic drugs in allergic rhinitis. The Panel has earlier discussed in this document both the "common cold" and allergic rhinitis. (See part II. paragraph B.3. above—The "common cold" and part II. paragraph B.6.a. above—Allergic rhinitis.)

The Panel concludes that the effectiveness of the antihistaminic drugs in relieving or allaying the symptoms of the "common cold" has not been established. If further studies on the effectiveness of the antihistaminic drugs in the treatment of the "common cold" are to be carried out, the Panel suggests that particular attention be directed to the selection of subjects and the means of recording symptoms using groups of patients large enough to give statistically meaningful results.

b. *General principles.* The symptoms of allergic rhinitis and the "common cold" have many similarities. A watery

nasal discharge is characteristic of allergic rhinitis and is usual in the "common cold" in the first 1 to 3 days. Sneezing is likewise common to both. Itching of the nose and eyes is more common in allergic rhinitis but also occurs in the "common cold." Nasal congestion occurs in both conditions. Coughing is not a frequent symptom of allergic rhinitis but it occurs in a small percent of cases. Cough likewise occurs in the "common cold," usually in the latter phase of the illness. Fever of low degree may occur in the "common cold," but it is not frequently present. Fever is absent in allergic rhinitis. Watering and redness of the eyes may occur in both conditions (Refs. 3, 4, and 5).

It is commonly stated in texts on allergic disease that examination of the patient with allergic rhinitis reveals swelling within the nose (swollen turbinates) which has a bluish or gray color (Ref. 5), whereas in the "common cold" their color is red (Ref. 4). No studies have been done to test the frequency with which this distinction is diagnostic and its reliability as a means of selecting patients for inclusion in a study of antihistaminic drugs in the treatment of the "common cold" remains uncertain. No other finding on examination appears to be useful in distinguishing between the early phases of the "common cold" and allergic rhinitis.

Because the symptoms of allergic rhinitis and the "common cold" are so similar, the two conditions are readily confused. The reported efficacy of the antihistaminic drugs in the treatment of the "common cold" has been attributed to the inadvertant inclusion of some cases of allergic rhinitis in some studies (Ref. 2) in which condition the antihistaminic drugs are recognized as effective. Unless steps are taken to eliminate subjects with allergic rhinitis from the study population, the results of the study of the "common cold" may be misleading.

c. *Selection of patients.* Since the distinction between allergic rhinitis and the "common cold," especially in its early phases, is difficult or impossible to make on the basis of symptoms and examination, the following means of minimizing inclusion of subjects with symptoms of allergic rhinitis should be adopted:

(1) Subjects giving a history of allergic rhinitis, e.g., hay fever or allergy to animals, should be excluded.

(2) Studies should be done in the months when allergic exposure is less likely and the "common cold" is more prevalent.

Selection of subjects according to these principles will minimize but cannot entirely eliminate the inclusion of some subjects who are having symptoms of allergic rhinitis and not a "common cold."

Subjects selected for the studies should be in good health except for the presence of a "common cold." The symptoms to be evaluated, i.e., runny nose, sneezing, etc., should have been present for 1 day but not longer than 3 days. Fever should be absent or should not exceed 100° F by mouth (adults) or 101° F by mouth (children under 12 years). Those with evidence of bacterial infection of the pharynx (exudative pharyngitis) or who have severe pharyngitis and severe sore throat should be excluded.

d. *Methods of study.* The drug(s) to be tested and a placebo should be identical in appearance and closely similar in taste identifiable by code only. Strict double-blind control throughout the study is essential. The groups of subjects should be matched by age, sex and severity and duration of illness.

Each group should contain 50 to 100 subjects. This large number is considered mandatory for the following reasons: a crossover design is not possible in so short an illness; the assessment is based on a subjective response; there are uncertainties in diagnosis; there is possible heterogeneity of the study population with respect to the type of virus causing the illness; and the effect of the antihistaminic drug in relieving symptoms of the "common cold" is not marked.

Medication other than the preparations in the test should not be taken during the course of the study. The design of the study should be such as to permit determination of each preparation's effect on each type of symptom and the stage in the disease in which this effect takes place. Therefore, each subject should maintain an appropriate tally of the type, duration and intensity of symptoms. The study should be of sufficient length to encompass the entire illness to provide data on all possible effects of the drug under test on the course of the disease. If a subject drops out of the study, the reason for doing so should be determined and recorded.

All data submitted to the Food and Drug Administration must present both favorable and any unfavorable results.

e. *Interpretation of data.* A recommended dose of the antihistamine should induce a statistically significant reduction in symptoms when compared to the placebo response. Results should be subjected to statistical analysis, a p value of 0.05 or less (95 percent confidence or more) being acceptable as evidence of a drug effect. A decision on drug effectiveness should be based on demonstrable drug effectiveness in a minimum of three positive comparable double-blind studies based on results from three different investigators or laboratories.

f. *Evaluation of safety.* If the safety of the drug has not been established, then the effect of the drug on the hepatic, renal and other systems should be monitored with particular emphasis on systems expected to be influenced by the drug. In the case of the antihistamines, the central nervous system is often affected, as indicated by such side effects as drowsiness and fatigue. These should not be induced by the drug at a frequency and intensity that might pose a hazard to the patient in the performance of a daily routine.

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VIII. NASAL DECONGESTANTS

A. GENERAL DISCUSSION

A nasal decongestant is an agent which reduces nasal congestion in patients with acute or chronic rhinitis. These agents may be administered topically as drops, sprays or inhaled vapors or orally in a solid or liquid dosage form. The drug effect is brought about by constriction of dilated blood vessels (vasoconstriction) within the nasal mucosa, thus temporarily reducing the swelling associated with inflammation of the mucous membrane lining the nasal passage (Ref. 1).

Topically administered nasal decongestants produce an intense degree of vasoconstriction, a factor responsible for the rapid and pronounced reduction in nasal obstruction. This intense local vasoconstriction also accounts for negligible absorption of the nasal decongestant into the general circulation. Consequently, negligible systemic effects occur following topical use of nasal decongestants unless excessive nasal solution is applied causing drainage into the stomach where it may be absorbed. Studies demonstrating minimal systemic absorption of radioactively labeled oxymetazoline following intranasal application (Ref. 2) and negligible cardiovascular effects following normal and excessive intranasal doses of phenylephrine or xylometrazoline (Refs. 3 through 7) support this point. Because of the remarkable degree of nasal decongestion which follows topical application of these agents, there is the tendency on the part of patients to administer nasal decongestants too frequently and for too long a period of time. Continued and intense drug-induced vasoconstriction can lead to rebound dilation of the blood vessels as the drug effect subsides. This phenomenon, which intensifies nasal congestion and perpetuates the rhinitis condition, has been termed "rebound congestion." This problem is minimized if topically applied decongestants are administered in accordance with label directions at recommended intervals for periods not exceeding 3 days.

Another practical caution with the use of topically applied decongestants is in regard to the possible spread of infection if the drug dispenser is used by more than one person. This can occur if the tip of the dropper or spray container comes in contact with the nose during drug administration.

Some of the nasal decongestants (sympathomimetic amines) are also effective when administered orally. Although the intensity of vasoconstriction in the nasal mucosa and associated symptomatic re-

lief of nasal congestion are less than that produced by the topical application of decongestants, the problem of rebound congestion is not a factor with use of the orally administered nasal decongestants. These orally administered sympathomimetic amines are distributed by the circulation to other target tissues as well as the nasal mucosa and thus produce side effects not seen following use of nasal decongestants topically.

In general, side effects associated with recommended oral doses of OTC nasal decongestants are minimal, but at higher doses may include nervousness, dizziness, and sleeplessness. Individuals with disease conditions which can be aggravated by sympathomimetic drug action, e.g., high blood pressure, heart disease, diabetes mellitus and hyperthyroidism, should not use decongestants orally except under the advice and supervision of a physician. Likewise, patients taking other drugs whose action can intensify the sympathomimetic drug action, e.g., monoamine oxidase inhibitors, should not take nasal decongestants orally except under the advice and supervision of a physician. The Panel does not feel these restrictions should apply to topically applied nasal decongestants when administered in recommended doses because of their localized action, i.e., minimal systemic absorption.

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B. CATEGORIZATION OF DATA

1. *Category I conditions under which nasal decongestant ingredients are generally recognized as safe and effective and are not misbranded.*

Category I Active Ingredients

The Panel has classified the following nasal decongestant active ingredients as generally recognized as safe and effective and not misbranded:

Ephedrine preparations (topical): Ephedrine, Ephedrine hydrochloride, Ephedrine sulfate, Racephedrine hydrochloride
Naphazoline hydrochloride (topical)
Oxymetazoline hydrochloride (topical)
Phenylephrine hydrochloride (oral/topical)
Phenylpropanolamine preparations (oral): Phenylpropanolamine bitartrate, Phenylpropanolamine hydrochloride, Phenylpropanolamine maleate
Propylhexedrine (inhalant)
Pseudoephedrine preparations (oral): Pseudoephedrine hydrochloride, Pseudoephedrine sulfate
Xylometazoline hydrochloride (topical)

a. *Ephedrine preparations (ephedrine, ephedrine hydrochloride, ephedrine sulfate, racephedrine hydrochloride) (topical).* The Panel concludes that ephedrine and its salts are safe and effective as topical nasal decongestants for OTC use as specified in the dosage section discussed below.

(1) *Safety.* Clinical experience has confirmed that ephedrine and its salts (topical) are safe in the dosage ranges used as nasal decongestants. Having been introduced from China in 1924 (Ref. 1) there has been a long experience with this drug which is used orally, chiefly from bronchodilation and usually in a dosage of 25 mg 4 times daily and topically in the nose as a 0.5 percent to 3 percent solution (Ref. 2). No reports describing adverse effects when used topically were encountered nor were there studies directed at the question of adverse local effects. Based on general clinical experience with topical nasal decongestants, rebound congestion would be expected with continued use. However, concentrations of 1 percent or less, as judged by the clinical experience of the Panel, would not be expected to cause this reaction if use is limited to a few days.

(2) *Effectiveness.* Extensive clinical experience indicates that ephedrine and its salts in 0.5 to 1 percent concentrations applied as drops or spray have a nasal decongestant effect (Ref. 3). Ephedrine as a prototype of the topical sympathomimetic nasal decongestant agents has been compared to other effective topical nasal decongestants in both objective measurement studies (Ref. 4) and subjective observation of nasal decongestant activity (Refs. 5 and 6) in patients with acute rhinitis. Ephedrine sulfate in 1 percent solution has been demonstrated to induce a prompt nasal decongestant effect which persists at maximal levels for up to 1 hour and gradually declines to pretreatment levels by the 4th hour.

(3) *Dosage.* Adult topical dosage is 2 to 3 drops or sprays in each nostril of a 0.5 percent aqueous solution not more frequently than every 4 hours. Children 6 to under 12 years topical dosage is 1 to 2 drops or sprays of a 0.5 percent solution not more frequently than every 4 hours. For children under 6 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients (see part VIII. paragraph B.1. below—Category I Labeling). In addition, the Panel recommends the following specific labeling: *Warning:* "Do not give this product to children under 6 years except under the advice and supervision of a physician".

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b. *Naphazoline hydrochloride (topical).* The Panel concludes that naphazoline hydrochloride is safe and effective as a topical nasal decongestant for OTC use as specified in the dosage section discussed below.

(1) *Safety.* Clinical experience has confirmed that naphazoline hydrochloride (topical) is safe in the dosage ranges used as a nasal decongestant. Studies involving visualization of the nasal mucosa following a single application of naphazoline, 0.05 to 0.1 percent, revealed rebound congestion as a fairly consistent sequel to the 4 to 6 hour period of nasal decongestion (Refs. 1 and 2). The tendency for frequent and continued use due to rebound congestion has been reported by several authors (Refs. 3 through 6). The continued use of naphazoline hydrochloride may result in dependence. To avoid this dependence, naphazoline use should not exceed 3 days duration.

In infants and young children, nasal administration as well as accidental ingestion of 0.05 to 0.1 percent naphazoline have been associated with systemic effects such as sedation, nervousness, increase in systolic blood pressure and bradycardia (Refs. 7 through 13). Furthermore, because rebound congestion with naphazoline is also a problem in infants, this nasal decongestant should probably not be used in children under 6 years (Ref. 1). For children 6 to 12 years, the pediatric concentration of 0.025 percent, should be used to minimize exposure to excess quantities of the drug.

(2) *Effectiveness.* Single dose applications of naphazoline, 0.1 percent in adult rhinitis patients using objective meas-

urement, revealed onset of nasal decongestion within 10 minutes and persisting up to 6 hours (Refs. 2 and 14). A single-dose objective measurement study in children demonstrated nasal decongestion of up to 5 hours duration (Ref. 1). The number and ages of the children and the concentration of naphazoline were not specified. In one study involving repeated administration of 0.05 percent naphazoline drops over a 1-week period, 34 of 35 patients experienced satisfactory nasal decongestion as judged subjectively by the patient and by visualization of the nasal mucosa (Ref. 15).

(3) *Dosage.* Adult topical dosage is 1 to 2 drops or sprays of a 0.05 percent aqueous solution in each nostril not more frequently than every 6 hours. Children 6 to under 12 years topical dosage is 1 to 2 drops or sprays of a 0.025 percent aqueous solution in each nostril not more frequently than every 6 hours. For children under 6 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling:

Warnings. (i) *For products containing a concentration of 0.025 percent naphazoline hydrochloride:* "Do not give this product to children under 6 years except under the advice and supervision of a physician".

(ii) *For products containing a concentration of 0.05 percent naphazoline hydrochloride:* "For adult use only. Do not give this product to children under 6 years since it may cause sedation if swallowed".

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c. *Oxymetazoline hydrochloride (topical).* The Panel concludes that oxymetazoline hydrochloride is safe and effective as a topical nasal decongestant for OTC use as specified in the dosage section discussed below.

(1) *Safety.* Clinical experience has confirmed that oxymetazoline hydrochloride (topical) is safe in the dosage ranges used as a nasal decongestant. Because the decongestant effect of oxymetazoline hydrochloride administered as drops or spray persists up to 5 to 6 hours and gradually declines thereafter, rebound congestion after single administration is negligible (Ref. 1). Twice a day dosing which should give adequate relief of nasal congestion should be expected to have a negligible incidence of rebound congestion. Several studies in adults with chronic rhinitis using either 0.05 percent drops or spray for 2 days to 4 weeks support this contention (Refs. 2 through 5). In one study 92 chronic rhinitis patients used 0.05 percent oxymetazoline spray in one nostril and 0.25 percent phenylephrine spray in the other nostril for 2 weeks. In this double-blind study rebound congestion was subjectively noted in one-third of the oxymetazoline-treated nostrils and two-thirds of the phenylephrine-treated nostrils (Ref. 6). No rebound congestion was noted over a 6 hour observation period following 5 drops of 0.025 percent oxymetazoline in each nostril of 33 children with allergic rhinitis (Ref. 7). In 30 children ages 4 to 10 years with allergic rhinitis, treatment with 0.025 percent oxymetazoline, 3 drops in each nostril 3 times a day, was associated with no loss of effectiveness during a 2-week treatment period as measured by electronic posterior rhinometry and no rebound congestion in a 2 week posttreatment evaluation period (Ref. 8).

Animal studies with radioactively labeled oxymetazoline indicate that the rate of systemic absorption from nasal application is too slow to achieve pharmacologic levels in the plasma (Ref. 9). Furthermore, double-blind studies in healthy adults reveal that 1.8 mg, the equivalent of 3.6 ml of a 0.05 percent solution, was the minimal orally administered dose of oxymetazoline producing any measurable effect on the cardiovascular system. Nonspecific EKG changes were not accompanied by blood pressure or heart rate changes (Ref. 10).

Because of these safety considerations the Panel recommends that oxymetazoline, which is currently a drug available only by prescription, be reclassified to permit OTC use as well.

(2) *Effectiveness.* In a double-blind subjective evaluation study, 92 adult patients with chronic rhinitis judged oxymetazoline, 0.05 percent spray, to induce nasal decongestion of 4 to 8 hours duration (Ref. 6). Objective studies in 20 patients with either chronic rhinitis due to allergy or acute rhinitis due to head cold showed effectiveness of a 0.05 percent oxymetazoline spray in two-thirds of the patients with airways still twice pretreatment size at the end of 6 hours (Ref. 1).

In a double-blind subjective evaluation study in 14 children, 2 to 6 years of age with allergic rhinitis, complete opening of the nasal airway was restored for 9 to 12 hours in 7 of the 14 patients receiving 1 drop of 0.025 percent oxymetazoline solution per nostril 2 times daily (Ref. 11). Objective studies in 30 children with allergic rhinitis, ages 4 to 10 years, receiving 0.025 percent oxymetazoline, 3 drops per nostril 3 times daily revealed persistent effectiveness over a 2-week treatment period (Ref. 8).

(3) *Dosage.* Adults and children 6 to under 12 years topical dosage is 2 to 3 drops or sprays of a 0.05 percent aqueous solution in each nostril 2 times daily (in the morning and evening). Children 2 to under 6 years topical dosage is 2 to 3 drops of a 0.025 percent aqueous solution in each nostril 2 times daily (in the morning and evening). Only drops should be used in children 2 to under 6 years since the spray is difficult to use in the small nostril. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. below—Category I Labeling).

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d. *Phenylephrine hydrochloride (oral/topical).* The Panel concludes that phenylephrine hydrochloride is safe and effective as an oral and as a topical nasal decongestant for OTC use as specified in the dosage section discussed below.

(1) *Safety.* (i) *As an oral nasal decongestant:* Clinical experience has confirmed that phenylephrine hydrochoride is safe in the dosage ranges used as an oral nasal decongestant.

Key and Violante reported that oral doses of 40 to 60 mg phenylephrine are necessary for consistent clinically meaningful cardiovascular effects such as increased diastolic pressure and reflex cardiac slowing (Ref. 1). Various reports reinforce the impression that in normal volunteers, blood pressure and pulse rate responses to 10 to 15 mg oral doses are equal to or only minimally greater than placebo. The maximum blood pressure increase does not exceed 2 to 7 mm Hg and the pulse rate changes do not exceed ±6 beats/minute. At doses of 25 mg, blood pressure increases up to 7 mm Hg and pulse changes of ±4–13 beats per minute were occasionally noted at some time intervals (Refs. 1 through 11). If patients were also receiving MAO inhibitors, however, even 10 mg doses of phenylephrine can induce clinically significant cardiovascular responses (Ref. 12).

Overtly perceived side effects at 10-mg doses approximate the incidence and pattern of a placebo response, whereas 15 to 25-mg doses are associated with an increasing incidence of symptoms related to mild central nervous system stimulation (Ref. 1).

(ii) *As a topical nasal decongestant:* Clinical experience has confirmed that phenylephrine hydrochloride is safe in the dosage ranges used as a topical nasal decongestant. Gundrum, Stambuck and Gaines reported a study in which supratherapeutic doses of 0.25 percent phenylephrine drops were chronically administered to rabbits (Ref. 13). The animals were given drops in each nostril either 3 times daily for 10 days or 10 times daily for 3 days. Examination of nasal tissue sections removed from these treated animals revealed no gross or microscopic changes from normal nasal mucosa.

Objective measurement studies showed transient rebound congestion in 3 of 12 adult rhinitis patients during 3 days of treatment with 0.5 percent phenylephrine spray (Ref. 14). Two thirds of 92 chronic rhinitis patients using 0.25 percent phenylephrine spray for 2 weeks noted rebound congestion (Ref. 15). Rhinoscopic observation revealed rebound congestion in 4 of 33 children following single doses of 0.25 percent phenylephrine drops, 5 drops in each nostril (Ref. 16).

Groups of patients with either cardiac, hypertensive and hyperthyroid disorders or diabetes mellitus were administered 5 drops of 0.25 percent or 1 percent phenylephrine solution into each nostril remaining in a head-low position for several minutes to maximize contact time (Refs. 17 and 18). No marked changes in blood pressure control readings were noted over a 45-minute observation period.

(2) *Effectiveness.* (i) *As an oral nasal decongestant:* Clinical studies have documented the effectiveness of phenylephrine as an oral nasal decongestant.

A series of five double-blind crossover placebo-controlled studies over a 3-year period in one laboratory revealed oral doses of phenylephrine from 5 to 25 mg to induce objectively measurable nasal decongestion when compared to placebo in patients with head cold as determined by an anterior rhinometry procedure (Refs. 5 through 9, and 19). Onset time was in 15 to 20 minutes with a duration of 2 to 4 hours. Maximum nasal decongestant effect was associated with the 25 mg dose. Two other laboratories conducted five similarly designed experiments, but because of greater apparent placebo response and variability in inpatient response the studies could not demonstrate a statistically significant difference of 10 to 25 mg from placebo (Refs. 20 through 24).

Subsequent studies measuring nasal airway resistance in head cold patients demonstrated significant nasal decongestant responses to 10 to 25 mg phenylephrine (Ref. 10). In these studies, 25 mg induced a maximal reduction of nasal resistance approaching that reported for noncongested normals, and 10 to 15 mg doses were clinically equivalent in inducing a decrease of nasal resistance about ⅔ maximal. Onset of these effects occurred within 15 minutes. The maximum effect occurred within 30 to 90 minutes with a gradual decline thereafter. A double-blind crossover study in 20 chronic rhinitis patients, however, could demonstrate no significant decrease in nasal airway resistance as compared to placebo with 10, 20, or 40 mg of phenylephrine, orally, over a 4-hour observation period (Ref. 25). In this study, phenylpropanolamine 40 mg and pseudoephedrine 60 mg each produced a significant decrease in nasal airway resistance persisting for at least 3 hours.

A recent double-blind controlled study involving 50 adult patients with nasal congestion associated with the "common cold" (25 patients in each group) demonstrated that a single oral 10 mg dose of phenylephrine led to a reduction in nasal airway resistance averaging 11 percent at 15 minutes, 21 percent at 30 minutes, 28 percent at 60 minutes and 26 percent at 120 minutes (Ref. 26). These reductions were all significantly different from placebo at the corresponding measurement times. These 50 patients were part of a 200-patient subjective evaluation study group with nasal congestion associated with the "common cold", 100 of each who received either 10 mg phenylephrine or placebo at 4-hour intervals over a 12-hour period. Patient subjective evaluation revealed that the phenylephrine treatment group experienced relief of nasal congestion, runny nose and sneezing throughout the 12-hour observation period. Symptom relief in each case was significantly different from that reported by the placebo group (Ref. 26).

(ii) *As a topical nasal decongestant:* In a double-blind crossover placebo-controlled study, phenylephrine was given as a 0.5 percent spray, 1 spray in each nostril repeated in 3 minutes, to one group of 16 patients with head cold and one group of 9 patients with allergic rhinitis. Objective measurements using both posterior electronic rhinometry and body plethysmography revealed significant nasal decongestion at the 30- and 60-minute recording times (Ref. 27).

In another study using 0.5 percent phenylephrine spray in 12 adult rhinitis patients, objectively measured nasal decongestant effects persisted from 1 to 3 hours following administration (Ref. 14). In a 2-week subjective evaluation study of phenylephrine 0.25 percent spray in 92 chronic rhinitis patients, the duration of effect following each dose was generally reported to be 4 hours or less (Ref. 15).

(3) *Dosage.* (i) *As an oral nasal decongestant:* Adult oral dosage is 10 mg every 4 hours not to exceed 60 mg in 24 hours. Children 6 to under 12 years oral dosage is 5 mg every 4 hours not to exceed 30 mg in 24 hours. Children 2 to under 6 years oral dosage is 2.5 mg every 4 hours not to exceed 15 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(ii) *As a topical nasal decongestant:* Adult topical dosage is 2 to 3 drops or sprays in each nostril of a 0.25 to 0.5 percent aqueous solution not more frequently than every 4 hours. Children 6 to under 12 years topical dosage is 2 to 3 drops or sprays in each nostril of a 0.25 percent aqueous solution not more frequently than every 4 hours. Children 2 to under 6 years topical dosage is 2 to 3 drops in each nostril of a 0.125 percent aqueous solution not more frequently than every 4 hours. Only drops should be used in children 2 to under 6 years since the spray is difficult to use in the small nostril. For children under 2 years, there

is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* (i) *As an oral nasal decongestant:* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. below—Category I Labeling.)

(ii) *As a topical nasal decongestant:* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Warnings:* (*a*) *For products containing a concentration of 0.125 percent phenylephrine hydrochloride:* "Do not give this product to children under 2 years except under the advice and supervision of a physician".

(*b*) *For products containing a concentration of 0.25 percent phenylephrine hydrochloride:* "Do not give this product to children under 6 years except under the advice and supervision of a physician".

(*c*) *For products containing a concentration of 0.5 percent phenylephrine hydrochloride:* "For adult use only. Do not give this product to children under 12 years except under the advice and supervision of a physician".

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e. *Phenylpropanolamine preparations (phenylpropanolamine bitartrate, phenylpropanolamine hydrochloride, phenylpropanolamine maleate) (oral).* The Panel concludes that phenylpropanolamine and its salts are safe and effective as oral nasal decongestants for OTC use as specified in the dosage section discussed below.

(1) *Safety.* Clinical experience has confirmed that phenylpropanolamine and its salts (oral) are safe in the dosage ranges used as nasal decongestants. Phenylpropanolamine is one of the most frequently used oral nasal decongestants, similar in action to ephedrine but with less central nervous system stimulation (Ref. 1). Subjective evaluation studies reveal that, in adults, phenylpropanolamine in plain capsules in doses up to 50 mg every 3 hours is associated with overt side effects either equal to or only slightly exceeding those of placebo. The side effects consisted of nervousness, insomnia, motor restlessness and nausea (Refs. 2 and 3).

Boyer reported three patients with prostatic hypertrophy who complained of urinary retention following ephedrine dosing but had no urinary retention at effective nasal decongestant doses of phenylpropanolamine (Ref. 3).

In three reports involving a total of over 200 children ages 2 to 15, phenylpropanolamine, in age-related doses of 6.25 to 25 mg 4 times daily in combination with acetaminophen and in one study also with phenyltoloxamine, was subjectively observed to relieve symptoms of nasal congestion with a low incidence of side effects (Refs. 4 through 6).

Individuals with normal blood pressure receiving phenylpropanolamine alone, either as a 50 mg plain capsule 4 times daily or as a 50 mg sustained release capsule 2 times daily had no significant effect on blood pressure or pulse rate. No adverse effect on cardiovascular systems was noted after 5 to 42 days of treatment (Refs. 7 through 10). Intravenous administration of phenylpropanolamine induced dose-related systolic blood pressure increases in humans. A 16 to 28 mm increase following 20 to 25 mg and a 44 to 82 mm increase following 50 mg were observed (Ref. 11).

Phenylpropanolamine 50 mg, in sustained release combination with belladonna alkaloids 0.2 mg, and chlorpheniramine 4 mg, was administered 2 times daily for 7 days to groups of patients with normal anterior chamber angle, with narrow angle but no glaucoma signs and to patients with frank glaucoma controlled by medication. No drug-induced alteration of intraocular tension was evidenced in any of the 3 groups of subjects (Refs. 12 and 13).

There have been isolated "letter to the editor" reports of individuals consuming therapeutic doses of phenylpropanolamine-containing preparations and experiencing an acute hypertensive episode (Ref. 14). Details relative to other contributing factors are usually too vague to determine if the phenylpropanolamine was entirely responsible. One "letter" reported an acute overdose of a sustained release phenylpropanolamine combination product, eight spansules containing 50 mg of phenylpropanolamine in combination with isopropamide and diphenylpyraline, was followed within 2 hours by an acute hypertensive response, severe headaches, restlessness and vomiting (Ref. 15).

One paper cited three cases of "psychotic episodes" associated with presumably therapeutic doses of phenylpropanolamine 50 mg, in combination with isopropamide and phenyltoloxamine (Ref. 16). The authors indicated that personality changes following phenylpropanolamine preparations were not an uncommon occurrence in patients in their hospitals.

In summary then, at therapeutic doses of phenylpropanolamine taken orally, the incidence of side effects in adults and

children is low. There have been isolated reports, however, of individuals experiencing idiosyncratic reactions of central nervous system stimulation and/or blood pressure rise following therapeutic doses. These effects would also be expected in most individuals with acute overdoses of the drug.

Prior MAO inhibitor treatment has been clearly shown to potentiate dangerously the blood pressure elevating effects of 30 to 50 mg phenylpropanolamine (Refs. 17 through 20).

A single incident was reported of phenylpropanolamine 50 mg, in combination with chlorpheniramine and isopropamide, antagonizing the antihypertensive effect of bethanidine sulfate, an analogue of guanethidine sulfate (Ref. 21). The antihypertensive effect of guanethidine can be antagonized by concurrent administration of amphetamine (Ref. 22). Current evidence suggests that phenylpropanolamine, being structurally similar to amphetamine, might be expected to exert a similar antagonistic effect (Ref. 23). However, this effect is important to note but not sufficiently documented to elicit a warning statement.

(2) *Effectiveness.* Three of five objective, double-blind, crossover studies comparing phenylpropanolamine with placebo in patients with chronic nasal congestion have demonstrated oral nasal decongestant effectiveness in 25 to 40 mg doses.

The earliest report, using anterior rhinometry in 88 patients, some with acute and some with chronic nasal congestion, showed that ephedrine sulfate 25 mg, orally was significantly better than placebo at the 1-hour time period; but phenylpropanolamine hydrochloride 25 mg, as well as pseudoephedrine hydrochloride, 60 mg, and phenylephrine hydrochloride 10 mg, were not significantly different from placebo. In this crossover study the patients were tested on 5 consecutive days (Ref. 24).

The second study measuring in 12 patients nasal airway resistance at a flow rate of 0.5 l/second demonstrated phenylpropanolamine hydrochloride 18 mg orally to yield greater reduction in nasal airway resistance from pre-drug state than placebo throughout a 4-hour period of observation. The validity of these results is unclear since acetaminophen 325 mg orally also induced a similar magnitude of response in this test (Ref. 25).

A similar followup study in 12 patients by the same author did show significant difference between phenylpropanolamine 25 mg orally and placebo during a 4-hour observation period (Ref. 26).

This author then compared 3 successive doses of 25 mg at 4-hour intervals with a single 75-mg dose in a timed-release formulation in a crossover design in 12 patients and demonstrated continued reduction in nasal airway resistance throughout a 13-hour test period in both cases (Ref. 27). Urinary excretion of phenylpropanolamine, administered as a 75-mg timed-release capsule, approximates 3 doses of 25 mg administered at 4-hour intervals (Ref. 28). Although blood level data more directly reflect rate of drug absorption and drug level at sites of action, these urinary excretion data are consistent with the sustained decrease in nasal airway resistance obtained with a 75 mg timed-release capsule and three consecutive doses of 25 mg.

Another investigation measuring nasal airway resistance at a flow rate of 0.2 l/second in trained volunteers, demonstrated that phenylpropanolamine 40 mg orally induces a peak affect up to 3 hours with gradual return toward control thereafter (Refs. 29 and 30). This investigator also demonstrated that a timed-release formulation of phenylpropanolamine hydrochloride 50 mg in combination with belladonna alkaloids 0.2 mg and chlorpheniramine maleate 4 mg induced a significant decrease in nasal resistance compared to placebo over a 10-hour testing interval (Ref. 31).

(3) *Dosage.*.Dosages are based on the phenylpropanolamine hydrochloride equivalent. Adult oral dosage is 25 mg every 4 hours or 50 mg every 8 hours not to exceed 150 mg in 24 hours. Children 6 to under 12 years oral dosage is 12.5 mg every 4 hours or 25 mg every 8 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is 6.25 mg every 4 hours or 12.5 mg every 8 hours not to exceed 37.5 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B. 1. below—Category I Labeling.)

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f. *Propylhexedrine (inhalant).* The Panel concludes that propylhexedrine (inhalant) is safe and effective as an inhalant nasal decongestant for OTC use as specified in the dosage section discussed below.

(1) *Safety.* Clinical experience has confirmed that propylhexedrine (inhalant) is safe in the dosage ranges used as a nasal decongestant. Because of a wide margin of safety and the relative freedom from toxic effects, use by inhalation is not contraindicated for patients in whom an ephedrine-like pressor or stimulant action would be undesirable (Ref. 1). Excessive doses, at least six inhalations per nostril, of propylhexedrine inhaler produced no undesirable side effects such as angina attacks, ECG changes, or vasopressor responses in 20 patients with history of severe angina pectoris due to arteriosclerosis (Ref. 2). Two inhalations of propylhexedrine inhaler, 250 mg per inhaler, is reported to deliver approximately 0.5 mg of the volatile amine to the nostril (Ref. 3).

Oral doses of propylhexedrine alone, 100 mg, in normal adults induces a 17 to 23 mm blood pressure rise and reflex bradycardia but no overt symptoms of euphoria, palpitation or dry mouth (Ref. 4). Another investigator reported that 250 mg by mouth induced only slight nervousness, anxiety and tachycardia (Ref. 5). A 3-year old who ingested 15 tablets of propylhexedrine, a total dose of 375 mg, developed pronounced symptoms of central nervous stimulation consisting of insomnia, tremor, muscular hypertonicity and tachycardia which subsided in 3 days (Ref. 6). Propylhexedrine is marketed outside of the United States as an anorexic.

One individual ingesting the contents of a propylhexedrine inhaler containing 250 mg of amine plus menthol and lavender oil, developed an extreme illness lasting 4 weeks and involved "shock lung" syndrome (Ref. 7). Two notes report psychotic behavioral changes in persons with a habit of chewing the inhaler or dissolving the contents in coffee and consuming it (Refs. 8, 9, and 10).

Rats inhaling propylhexedrine, 0.55–0.70 mg/800 ml air, for 6 to 10 minute periods daily for 30 days revealed no histological evidence of tracheobronchial mucosal irritation (Ref. 11). A double-blind study was undertaken to assess the effect of inhaler administration every 4 hours of propylhexedrine plus menthol vapors to 20 normal human volunteers and menthol vapors alone to 18 normal human volunteers over a 2-week period (Ref. 12). Nasal airway resistance measurements on days 1, 7 and 14 revealed no evidence of diminished responsiveness to the propylhexedrine inhaler with this repeated use. The results indicate that under these conditions of dosing, rebound congestion is not a prominent feature.

(2) *Effectiveness.* Four noncontrolled subjective evaluation studies of propylhexedrine inhaler in a total of 140 patients with various types of nasal congestion problems revealed subjective improvement with minimal side effects. Slight stinging occurred in some cases (Refs. 13 and 14). In one of these studies of 20 patients, the onset of subjective relief was noted between 30 seconds to 5 minutes following two inhalations per nostril with "clear nasal breathing" reported to persist for 30 to 120 minutes.

A recent well-controlled double-blind trial of adults with head colds has been done with inhalers containing either propylhexedrine plus menthol or menthol alone, and using single nostril airway resistance measurements (Ref. 15). Unfortunately, propylhexedrine alone was not used. However, menthol in an inhaler alone appeared to have no significant effect on nasal airway resistance but menthol plus propylhexedrine did significantly reduce nasal airway resistance for about 2 hours with a maximum effect at about 30 minutes. It should be noted that two inhalations were used in one nostril and then repeated after 2 hours. Measurements made 4 hours after the initial inhalation, that is, 2 hours after the repeat inhalation, suggest a possible rebound congestion.

A subsequent double-blind objective measurement study by another investigator compared the nasal decongestant effect of a propylhexedrine inhaler with a placebo inhaler in 50 adult patients with nasal congestion due to head cold, divided equally between active and placebo group (Ref. 16). Following a control period for recording baseline nasal airway resistance, each patient administered two inhalations per nostril from their coded inhaler. Nasal airway resistance (NAR) measured at intervals up to 4 hours demonstrated significant decrease in NAR in the propylhexedrine group compared to placebo for up to 90 minutes and decline toward control levels thereafter. These results were associated with patient perception of decreased nasal congestion during the first 90 minutes. In this single dose administration study no side effects or evidence of rebound congestion was noted.

(3) *Dosage.* Adults and children 6 to under 12 years inhalant dosage from an inhaler that shall deliver in each 800 ml of air 0.40 to 0.50 mg of propylhexedrine is 2 inhalations in each nostril not more frequently than every 2 hours. For children under 6 years, there is no recommended dosage except under the advice and supervision of a physician. The inhaler should retain effectiveness for a minimum of 2 to 3 months.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. below—Category I Labeling.)

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g. *Pseudoephedrine preparations (pseudoephedrine hydrochloride, pseudoephedrine sulfate) (oral).* The Panel concludes that the pseudoephedrine and its salts are safe and effective as oral nasal decongestants for OTC use as specified in the dosage section discussed below.

(1) *Safety.* Clinical experience has confirmed that pseudoephedrine and its salts (oral) are safe in the dosage ranges used as nasal decongestants. In a series of 21 patients who took 60 mg of pseudoephedrine orally, mild side effects such as drowsiness, insomnia, and headache occurred in six of these patients (Ref. 1).

In a study of cardiovascular effects, dose responses in four subjects showed that 210 to 240 mg or 3.0 to 3.4 mg/kg were required to raise diastolic blood pressure to 90 mm Hg or above (Ref. 2).

Acute blood pressure rises may occur, however, if pseudoephedrine in therapeutic doses is taken with MAO inhibitors (Refs. 3 and 4).

(2) *Effectiveness.* A double-blind subjective study in allergic rhinitis patients showed pseudoephedrine to be better than placebo (Ref. 1). In children, a double-blind subjective study showed pseudoephedrine to be better than placebo in allergic respiratory disease and possibly also in non-allergic respiratory conditions, but no statistics are given (Ref. 5). In a study of 88 patients, there were no differences between the drug and placebo group subjectively or by rhinometry (Ref. 6). However, significant increases in na-

sal flow rates up to 20 percent after 60 mg orally and lasting at least 2 hours have been shown in other series (Refs. 7 and 8). Recent work with measurements of nasal airway resistance confirms a nasal decongestant effect, after an oral dose of 60 mg lasting up to 4 hours and returning to control values by 6 hours (Ref. 9).

(3) *Dosage.* Adult oral dosage is 60 mg every 4 hours not to exceed a maximum of 360 mg in 24 hours. Children 6 to under 12 years oral dosage is 30 mg every 4 hours not to exceed 180 mg in 24 hours. Children 2 to under 6 years oral dosage is 15 mg every 4 hours not to exceed 90 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. below—Category I Labeling).

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h. *Xylometazoline hydrochloride (topical).* The Panel concludes that xylometazoline is safe and effective as a topical nasal decongestant for OTC use as specified in the dosage section discussed below.

(1) *Safety.* Clinical experience has confirmed that xylometazoline hydrochloride (topical) is safe in the dosage ranges used as a nasal decongestant. Because the decongestant effect of xylometazoline hydrochloride, administered as drops or sprays, persists up to 5 hours with gradual decline thereafter, objective measurement studies in adults revealed no rebound congestion after single administration of 0.05 or 0.1 percent solutions (Refs. 1 through 4). Both objective and subjective measurement studies of 0.05 percent xylometazoline in infants and 0.05 or 0.1 percent, in children, reveal negligible rebound congestion with 3 times daily dosing for periods of 2 days to 2 weeks (Refs. 5 through 9). No cardiovascular changes were produced by nasal application of xylometazoline (Refs. 5, 7, and 10). Because of these safety considerations, the Panel recommends that xylometazoline, which is currently a drug available only by prescription, be reclassified to permit OTC usage as well.

(2) *Effectiveness.* Objective measurement studies in acute and chronic rhinitis among adults showed a single application of xylometazoline, 0.1 percent drops or sprays, to induce a rapid (5 to 10 minutes) and a prolonged (up to 10 hours) decrease, in nasal airway resistance (Refs. 1 through 4). In infants and children, objective measurement studies (Ref. 5) and subjective evaluation (Refs. 7, 9, and 11) demonstrated the nasal decongestant effectiveness of 0.01, 0.05 and 0.1 percent xylometazoline drops or sprays.

(3) *Dosage.* Adult topical dosage is 2 to 3 drops or sprays in each nostril of a 0.1 percent aqueous solution every 8 to 10 hours. Children 2 to under 12 years topical dosage is 2 to 3 drops or sprays in each nostril of a 0.05 percent aqueous solution every 8 to 10 hours. Only drops should be used in children 2 to under 6 years since the spray is difficult to use in the small nostril. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. below—Category I Labeling.) In addition, the Panel recommends the following specific labeling: *Warnings:* (i) *For products containing a concentration of 0.05 percent xylometazoline hydrochloride:* "Do not give this product to children under 2 years except under the advice and supervision of a physician".

(ii) *For products containing a concentration of 0.1 percent xylometazoline hydrochloride:* "For adult use only. Do not give this product to children under 12 years except under the advice and supervision of a physician".

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Category I Labeling

The Panel recommends the following Category I labeling for nasal decongestant active ingredients to be generally recognized as safe and effective and not misbranded as well as the specific labeling discussed in the individual ingredient statements:

a. *Indications.* (1) "For temporary relief of nasal congestion due to the common cold".

(2) "For temporary relief of nasal congestion due to hay fever or other upper respiratory allergies".

(3) "For temporary relief of nasal congestion associated with sinusitus".

(4) "For the temporary relief of stuffy nose (stopped up nose, nasal stuffiness, clogged up nose)".

(5) "Reduce swelling of nasal passages; shrinks swollen membranes".

(6) "Decongests nasal passages".

(7) "Temporarily restores freer breathing through the nose".

(8) "Helps clear nasal passages".

(9) "Helps decongest sinus openings, sinus passages".

(10) "Promotes nasal and/or sinus drainage".

(11) For products with claims for duration of effect: Statements as to duration of effect must be substantiated and

accompanied by a specific time period expressed in minutes or hours, as appropriate.

(12) For products used as topical nasal decongestants with claims for rapid onset of action: Statements relating to time to onset of action, such as, "fast" or "quick", must be accompanied by a specific time period expressed in minutes.

(13) For topical nasal decongestants which can demonstrate a cooling sensation: (i) "Provides cooling sensation".

(ii) "Cooling".

(iii) "Cools nasal passages".

b. *Warnings.* (1) *For products used as topical nasal decongestants:* (i) "Do not exceed recommended dosage because symptoms may occur such as burning, stinging, sneezing, or increase of nasal discharge".

(ii) "Do not use this product for more than 3 days. If symptoms persist, consult a physician".

(iii) "The use of this dispenser by more than one person may spread infection".

(2) *For products used as oral nasal decongestants:* (i) "Do not exceed recommended dosage because at higher doses nervousness, dizziness, or sleeplessness may occur".

(ii) "If symptoms do not improve within 7 days or are accompanied by high fever, consult a physician before continuing use".

(iii) "Do not take this product if you have high blood pressure, heart disease, diabetes or thyroid disease except under the advice and supervision of a physician.

(iv) *"Drug interaction precaution:* Do not take this product if you are presently taking a prescription antihypertensive or antidepressant drug containing a monoamine oxidase inhibitor except under the advice and supervision of a physician".

(3) *For products used as inhalant nasal decongestants:* (i) "This inhaler should be warmed in the hand before use to increase effectiveness".

(ii) "Do not give this product to children under 6 years except under the advice and supervision of a physician".

(iii) "Children should not have unsupervised access to this inhaler".

(iv) *"Caution:* Not for use by mouth".

2. *Category II conditions under which nasal decongestant ingredients are not generally recognized as safe and effective or are misbranded.* The use of nasal decongestants under the following conditions is unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel concludes that the following active ingredients and labeling should be removed from the market until scientific testing supports its use.

Category II Active Ingredients

The Panel has classified the following nasal decongestant active ingredients as not generally recognized as safe and effective or as misbranded:

Mustard oil (allylisothiocyanate) (topical/inhalant)

Turpentine oil (spirits of turpentine) (oral)

a. *Mustard oil (allylisothiocyanate) (topical/inhalant).* The Panel concludes that mustard oil is neither safe nor effective for topical or inhalant OTC use as a nasal decongestant.

(1) *Safety.* Mustard oil is obtained from Black mustard. Black mustard, which is official in the National Formulary XI, consists of dried, ripe seeds from various varieties of either or both of two species of the genus *Brassica (Cruciferae)*, namely, *Brassica nigra* (Brown mustard) and *Brassica juncea* (Chinese mustard) (Ref. 1). The formation of the irritant constituent, allylisothiocyanate (active ingredient), in black mustard seed results from the hydrolytic activity of the enzyme mirosin, on a glycoside substrate sinigrin (potassium mironate). Allylisothiocyanate is designated as the volatile oil of mustard (Ref. 1), as opposed to the fixed (expressed) oil of mustard, which is composed chiefly of the glycerides of oleic, arachidic, and other fatty acids (Ref. 2). Allylisothiocyanate, the volatile oil of mustard, is isolated from black mustard by distillation (Ref. 3).

The active ingredient of mustard oil, allylisothiocyanate, is present in about 0.6 percent concentration in mustard seed powder. Mustard powder, because of this substance, is a local irritant which has been used in topically applied preparations, e.g., "mustard plaster," for its rubefacient and counterirritant effects and by oral administration for its emetic effect. The vapors of mustard oil are reported to cause irritation of conjunctival, nasal and bronchial mucosa (Refs. 4, 5, and 6). A 15 percent solution of mustard oil in liquid petrolatum has been used to induce mucosal inflammation in an experimental protocol to study anti-inflammatory agents (Refs. 4 and 7).

The Panel is unable to determine a safe dose for mustard oil for topical use or as an inhalant that is also effective as a nasal decongestant.

(2) *Effectiveness.* The effectiveness of mustard oil as a nasal decongestant is uncertain. Black mustard has been used for centuries as a rubefacient and a counterirritant. Mustard plaster, a poultice type of medicament, is used for relieving the pain resulting from bruises and sprains. Mustard preparations are commonly used internally as emetics and as food condiments (Ref. 1). The usual emetic dose of black mustard is 10 gm (Ref. 8).

There is no evidence to support the effectiveness of mustard oil (allylisothiocyanate) as a nasal decongestant when applied topically or used as an inhalant. The Panel is aware that the official preparation Mustard Plaster, National Formulary XI, is indicated for use as a local irritant. The Panel is also aware of a marketed product containing mustard oil in combination with other volatile oils for OTC use. The product is administered by inhalation from the cork that seals the OTC medicine vial (Ref. 9). There is no evidence in the literature that this oil or its active ingredient, allylisothiocyanate, possesses nasal decongestant properties. Literature sources all refer to the local irritant effect only (Refs. 4, 5, 8, and 9).

(3) *Evaluation.* The Panel is unable to determine a safe topical or inhalant dosage for mustard oil for use as a nasal decongestant. The Panel is of the opinion that the risk from topical or inhalant administration outweighs whatever benefit might occur. Therefore, the Panel concludes that mustard oil is not safe for topical or inhalant use as a nasal decongestant.

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b. *Turpentine oil (spirits of turpentine) (oral).* The Panel concludes that oil of turpentine is not safe for OTC use when taken orally as a nasal decongestant.

(1) *Safety.* Oil of turpentine is a volatile oil distilled from turpentine, an oleoresin obtained from the pine tree. It has a characteristic odor and taste. The substance has been administered orally, topically, and by inhalation.

In doses of 15 ml in children and 150 ml in adults, fatal poisoning may occur (Ref. 1). Excessive oral doses produce marked irritation of the alimentary tract, especially of the stomach and of the pelvic organs. Toxic symptoms include vomiting, diarrhea, acute pain, renal irritation, bloody stools and hyperemia of all abdominal organs. Continued use may lead to cloudy swelling and fatty degeneration of the liver. Abnormal central nervous system symptoms may develop (Refs. 2 and 3).

Since no safe oral dose has been established for effective use as a nasal decongestant, the Panel concludes that turpentine oil should not be available for oral OTC use as a nasal decongestant. However, elsewhere in this document, the Panel concludes that the ingredient is safe when applied topically or used as

an inhalant but that there are insufficient data to permit final classification of its effectiveness for inhalant or topical use as a nasal decongestant. (See part VIII. paragraph B.3.m. below—Turpentine oil (spirits of turpentine) (topical/inhalant).)

(2) *Effectiveness.* Oil of turpentine is irritating and its chief suggested uses are based on this property (Refs. 1 and 4). There is no evidence to support its effectiveness as a nasal decongestant when taken orally.

(3) *Evaluation.* The Panel is unable to determine a safe oral dosage for turpentine oil for use as a nasal decongestant. The Panel is of the opinion that the risk from oral administration outweighs whatever benefit might occur. Therefore, the Panel concludes that turpentine oil is not safe for oral use as a nasal decongestant.

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Category II Labeling

All claims that state or imply a therapeutic action or safety property peculiar to the preparation that cannot be demonstrated in controlled studies are not acceptable. The Panel has previously discussed such labeling. (See part II. paragraph O. above—CCABA Product Labeling Claims Not Supported by Scientific Evidence.) However, labeling that is descriptive of the product such as its taste or appearance are acceptable.

The Panel concludes that the examples of language expressed in the following misleading claims are excessive and claims either too much or claims effects which do not occur and therefore such labeling should be removed from the market until scientific testing supports their use:

a. *Topical nasal decongestants.* (1) Reference to "germ-laden mucous" is unacceptable because it implies a curative action rather than symptom-relieving.

(2) The statement "Seldom causes rebound distress like others" is unacceptable because Category I topical nasal decongestants if used in accordance with labeled instructions as to dose and frequency should seldom cause rebound distress.

(3) The term "nonirritating base" is unacceptable because it may encourage a misleading conclusion about the safety characteristics of the total product.

b. *Oral nasal decongestants.* (1) The statement "Mild stimulant to overcome drowsiness", is unacceptable because there is no evidence to prove that an OTC decongestant could overcome drowsiness caused by antihistamine.

(2) Reference to "fast" or "prompt" onset of relief is unacceptable for oral products because this action does not occur and is a claim allowed only for topical products.

c. *Topical or oral nasal decongestants.* (1) Reference to effect on "local congestion" is unacceptable since this may be confused with congestion in the bronchioles and chest.

(2) Reference to "extra strength", the "most effective", "improved remedy" are unacceptable because they suggest the product is particularly effective. All Category I ingredients have been judged effective but no acceptable controlled studies were submitted to the Panel documenting one preparation as more effective than another.

(3) Reference to "used by" or "most recommended by doctors or scientists" is unacceptable because it is difficult to substantiate.

(4) "Checks irritation caused by cold virus" is unacceptable because it implies a curative action rather than symptom-relieving.

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel concludes adequate and reliable scientific evidence is not available at this time to permit final classification of the claimed ingredients and conditions listed below. The Panel believes it reasonable to provide 3 years for the development and review of such evidence. Marketing need not cease during this time if adequate testing is undertaken. If adequate effectiveness data are not obtained within 3 years, however, the conditions listed in this category should no longer be marketed in over-the-counter nasal decongestant products. Effectiveness as a nasal decongestant must be demonstrated by determining the ability of a drug to reduce nasal obstruction in patients with acute or chronic rhinitis.

Category III Active Ingredients

The Panel concludes that the available data are insufficient to permit final classification of the following claimed nasal decongestant active ingredients:

Beechwood creosote
Bornyl acetate (topical)
Camphor (topical/inhalant)
Cedar leaf oil (topical)
1-Desoxyephedrine (inhalant)
Ephedrine preparations (oral): Ephedrine, Ephedrine hydrochloride, Ephedrine sulfate, Racephedrine hydrochloride
Eucalyptol/eucalyptus oil (topical/inhalant)
Menthol/peppermint oil (topical/inhalant)
Phenylpropanolamine hydrochloride (topical)
Thenyldiamine hydrochloride (topical)
Thymol (inhalant)
Turpentine oil (spirits of turpentine) (topical/inhalant)

a. *Beechwood creosote.* The Panel concludes that beechwood creosote is safe in the dosage ranges used as a nasal decongestant but there are insufficient data to permit final classification of its effectiveness for OTC use as a nasal decongestant.

(1) *Safety.* Clinical experience has confirmed that beechwood creosote in the usual dosages contained in lozenges or cough mixtures for nasal decongestant activity is safe.

Creosote is a distillate of wood tar and has a smoky color and a pungent taste. Dosages in excess of 4 gm 3 times daily produces giddiness, dimness of vision, circulatory collapse, convulsions and coma (Ref. 1). Because of the taste, it is normally given well-diluted (Ref. 2). Occasional adverse gastrointestinal side effects are mentioned in one report but are poorly documented (Ref. 3). Based on the available data and the presence of beechwood creosote on the market for many years, the Panel concludes that this ingredient is safe for OTC use.

(2) *Effectiveness.* Except for a recent submission (Ref. 4), there have been no well-controlled studies documenting the effectiveness of beechwood creosote alone or in combination as a nasal decongestant. A single study is reported dealing with nasal airway resistance in 66 patients with degrees of the "common cold." These patients were studied by objective techniques and this study showed significant reduction in nasal resistance for beechwood creosote combination as compared with a placebo 2 hours following administration. Subjective studies with respect to runny nose should note significant changes from the placebo. It is stated that the investigator global evaluations were too small in number to permit statistical interpretation. In reviewing this study it is difficult for the Panel to interpret these statistical analyses which appear to be cumbersome and confusing. In addition, since no dosage information is supplied, the Panel questions the acceptability of the study.

According to the standard compendia (Refs. 1 and 5), an average dosage of beechwood creosote is 250 mg 3 or 4 times daily. In the two submissions to the Panel listing creosote, the dosages are 3.29 mg/lozenge and 33 mg/15 ml every 3 hours (Refs. 6). This 40- to 80-fold difference in dose (3.29 mg/lozenge, 8 doses/day) appears illogical and there is no evidence to indicate that creosote is effective in such low doses. The Panel concludes that further studies are needed to determine effectiveness.

(3) *Proposed dosage.* Adult oral dosage is 250 mg every 4 to 6 hours not to exceed 1500 mg in 24 hours. Children 6 to under 12 years oral dosage is 125 mg every 4 to 6 hours not to exceed 750 mg in 24 hours. Children 2 to under 6 years oral dosage is 62.5 mg every 4 to 6 hours not to exceed 375 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part IV. paragraph B.1. above—Category I Labeling).

(5) *Evaluation.* Data to demonstrate effectiveness as a nasal decongestant will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part IV. para-

graph C. below—Data Required for Evaluation.)

REFERENCES

(1) "The United States Dispensatory and Physicians' Pharmacology," 26th Ed., Edited by Osol, A., R. Pratt and M. D. Altschule, J. B. Lippincott Co., Philadelphia, p. 341, 1967.

(2) "Drill's Pharmacology in Medicine," 2d Ed., Edited by DiPalma, J. R., McGraw-Hill Co., New York, p. 690, 1958.

(3) Stevens, M. E., A. K. Ronan, T. S. Sourkes and E. M. Boyd, "On the Expectorant Action of Creosote and the Guaiacols," *Canadian Medical Association Journal*, 48:124–127, 1943.

(4) OTC Volume 040289.

(5) "The National Formulary," 7th Ed., American Pharmaceutical Association, Washington, D.C., pp. 105–106, 1942.

(6) OTC Volume 040208 and 040235.

b. *Bornyl acetate (topical)*. The Panel concludes that bornyl acetate is safe in the dose ranges used when applied topically but there are insufficient data to permit final classification of its effectiveness for topical OTC use as a nasal decongestant.

(1) *Safety*. Clinical experience has apparently confirmed that bornyl acetate (topical) is safe in the dosage ranges used as a nasal decongestant. There are no studies to substantiate its safety. The Merck Index (Ref. 1) states that this compound may cause nausea and vomiting, mental confusion, dizziness and convulsions. The dose is not given. The amount present in a commercially available inhaler is not given (Ref. 2). It is one of several aromatic substances in the inhaler.

(2) *Effectiveness*. There are no well-controlled studies documenting the effectiveness of bornyl acetate (topical) as a nasal decongestant. In a report (Ref. 3), bornyl acetate was one of eleven aromatic substances evaluated as nasal decongestants. Patients presumably with nasal congestion were used. Nasal resistance was measured before treatment and at 5, 15, 30, 60, 90 and 120 minutes after treatment. Bornyl acetate 112.5 mg was impregnated on a cotton wick through which air was forced and the patient inhaled. In the morning, 50 cc of air was administered in each nostril and 150 cc in each nostril in the afternoon. In 11 patients, there was a statistically significant decrease in the nasal resistance at the higher dose. This was not a well designed study.

(3) *Proposed dosage*. The Panel is unable to determine a proposed dosage. The Panel concludes that the pharmaceutical industry should consult with the Food and Drug Administration as to a suitable proposed dosage for testing. Otherwise, the Panel recommends that each drug manufacturer evaluate the dosage as labeled on the manufacturer's marketed product(s).

(4) *Labeling*. The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation*. Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

REFERENCES

(1) "The Merck Index," 8th Ed., Merck and Company, Inc., Rahway, New Jersey, p. 160, 1968.

(2) OTC Volume 040065.

(3) Grubb, T. C., "The Nasal Decongestant Effect of Aromatic Substances," Draft of unpublished study is included in OTC Volume 040298.

c. *Camphor (topical/inhalant)*. The Panel concludes that camphor is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical/inhalant OTC use as a nasal decongestant.

(1) *Safety*. Clinical experience has confirmed that camphor (tropical/inhalant) is safe in the dosage ranges used as a nasal decongestant.

Camphor is a local irritant producing skin redness when rubbed on the skin. However, when not vigorously applied, it may produce a feeling of coolness on the skin as does menthol. It acts similarly on the respiratory tract. Taken orally in small doses it produces a feeling of warmth and comfort in the stomach but in larger doses it is irritating and can cause nausea and vomiting. Camphor also has a mild local anesthetic action and its application to the skin may be followed by numbness. The systemic effects are primarily related to stimulation of the central nervous system. The ingestion of solid camphor by children can cause convulsions (Ref. 1). As little as 0.75 gm of camphor equivalent to a teaspoonful of liniment of camphor or camphorated oil which contains 20 percent camphor has been fatal to a child. Commercially available ointments containing mixtures of volatile substances for use as decongestants or antitussives contain about 5 percent camphor. Since it is conceivable that ingestion of a sufficient amount of such a preparation could produce toxic effects in a young child, a suitable warning should be present on the label. The ingestion of 2 gm of camphor generally produces toxic effects in an adult although up to 1.5 oz has been ingested with recovery (Ref. 2).

(2) *Effectiveness*. There are no well-controlled studies documenting the effectiveness of camphor (topical/inhalant) as a nasal decongestant. Its effectiveness is uncertain due to lack of properly controlled studies of the substance by itself.

Using an electronic technique for measuring nasal airflow in infants and children, Noller reported that following application of a camphor-containing ointment to the nasal passageway resulted in an initial reduction in airflow followed by an increase in airflow over the pretreatment level. The study report did not, however, indicate the concentration of camphor applied nor were data supplied in the report (Ref. 3). Other studies involving the objective measurement of the nasal decongestant activity of camphor utilized mixtures of volatile substances in topically applied ointments (Refs. 4 through 6) and in steam inhalations (Ref. 7). In these studies, although significant nasal decongestion compared to placebo has been demonstrated, it is not evident whether the camphor component contributed to this effect.

(3) *Proposed dosage*. Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 5 percent ointment preparation: To be rubbed on the throat, chest and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapor rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 7 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in any hot steam vaporizer, bowl or washbasin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For topical use as a lozenge 0.2 to 15 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every ½ to 1 hour.

For children under 2 years, there is no recommended topical or inhalant dosage except under the advice and supervision of a physician.

(4) *Labeling*. The Panel recommends the Category I labeling for topical nasal decongestant active ingredients. (See part VIII. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: Warning "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: Warning: "For steam inhalation only. Do not take by mouth".

(5) *Evaluation*. The Panel made the following recommendations: (i) For topical ointment use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation).

(iii) For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation).

REFERENCES

(1) Swinyard, E. A. "Demulcents, Emollients, Protectives and Absorbents, Antiperspirants and Deodorants, Absorbable Hemostatics, Astringents, Irritants, Sclerosing Agents, Caustics, Keratolytics, Antiseborrheics, Melanizing and Demelanizing Agents, Mucolytics, and Certain Enzymes," *in* "The Pharmacological Basis of Therapeutics," 4th Ed., Edited by Goodman, L. S. and A. Gilman,

The MacMillan Co., New York, p. 993, 1970.
(2) Thienes, C. H. and T. J. Haley, "Clinical Toxicology of Commercial Products," 3d Ed., Lea and Febiger, Philadelphia, pp. 24–25, 1955.
(3) Noller, H. G., "Electronic Measurements on the Nasal Mucous Membrane During Exposure to Menthol," (English translation), ("Elektronische Messungen an der Nasenschleimhaut unter Methol-wirkung"), *in* "Menthol and Menthol-containing External Remedies," Edited by Dost, F. H. and B. Leiber, Georg Thieme Verlag, Stuttgart, Germany, pp. 146–153, 1966.
(4) Blanchard, C. L., S. J. Borsanyi and T. C. Grubb, "Evaluation of Nasal Decongestant Drugs," *The Eye, Ear, Nose and Throat Monthly*, 43:76–82, 1964.
(5) Stamos, E., "Vaporub. Nasal Decongestant Study: Vick Rhinorrheometer. CRD 71–1," Draft of unpublished data is included in OTC Volume 040298.
(6) Carter, V. H., "Vaporub. Nasal Decongestant Study: Vick Rhinorrheometer. CRD 72–7," Draft of unpublished data is included in OTC Volume 040298.
(7) Ciampi, L. A., "Vaposteam. Nasal Decongestant Vick Rhinorrheometer. CRD 71–5," Draft of unpublished data is included in OTC Volume 040298.

d. *Cedar leaf oil (topical)*. The Panel concludes that cedar leaf oil is safe in the dosage ranges used when applied topically but there are insufficient data to permit final classification of its effectiveness for topical OTC use as a nasal decongestant.

(1) *Safety*. Clinical experience has confirmed that cedar leaf oil (topical) is safe in the dosage ranges used as a nasal decongestant.

Cedar leaf oil is the volatile oil steam distilled from the fresh leaves of Thuja occidentialis. The oil is reputed to be ecbolic but abortions cannot be induced with safe doses. The actions are like turpentine but the toxicity greater. In most cases oral ingestion of a teaspoonful may cause illness in an adult and less than 1 oz may be lethal (Refs. 1 and 2).

Several studies support the safety of a topically applied mixture of volatile oils, 16 percent weight/weight, in petrolatum. Although this mixture contains cedar leaf oil, the concentration of individual ingredients is not specified (Ref. 3).

(2) *Effectiveness*. There are no well-controlled studies documenting the effectiveness of cedar leaf oil (topical) as a nasal decongestant. Cedar leaf oil by inhalation is probably transiently effective as a nasal decongestant.

In a study of 10 patients with head colds, not double-blind or placebo-controlled, inhalation of a measured volume of cedar leaf oil vapors induced a significant nasal decongestant effect persisting for 30 minutes as measured by anterior rhinometry. Increasing the volume of inhaled vapors intensified but did not prolong the decrease in nasal resistance (Ref. 4).

In a placebo-controlled crossover study of 36 patients with head colds, application to the chest of a 16 percent weight/weight mixture of volatile oils in petrolatum containing cedar leaf oil demonstrated an apparently significant decrease in nasal resistance compared to the petrolatum control over a 4 hour observation period. The concentration of the cedar leaf oil was not specified. A similar study in 20 additional patients resulted in control and treatment data with overlapping standard errors (Ref. 4). Other studies involving the objective measurements of the nasal decongestant activity of cedar leaf oil utilized mixtures of volatile substances in topically applied ointments (Refs. 5 through 7) and in steam inhalations (Ref. 8). In these studies, although significant nasal decongestion compared to placebo was demonstrated, it was not evident whether the cedar leaf oil component contributed to this effect.

(3) *Proposed dosage*. The Panel is unable to determine a proposed dosage. The Panel concludes that the pharmaceutical industry should consult with the Food and Drug Administration as to a suitable proposed dosage for testing. Otherwise, the Panel recommends that each drug manufacturer evaluate the dosage as labeled on the manufacturer's marketed product(s).

(4) *Labeling*. The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. above—Category I Labeling).

(5) *Evaluation*. Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation).

REFERENCES

(1) "Clinical Toxicology of Commercial Products. Acute Poisoning," 3d Ed., Edited by Gleason, M. N., R. E. Gosselin, H. C. Hodge and R. P. Smith, The Williams and Wilkins Co., Baltimore, p. 65, 1969.
(2) "The Dispensatory of the United States of America," 25th Ed., Edited by Osol, A. and G. E. Farrar, Jr., J. B. Lippincott, Philadelphia, p. 1901, 1960.
(3) OTC Volume 040057.
(4) Grubb, T. C., "The Nasal Decongestant Effect of Aromatic Substances," Draft of unpublished study is included in OTC Volume 040298.
(5) Blanchard, C. L., S. J. Borsany and T. C. Grubb, "Evaluation of Nasal Decongestant Drugs," *The Eye, Ear, Nose and Throat Monthly*, 43:76–82, 1964.
(6) Stamos, E., "Vaporub. Nasal Decongestant Study: Vick Rhinorrheometer. CRD 71–1" Draft of unpublished data included in OTC Volume 040298.
(7) Carter, V. H., "Vaporub. Nasal Decongestant Study: Vick Rhinorrheometer. CRD 72–7," Draft of unpublished data is included in OTC Volume 040298.
(8) Ciampi, L. A., "Vaposteam. Nasal Decongestant Vick Rhinorrheometer. CRD 71–4," Draft of unpublished data is included in OTC Volume 040298.

e. *1-Desoxyephedrine (inhalant)*. The Panel concludes that 1-desoxyephedrine is safe in dosage ranges used when used as an inhalant but there are insufficient data to permit final classification of its effectiveness for inhalant OTC use as a nasal decongestant.

(1) *Safety*. Clinical experience has confirmed that 1-desoxyephedrine (inhalant) is safe in the dosage ranges used as a nasal decongestant.

Aqueous nose drops and aqueous spray in concentrations up to 1 percent caused burning, stinging, rhinorrhea and sneezing in up to 21.5 percent of subjects. Palpitations were rare (Ref. 1). With oral doses of 50 to 100 mg two of ten subjects had transient dizziness and nervousness but no blood pressure changes were seen (Ref. 2). No untoward effects of an oral dose of 25 mg 3 times daily for up to 28 days were observed in eight patients (Ref. 2).

(2) *Effectiveness*. There are no well-controlled studies documenting the effectiveness of 1-desoxyephedrine as a nasal decongestant. The effectiveness is therefore uncertain, as data are conflicting and properly controlled objective studies have not been presented.

Uncontrolled studies using nasal drops, 0.25 percent to 1.0 percent concentration, suggest that nasal mucous membrane constriction does occur at the higher concentrations (Ref. 1). An uncontrolled subjective study using an inhaler in 100 patients showed relief of nasal obstruction in 89 percent of cases. Onset of relief was usually in 1 minute and lasted up to 4 hours (Ref. 3). In another similar study duration of relief varied from ½ to 2 hours (Ref. 4). Two double-blind studies of inhalers containing aromatic oils with and without 1-desoxyephedrine showed no differences in nasal airflow studies using the Butler-Ivy technique (Refs. 5 and 6). However, one study (Ref. 6) showed that the inhalers with or without 1-desoxyephedrine were more effective than a placebo inhaler. This suggests the possibility that at least part of the effectiveness of the inhaler might be due to the aromatic oils. Some improvement for less than 30 minutes in airway resistance was shown for camphor, menthol, and bornyl acetate (Ref. 7).

Two single-blind studies comparing an inhaler containing aromatic oils and 1-desoxyephedrine, an inhaler containing only 1-desoxyephedrine, and a placebo inhaler were done using nasal airway resistance measured by a rhinorrheometer (Refs. 8 and 9). Both studies showed that the inhaler with aromatic oils and 1-desoxyephedrine was better than the inhaler containing only 1-desoxyephedrine and both were better than the placebo. Activity was maintained for at least 30 minutes with a maximum at 5 minutes but for less than 60 minutes. These studies suggest that 1-desoxyephedrine has some transient nasal vasoconstrictor effect.

In a recent double-blind, noncrossover, subjective rhinoscopic study of 100 male patients both the drug containing inhaler and placebo inhaler gave significant subjective effect for up to 60 minutes (Ref. 10). Slight rhinoscopic improvement was present in both groups. However, the drug containing inhaler groups, when compared with placebo had significantly greater subjective relief and greater improvement in rhinoscopic parameters.

The above review suggests that 1-desoxyephedrine probably has a nasal vasoconstrictor effect which is relatively brief. However, to be certain of effectiveness, double-blind studies with objective measurements of nasal airway resistance are required. These studies should also provide information as to rebound congestion with repeated nasal use.

(3) *Proposed dosage.* Adult inhalant dosage from an inhaler that shall deliver in each 800 ml air 40 to 150 mcgm l-desoxyephedrine is 2 inhalations in each nostril not more frequently than every 2 hours. Children 6 to under 12 years inhalant dosage from an inhaler that shall deliver in each 800 ml air 40 to 150 mcgm l-desoxyephedrine is 1 inhalation in each nostril not more frequently than every 2 hours. For children under 6 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients (See part VIII. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required from one additional objective nasal airway resistance study in patients with nasal congestion due to acute rhinitis in accordance with the guidelines set forth below for nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

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(1) Fabricant, N. D. et al., "Clinical Evaluation," Draft of unpublished data is included in OTC Volume 040298.

(2) Batterman, R. C., "Studies with Levodesoxyephedrine," Draft of unpublished data is included in OTC Volume 040298.

(3) Greenberg, L., "Resume of Clinical Study of l-Desoxyephedrine Inhaler," Draft of unpublished data is included in OTC Volume 040298.

(4) Memo to Moore, H. L. from J. S. Scanlan, "Improved Inhaler," is included in OTC Volume 040298.

(5) Memo to Scanlan, J. S. from W. E. Burke, "Current Domestic Inhaler—Clinical Evaluation," is included in OTC Volume 040298.

(6) Sanford, T., "Inhaler," Draft of unpublished data is included in OTC Volume 040298.

(7) Grubb, T. C., "The Nasal Decongestant Effect of Aromatic Substances," Draft of unpublished data is included in OTC Volume 040298.

(8) Mendoza, J. A., "Vick Inhaler," Draft of unpublished data is included in OTC Volume 040298.

(9) Turgeon, R. F., "Vick Inhaler," Draft of unpublished data is included in OTC Volume 040298.

(10) OTC Volume 040231.

f. Ephedrine preparations (ephedrine, ephedrine hydrochloride, ephedrine sulfate, racephedrine hydrochloride) (oral). The Panel concludes that ephedrine and its salts are safe in the dosage ranges used orally but there are insufficient data to permit final classification of their effectiveness for oral OTC use as nasal decongestants.

(1) *Safety.* Clinical experience has confirmed that ephedrine and its salts (oral) are safe in the dosage ranges used as a nasal decongestant.

Ephedrine has both central and peripheral effects when absorbed systemically and stimulates, directly or indirectly, both alpha and beta receptors (Ref. 1). In clinical usage the central effects are stimulatory and include tenseness, nervousness, tremor and sleeplessness. Peripheral effects include bronchodilation, and possible shrinkage of mucous membranes (decongestion) although this has not been documented. Other peripheral effects include awareness of heartbeat and tachycardia accompanied usually by some elevation of blood pressure, both systolic and diastolic. The cardiovascular and central effects set limits on dosage, limits which vary widely among patients as judged by clinical experience. Anorexia and nausea also occur in some patients. Difficulty in urination may occur in older males with prostatic hypertrophy. Overdosage results in exaggeration of the side effects which patients describe as disagreeable and can usually be depended upon to prevent overuse or abuse. Ordinary doses may cause marked and potentially dangerous increases in blood pressure in patients taking monoamine oxidase (MAO) inhibitors.

(2) *Effectiveness.* There are insufficient studies documenting the effectiveness of ephedrine and its salts (oral) as nasal decongestants. One controlled objective measurement study in patients with nasal obstruction demonstrated nasal decongestant effectiveness of orally administered ephedrine sulfate in doses of 25 mg (Ref. 2). No conclusive data were found to support claims of effectiveness for doses 8 to 12 mg contained in OTC submissions.

(3) *Proposed dosage.* Adult oral dosage is 8 to 12 mg not more than every 4 hours not to exceed 72 mg in 24 hours. Children 6 to under 12 years oral dosage is 4 to 6 mg not more than every 4 hours not to exceed 36 mg in 24 hours. Children 2 to under 6 years oral dosage is 2 to 3 mg not more than every 4 hours not to exceed 18 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

REFERENCES

(1) "The Pharmacological Basis of Therapeutics," 3d Ed., Edited by Goodman, L. S. and A. Gilman, The MacMillan Co., New York, pp. 505–506, 1965.

(2) McLaurin, J. W., W. F. Shipman and R. Rosedale, "Oral Decongestants," *Laryngoscope*, 71:56–67, 1961.

g. Eucalyptol/eucalyptus oil (topical/inhalant). The Panel concludes that eucalyptol/eucalyptus oil is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as a nasal decongestant.

(1) *Safety.* Clinical experience has confirmed that eucalyptol/eucalyptus oil (topical/inhalant) is safe in the dosage ranges used as a nasal decongestant.

Eucalyptus oil is about 70 percent active eucalyptol. Fatalities have followed doses of the oil as small as 3.5 ml although recovery has occurred after doses of 20 and even 30 ml. Symptoms include epigastric burning with nausea and vomiting, vertigo, ataxia, muscle weakness and stupor (Refs. 1 and 2). A study of 223 subjects in which an ointment containing several volatile substances including eucalyptus oil 1.3 percent was applied for 48 hours to both areas of intact skin under a patch and to abraded skin revealed no instances of irritation, inflammation, wheal or hives following the period of exposure (Ref. 3). A study of 10 subjects who received application of an ointment containing several volatile substances including eucalyptus oil 1.3 percent to their trunks 3 times daily for 3 weeks, then 1 week off followed by another 1 week of treatment, revealed no local reactions during this subsequent challenge phase (Ref. 4). A study of infants and children with respiratory infection who received an ointment containing a mixture of volatile oils including eucalyptus oil 1.3 percent applied to the chest and neck demonstrated no adverse effect from inhaled vapors by that route of administration on the rate of clearing of laryngeal edema (Ref. 5). A liquid mixture of volatile substances including eucalyptus oil 1.7 percent is placed in the water of a hot steam vaporizer and administered via inhalation. Exaggerated use studies in adults and children, i.e., exposure for several hours to higher than recommended exposure concentrations either due to sitting in closer proximity to the vaporizer or placing 2 to 5 times the recommended dose of the volatile substance in the vaporizer, was not associated with irritating or toxic effects (Refs. 6 and 7).

A series of studies assessing buccal safety and overt side effects from lozenges containing a mixture of volatile oils was conducted in over 300 subjects. Lozenges containing up to 5.5 mg eucalyptus oil were dissolved in the mouth every hour for 8 hours on 2 successive days. Mild erythema of the buccal mucosa and tongue was observed but did not differ appreciably from the response to dissolving lozenge sugar base without volatile oils. The incidence of gastrointestinal symptoms did not differ from control either (Refs. 8 through 11).

An aerosolized dosage form of volatile substances including 1 percent eucalyptus oil has also been utilized for treatment of nasal congestion. In humans, such aerosol sprays have been generally safe when used as directed but there have been reports of deaths from deliberate sniffing abuse, particularly when the subject inhales from a plastic bag into which the material has been sprayed (Ref. 12). Furthermore, one commercial preparation containing a particular solvent, 1,1,1-trichloroethane, was recently recalled from the market due to potential hazards of this substance (Ref. 13).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of eucalyptol/eucalyptus oil (topical/inhalant) as a nasal decon-

gestant. Its effectiveness is uncertain due to lack of properly controlled studies of the substance by itself.

In a study of nine patients with head colds, which was not double-blinded or placebo controlled, inhalation of 50 ml volume of eucalyptus vapors did not induce a significantly decreased airway resistance as measured by anterior rhinometry. Increasing the inhaled volume to 300 ml of eucalyptus oil vapors did induce a significant decrease in airway resistance for 15 minutes, but this was followed by increased nasal resistance over the next 100 minutes (Ref. 14). Other studies involving objective measurement of nasal decongestant activity of eucalyptus oil involved mixtures of volatile substances topically applied as ointments (Refs. 15 through 17), in steam inhalations (Refs. 18 and 19) and room aerosol sprays (Refs. 20 through 23). In these studies, although significant nasal decongestant activity as compared to placebo was demonstrated, whether the eucalyptus oil component contributed to this effect is not evident.

The effect of rinsing and gargling twice daily with an aqueous mixture of volatile substances on the incidence of colds and the severity of the symptoms associated with colds was evaluated in a long-term double-blind placebo-controlled subjective study in school children. The results of the study revealed milder nasal symptoms and cough symptoms in individuals using the medicated mouthwash as compared to the placebo. Although the medicated mouthwash contained 0.91 mg/ml eucalyptol, the results did not demonstrate the contribution of this component to the overall alleviation of symptoms (Ref. 24).

(3) *Proposed dosage.* Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 1.3 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapors rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 1.7 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl or washbasin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For inhalation use as a 1 percent room spray: Spray room for 15 to 20 seconds in the vicinity of the patient. May be repeated at ½ to 1 hour intervals as needed.

(iv) For topical use as a lozenge 0.2 to 15.0 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every ½ to 1 hour.

(v) For use as a mouthwash 0.91 mg/ml solution: Gargle with ⅔ oz (20 ml) twice daily.

For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: *Warning:* "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: *Warning:* "For steam inhalation only. Do not take by mouth".

(5) *Evaluation.* The Panel made the following recommendations: (i) For topical ointment use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(iii) For inhalation use as a room spray: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(iv) For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(v) For use as a mouthwash: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

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h. *Menthol/peppermint oil (topical/inhalant).* The Panel concludes that menthol/peppermint oil is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as a nasal decongestant.

(1) *Safety.* Clinical experience has confirmed that menthol/peppermint oil (topical/inhalant) is safe in the dosage ranges used as a nasal decongestant.

Menthol is the chief constituent of peppermint oil, comprising not less than 50 percent, and may be obtained by distillation of the oil or by synthesis (Ref. 1). Toxic effects with an excess ingestion of peppermint oil or mentholated products can include abdominal pain, nausea, vomiting and symptoms of central nervous system depression such as dizziness, staggering gait, slowed respiration, flushed face, sleepiness and coma (Refs. 2 and 3). The fatal oral dose of menthol itself in man is about 2 gm (Ref. 4). Topically applied menthol produces a cooling sensation presumably due to

stimulation of the cold sensory receptors, whereas higher concentrations have irritant properties. In one study, a 20 percent solution of menthol in oil rubbed on to the skin induced an intense and lasting cooling sensation followed by numbness with slight burning and skin redness. A 0.5 percent solution applied to the nasal or oral mucosa was subjectively irritating whereas a 0.2 percent solution was judged nonirritating (Ref. 5). A study of 223 subjects in which an ointment containing several volatile substances including menthol 2.8 percent was applied for 48 hours to both areas of intact skin under a patch and to abraded skin revealed no instances of inflammation, wheal, hives or primary irritation following the period of exposure (Ref. 6). Repeated topical application of mentholated products has been reported to give rise to hypersensitivity reactions including contact dermatitis (Ref. 4). A study of 10 subjects who received application of an ointment containing several volatile substances including menthol 2.8 percent to their trunks 3 times daily for 3 weeks, then 1 week off followed by another week of treatment, revealed no local reactions during this subsequent challenge phase (Ref. 7). The incidence of hypersensitivity to menthol appears to increase with increased duration of use. For example, one survey revealed an incidence of less than 1 percent menthol hypersensitivity in 542 patients using a mentholated ointment for less than 10 years whereas an incidence of 3.4 percent hypersensitivity was seen in 144 patients using this type of a preparation for longer than 10 years (Ref. 8).

In infants and small children nasal ointment or drops containing menthol may cause spasm of the glottis and cases of dangerous asphyxiation have been reported in infants following local application of menthol. For this reason a warning against the topical application of menthol-containing products directly to the nostrils of infants has been recommended (Refs. 4 and 9). A study of infants and children with respiratory infection who received an ointment containing a mixture of volatile oils including a 2.8 percent menthol applied to the chest and neck demonstrated no adverse effect from the inhaled vapors by that route of administration on the rate of clearing of laryngeal inflammation. In this study 35 children (23 under 2 years of age) with respiratory infection received only standard forms of therapy, e.g., antibiotics and fluids, while 37 children (30 under 2 years of age) received standard therapy plus the mentholated ointment to the chest and neck. Laryngoscopic examination revealed comparable rates of clearing of laryngeal inflammation (Ref. 10).

A liquid mixture of volatile substances including 3.66 percent menthol is placed in the water of a hot steam vaporizer and administered via inhalation. A number of studies involving nearly 900 subjects in which this mixture was administered at recommended doses was not associated with significant complaints of subjectively perceived adverse effects (Refs. 11 through 23). Exaggerated use studies in adults and children, i.e., exposure for several hours to higher than recommended exposure concentrations either due to sitting in closer proximity to the vaporizer or placing 2 to 5 times the recommended dose of the volatile substance in the vaporizer, was not associated with irritating or toxic effects (Refs. 24 and 25).

In two studies involving 40 healthy subjects who were asked to dissolve 2 candy-base lozenges every 20 minutes for 2 hours, each containing 1.36 mg of menthol together with other volatile oils, exhibited no adverse effects with the exception of one report of nausea and vomiting. This was attributed to a dislike for the wild cherry flavor of the lozenge (Refs. 26 and 27). In a group of 70 healthy subjects (50 adults and 20 children, ages 8 to 12), half of the subjects dissolved a menthol-eucalyptus lozenge, 9.62 mg menthol and 5.55 mg eucalyptus oil, every hour for 8 hours on 2 successive days, the other half dissolved the cough drop base without the aromatics. In this intensive dosage schedule, a slightly larger number of subjects demonstrated mild irritation of the oral mucosa on days 1 and 2, but there were no differences between the two groups in the severity of irritation or residual findings after day 2. No systemic complaints were reported (Ref. 28). A similar study using a lozenge formulation containing menthol 8.14 mg and eucalyptus oil 4.625 mg versus a lozenge base without volatile substances produced comparable results (Ref. 29).

An aerosolized dosage form of volatile substances including 1 percent menthol has also been utilized for treatment of nasal congestion and cough symptoms. Rats exposed to acute overdoses of the spray in a confined chamber for 6 hours revealed no untoward behavorial response or airway tissues abnormality upon autopsy examination (Ref. 30). A group of four monkeys were exposed to 200 gm per day of the aerosol, i.e., 2 gm of menthol total dose in divided doses over an 8 hour period for 14 consecutive days in a confined chamber. Eye irritation was the only pharmacotoxic sign observed during the study (Ref. 31). In humans, such aerosol sprays have been generally safe when used as directed but there have been reports of deaths from deliberate sniffing abuse, particularly when the subject inhales from a plastic bag into which the material has been sprayed (Ref. 32). Furthermore, one commercial preparation containing a particular solvent, 1,1,1-trichloroethane, was recently recalled from the market due to potential hazards of this substance (Ref. 33).

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of menthol/peppermint oil (topical/inhalant) as a nasal decongestant. Its effectiveness is uncertain due to lack of properly controlled studies of the substance by itself.

Menthol has been used in external preparations for its effects in the nasal passages. A decided cooling sensation is noticed when the substance is applied to the skin or to the mucous membrane. A cooling sensation noted in nasal passages is associated with a feeling of decreased nasal congestion. The cooling sensation, however, is not associated with an actual decrease in surface temperature, thus it is not dependent upon nasal constriction but rather appears to result from an influence on sensory nerve endings responsible for cold reception (Ref. 34). Standard texts, in fact, have noted that the feeling of nasal decongestion accompanying menthol vapor action may be an illusion and, in fact, may be accompanied by increased congestion (Ref. 1).

Using an electronic technique for measuring nasal airflow in 18 infants and children, Noller demonstrated that intranasal application of a 2.82 percent mentholated ointment induced a reduction in airflow during the first 20 minutes which was followed by an increase in airflow over the pretreatment level, lasting 1 to 3 hours (Ref. 35). In three children the menthol ointment was applied to the chest and back with one nostril remaining closed throughout the experiment except during measurement. Increased airflow was noted only in the open nostril up to 4 hours after administration, leading to the conclusion that the effect of menthol was due to the inhaled vapors (Ref. 35).

In a study of 50 patients with head colds, 15 of whom also received a petrolatum placebo application, application to the chest of an ointment containing a mixture of volatile substances including 2.8 percent menthol induced a significant degree of nasal decongestion compared to placebo over an 8 hour period as determined by a modified Butler-Ivy procedure (Ref. 36). Two additional objective-measurement placebo-controlled crossover studies involving chest, throat and back application of an ointment containing a mixture of volatile substances including 2.8 percent menthol revealed a significant nasal decongestant effect compared to placebo over an 8 hour period in a total of 90 patients with head colds (Refs. 37 and 38).

A liquid mixture of volatile substances which is to be added to the water in a hot steam vaporizer and administered via inhalation contains menthol 3.66 percent, camphor 7 percent, eucalyptus oil 1.7 percent and tincture of benzoin 5 percent. Two objective-measurement placebo-controlled studies in patients with nasal congestion due to head cold revealed that this liquid containing volatile substances placed in hot water in a dose of 1 tablespoon per quart induced a statistically significant decrease in nasal airway resistance compared to inhalation of steam alone during the period of steam inhalation (Refs. 24 and 39). It was demonstrated that an optimal distance between the subject and the vaporizer to elicit this effect was 4 to 6 feet (Ref. 24).

An aerosolized mixture of volatile substances to be sprayed in the room and containing menthol 1 percent and eucalyptus oil 1 percent has been studied for its nasal decongestant effect by ob-

jective measurement studies. When sprayed into the room for 15 seconds in the vicinity of the subject's head, measurement of expiratory nasal flow rate in 25 head cold patients revealed at least a 20 percent increase in expiratory flow rate in 19 of the patients when compared to pretreatment control readings. No placebo was utilized, however, and since measurements were only made for 6 minutes after drug administration, the average duration of effect was not determined (Ref. 40). In a subsequent study on five patients with head colds, the aerosolized mixture of volatile substances readministered at 0, 2, 4 and 7 hours led to a transient increase in expiratory nasal flow rate over the pretreatment level each time. Duration of this effect following each dose was not determined (Ref. 41). In an objective-measurement placebo-controlled study of 15 patients with head colds, nasal airway resistance was determined following a 20-second placebo aerosol spray and then for 30 minutes after a 20-second spraying of the volatile oil mixture which provided a total of 20 gm of aerosolized material. A significant decrease in nasal airway resistance was obtained with the medicated aerosol compared to placebo in 9 of the 15 subjects, but in only 3 of these subjects did the effect persist throughout the 30-minute period of observation (Ref. 42). A similar study with an additional 15 patients having partial nasal congestion due to head colds revealed comparable results (Ref. 43).

Use of a sensitive gas chromatographic technique has revealed the presence of menthol vapors in air expired through the nasal passage during the time a menthol-containing lozenge was dissolving in the subject's mouth (Ref. 44). Patients with nasal congestion due to head colds were divided into 2 groups of 15 each. One group received a 4.27 gm lozenge containing 0.15 percent menthol and 0.04 percent eucalyptus oil while the other group received a nonmedicated lozenge base. No significant difference in nasal airway resistance between the placebo and active medication group could be demonstrated (Ref. 45). In a subjective evaluation study using allergic rhinitis patients, 78.4 percent of the patients using the menthol-eucalyptol lozenge compared to 65.4 percent of the placebo groups claimed relief of their stuffy nose after 1 day of treatment. The difference between the groups was not, however, statistically significant (Ref. 46).

The effect of rinsing and gargling twice daily with an aqueous mixture of volatile substances on the incidence of colds and the severity of the symptoms associated with colds was evaluated in a long-term double-blind placebo-controlled subjective study in school children. The results of the study revealed milder nasal symptoms and cough symptoms in individuals using the medicated mouthwash as compared to the placebo. Although the medicated mouthwash contained 0.42 mg/ml menthol, the results did not demonstrate the contribution of this component to the overall alleviation of symptoms (Ref. 47).

(3) *Proposed dosage.* Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 2.8 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapors rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 3.66 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl or washbasin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For inhalation use as a 1 percent room spray: Spray room for 15 to 20 seconds in the vicinity of the patient. May be repeated at ½ to 1 hour intervals as needed.

(iv) For topical use as a lozenge 1.0 to 10 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every ½ to 1 hour.

(v) For use as a mouthwash 0.42 mg/ml solution: Gargle with ⅔ oz (20 ml) twice daily.

For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: *Warning:* "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: *Warning.* "For steam inhalation only. Do not take by mouth".

(5) *Evaluation.* The Panel made the following recommendations: (i) For topical ointment use: Data to demonstrate effectiveness will be required from one additional controlled objective measurement study in patients with nasal congestion due to acute rhinitis in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(iii) For inhalation use as a room spray: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(iv) For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(v) For use as a mouthwash: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

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i. *Phenylpropanolamine hydrochloride (topical)*. The Panel concludes that phenylpropanolamine hydrochloride is safe in the dosage ranges used when applied topically but there are insufficient data to permit final classification of its effectiveness for topical OTC use as a nasal decongestant.

(1) *Safety*. Clinical experience has confirmed that phenylpropanolamine hydrochloride (topical) is safe in the dosage ranges used as a nasal decongestant. Phenylpropanolamine hydrochloride as 1 to 5 percent aqueous solution administered by drops or intranasal tampon was well tolerated by most patients, although a few complained of transitory stinging (Refs. 1, 2, and 3). Rhinoscopic examination revealed little or no evidence of nasal irritation following prolonged and continuous use of 3 percent phenylpropanolamine nasal solution but details of time parameters of drug administration were not given (Ref. 2). There is a need for additional data relating frequency of use with incidence and intensity of rebound nasal congestion in adults and children.

(2) *Effectiveness*. There are no well-controlled studies documenting the effectiveness of phenylpropanolamine hydrochloride (topical) as a nasal decongestant. Its effectiveness is uncertain because no properly controlled objective measurement studies have been presented.

Phenylpropanolamine hydrochloride is generally considered to exert a nasal decongestant effect when topically applied as a 1 to 3 percent solution (Refs. 1 through 5). Administration as drops or soaked intranasal tampons (3 to 5 minutes contact time) to adult chronic rhinitis patients resulted in subjective and rhinoscopic evidence of nasal decongestion persisting up to 2 hours. None of these studies were controlled, double-blind or contained objective measurements in their design. No data from studies in children were presented. Studies of nasal decongestant effectiveness of topical phenylpropanolamine hydrochloride in 0.25 percent to 0.5 percent concentrations are currently in progress and the Panel was told that a report will be submitted when completed (Ref. 6).

(3) *Proposed dosage*. Adults and children above 6 to under 12 years topical dosage is 2 to 3 drops or sprays of a 1 percent solution in each nostril every 2 to 4 hours. For children under 6 years, there is no recommended dosage except under the advice and supervision of a physician. Concentrations and frequency of administration for safe and effective use have not been established in children under 6 years.

(4) *Labeling*. The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation*. Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

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j. *Thenyldiamine hydrochloride (topical)*. The Panel concludes that thenyldiamine hydrochloride is safe in the dosage ranges used when applied topically but there are insufficient data to permit final classification of thenyldiamine hydrochloride as safe and effective for OTC use as a topical nasal decongestant.

(1) *Safety*. Clinical experience has confirmed that thenyldiamine hydrochloride (topical) is safe in the dosage ranges used as a nasal decongestant. Topically, 0.1 percent or 0.2 percent thenyldiamine hydrochloride in combination with phenylephrine hydrochloride, 0.25 and 0.5 percent, produced only "slight" or "moderate" stinging in some of the subjects in human intranasal irritation studies conducted by a manufacturer (Ref. 1). Preparations containing 0.5 percent thenyldiamine hydrochloride produced "moderate" to "severe" stinging in all subjects and irritation of the larynx in a few subjects. There are no data available on the incidence of rebound congestion.

(2) *Effectiveness*. There are no well-controlled studies documenting the effectiveness of thenyldiamine hydrochloride (topical) as a nasal decongestant. In a randomized, double-blind, and

crossover study of patients with acute rhinitis, a combination of thenyldiamine hydrochloride, 0.1 percent, with other active ingredients applied intranasally as a sprayed solution produced a subjectively evaluated nasal decongestant effect which was significant as compared to that produced by a placebo solution (Ref. 2). However, in this study the effectiveness of the combination product, thenyldiamine with phenylephrine and benzalkonium, was not significantly different from that of the product minus thenyldiamine. In fact, the nasal decongestant effect produced by phenylephrine alone and the nasal decongestant effect produced by thenyldiamine alone were not significantly different from the nasal decongestant effect produced by the combination commercial product. The three preparations did not differ at the 95 percent confidence level.

In another controlled study to determine the therapeutic contribution of topically applied thenyldiamine in a combination product with phenylephrine and benzalkonium chloride, no additive or synergistic effect was evident over that obtained by phenylephrine 0.5 percent alone, when measured by posterior electronic rhinometry or by a plethysmograph with a face mask (Ref. 3).

The manufacturer's labeling states that thenyldiamine hydrochloride "offsets the results of mediator release to the extent it is producing obstruction and at the same time opposes cholinergic hyperemia and rhinorrhea." Thacker (Ref. 4) supports inclusion of antihistamines in OTC nasal decongestant products to prevent engorgement from migration of excessive body fluids from the vascular system into tissue spaces and to aid in alleviating allergic reactions to ingredients in the solution. This supposition, however, is not supported by scientific evidence.

Studies with topical thenyldiamine indicate it may be a nasal decongestant but no nasal decongestant claims are made for this ingredient in the commercially available OTC products, although the products themselves are nasal decongestants. Present claims made for thenyldiamine are based on topical application of an antihistamine but there are no studies on the antihistamine activity of the drug applied topically.

There are no data on the use of this drug in children.

(3) *Proposed dosage.* Adult topical dosage is 1 to 3 drops or sprays of a 0.1 percent solution in each nostril not more than every 4 hours. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

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(3) Gould, W. J., "Clinical Summary of NTZ Study, MRD, 70-65," Draft of unpublished paper is included in OTC Volume 040298.

(4) Thacker, E. A., "Nasal Solutions with Combined Therapeutic Effects," *The Eye, Ear, Nose and Throat Monthly*, 29:609-613, 1950.

k. *Thymol (topical/inhalant).* The Panel concludes that thymol is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical/inhalant OTC use as a nasal decongestant.

(1) *Safety.* Clinical experience has apparently confirmed that thymol (inhalant) is safe in the dosage ranges used as a nasal decongestant.

Thymol is an alkyl derivative of phenol and has bactericidal, fungicidal, and anthelmintic properties (Ref. 1). When hydrogenated, thymol is converted to the closely related drug, menthol (Ref. 2). The LD_{50} of thymol in mice is 1,800 mg/kg orally (Ref. 3). No data were found bearing on the drug's toxicity in man. In view of thymol's relative inactivity compared to menthol, of which 50 to 120 gm "would have to be absorbed to cause poisoning" (Ref. 4), thymol is presumed to be relatively nontoxic.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of thymol (inhalant) as a nasal decongestant. Experiments in anesthetized rabbits have indicated that thymol administered by steam inhalation augmented the concentration of soluble mucous in the respiratory tract fluid (Ref. 2). The dose administered was unknown but the concentration in the vaporizer was in excess of 81 mg/kg. The volume of secretions did not change. Much lower concentrations of menthol were effective (1 mg/kg). In man no data on effectiveness of thymol alone were found although a mixture containing thymol, menthol, eucalyptol, and propylene glycol appeared to suppress citric acid induced cough (Ref. 5) and to reduce resistance in the nasal and bronchial airways (Ref. 6).

Studies involving the objective measurement of the nasal decongestant activity of thymol were done with mixtures of volatile substances, topically applied as ointments (Refs. 7, 8 and 9), and in steam inhalations (Refs. 10 and 11). Although significant nasal decongestant activity as compared to placebo was demonstrated, it was not evident whether the thymol component contributed to this effect.

The effect of rinsing and gargling twice daily with an aqueous mixture of volatile substances on the incidence of colds and the severity of the symptoms associated with colds was evaluated in a long-term double-blind placebo-controlled subjective study in school children. The results of the study revealed milder nasal symptoms in individuals using the medicated mouthwash as compared to the placebo. Although the medicated mouthwash contained 0.63 mg/ml thymol, the results did not demonstrate the contribution of this component to the overall alleviation of symptoms (Ref. 12).

(3) *Proposed dosage.* Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 0.1 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapors rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 0.13 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl or washbasin; or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

(iii) For inhalation use as a 0.1 percent room spray: Spray room for 15 to 20 seconds in the vicinity of the patient. May be repeated at ½ to 1 hour intervals as needed.

(iv) For topical use as a lozenge 0.02 to 2.0 mg: Allow lozenge to dissolve slowly in mouth. May be repeated every ½ to 1 hour.

(v) For use as a mouthwash 0.63 mg/ml solution: Gargle with ⅔ oz (20 ml) twice daily.

For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling:

(i) For topical ointment use: *Warning:* "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: *Warning:* "For steam inhalation only. Do not take by mouth".

(5) *Evaluation.* The Panel made the following recommendations: (i) For topical ointment use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(iii) For inhalation use as a room spray: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(iv) For topical use as a lozenge: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(v) For use as a mouthwash: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

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(10) Shapiro, M., "Steam Alone vs. Vaposteam in Steam," Draft of unpublished data is included in OTC Volume 040298.

(11) Ciampi, L. A., "Vaposteam. Nasal Decongestant Vick Rhinorrheometer. CRD 75–1," Draft of unpublished data is included in OTC Volume 040298.

(12) OTC Volume 040278.

1. *Turpentine oil (spirits of turpentine) (topical/inhalant).* The Panel concludes that turpentine oil is safe in the dosage ranges used when applied topically or as an inhalant but there are insufficient data to permit final classification of its effectiveness for topical or inhalant OTC use as a nasal decongestant.

(1) *Safety.* Clinical experience has confirmed that turpentine oil (topical/inhalant) is safe in the dosage ranges used as a nasal decongestant.

Oil of turpentine is a volatile oil consisting of a mixture of pinenes derived from the oleoresin obtained from *Pinus palustris*. Nelson et al. (Ref. 1) found exposure to a vapor of 420 to 560 mcg/l acceptable to most of their human subjects. The threshold for industrial exposure for 8 hours has been set at 560 mcg/l. The maximum concentration obtainable with a currently marketed OTC preparation is 36 mcg/l (Refs. 2 and 3). No histological evidence of pulmonary lesions were seen in mice and rats exposed to lethal concentrations of turpentine vapors (Ref. 4). Inhalation of 300 mcg/l of turpentine vapor by mice for 15 minutes did not influence the electrocardiogram, respiratory minute volume, pulmonary airway resistance or compliance (Ref. 5). One study conducted in mice using a mixture of volatile oils, one of which was turpentine, showed a decrease in pulmonary antibacterial activity (Ref. 6). Two other studies showed no change when the mixture was used (Refs. 7 and 8).

In several studies in children and infants suffering from minor breathing discomforts associated with the "common cold" no side effects that were drug related were observed when a medicated steam was administered (Refs. 9 through 13). Turpentine has been widely used as a part of a mixture of volatile oils for many years with approximately two complaints per million packages purchased (Ref. 14).

(2) *Effectiveness.* Studies involving the objective measurement of the nasal decongestant activity of turpentine were done with mixtures of volatile substances, topically applied as ointments (Refs. 15, 16, and 17), and in steam inhalation (Refs. 18 and 19). Although significant nasal decongestant activity as compared to placebo was demonstrated in these studies, it was not evident whether the turpentine contributed to this effect.

(3) *Proposed dosage.* Dosage for adults and children 2 to under 12 years is as follows: (i) For topical use as a 4.0 percent ointment preparation: To be rubbed on the throat, chest, and back as a thick layer. The area of application may be covered. However, clothing should be left loose about the throat and chest to help the vapor rise to reach the nose and mouth. Applications may be repeated up to 3 times daily.

(ii) For steam inhalation use as a 5.5 percent solution: 1 tablespoonful of solution per quart of water is added directly to the water in a hot steam vaporizer, bowl, or 2 teaspoonfuls of solution per pint of water are added to an open container of boiling water. Breathe in vapors during the period of medicated steam generation. May be repeated 3 times daily.

For children under 2 years, there is no recommended topical or inhalant dosage except under the advice and supervision of a physician.

(4) *Labeling.* The Panel recommends the Category I labeling for nasal decongestant active ingredients. (See part VIII. paragraph B.1. above—Category I Labeling.) In addition, the Panel recommends the following specific labeling: (i) For topical ointment use: *Warning:* "For external use only. Do not take by mouth or place in nostrils".

(ii) For steam inhalation use: *Warning:* "For steam inhalation only. Do not take by mouth".

(5) *Evaluation.* The Panel made the following recommendations: (i) For topical ointment use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

(ii) For steam inhalation use: Data to demonstrate effectiveness will be required in accordance with the guidelines set forth below for testing nasal decongestant drugs. (See part VIII. paragraph C. below—Data Required for Evaluation.)

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Category III Labeling

The Panel concludes that the available data are insufficient to permit final

classification of the labeling claims identified below for nasal decongestants. Additional data are required to support the following nasal decongestant claims:

Reference to "preventing sneezing", "drying runny nose" or "checking post nasal drip" are unsubstantiated claims for nasal decongestants unless studies specifically designed to assess these activities are presented. Studies of nasal decongestants have assessed the effect on nasal airway resistance or the ease of breathing but not the effect on rhinorrhea.

Reference to an indirect effect in "preventing or alleviating cough" by an effect on nasal congestion is an unsubstantiated claim unless studies specifically designed to assess this activity are presented.

Reference to an effect "to reduce sinus pressure" is an unsubstantiated claim since studies of nasal decongestant activity assess the effect on nasal airway resistance. Although it is assumed that this effect on the nasal mucosa may indirectly facilitate sinus drainage and thus decrease sinus congestion, it would be unsubstantiated to claim a drug effect to decrease sinus pressure without evidence to support this claim.

Reference to the extent of the penetration of topically applied nasal decongestants is unsubstantiated without specific studies to demonstrate the extent of penetration (depth of penetration into the nasal cavity and/or the extent of penetration into the nasal mucosa).

Pressure within the antrum can be measured and recorded in terms of centimeter of water compared to ambient pressure by means of a suitable needle or small trocar placed in the antrum under topical anesthesia. This would be performed in a small number of patients (5 to 10) with nasal congestion associated with an acute respiratory infection who complain of localized headache and/or tenderness in the sinus areas. These pressure measurements would be repeated following the administration of the test preparation or placebo in the dosage range and time intervals recommended for OTC usage. Subjective symptoms such as headache, tenderness, etc., could be evaluated in conjunction with the pressure measurements.

C. DATA REQUIRED FOR EVALUATION

The Panel has agreed that the protocols recommended in this document for the studies required to bring a Category III drug into Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved methodology in the future.

1. *Principles in the design of an experimental protocol for testing nasal decongestant drugs.* a. *General principles.* The effectiveness of a nasal decongestant drug should be determined by its ability to reduce nasal obstruction in patients with acute or chronic rhinitis. Tests should involve double-blind placebo-controlled assessment of the drug's ability to decrease nasal airway resistance. Patient-reported subjective assessment is also desirable. The drugs used should be the same as in the OTC preparation and should be given in the same dosage as the recommended label instructions for the preparation. Since either oral or topical nasal decongestants may be administered repeatedly during episodes of nasal congestion, studies should bear on the appropriate interval for dosing to maintain optimal relief of symptoms. For locally applied nasal decongestants, wherein rebound congestion with repeated use is a concern, labeling should specify short-term use in providing temporary relief of nasal congestion. Specific data on this matter should be obtained by testing the topical nasal decongestant in the concentrations and maximal dosage frequencies to be recommended for periods of at least 1 week in order to assess the incidence and severity of a drug-induced increase in nasal airway resistance.

b. *Selection of patients.* Selection of patients for testing should be based on the diagnosis of rhinitis with nasal congestion. Patients with chronic allergic or vasomotor rhinitis present relatively stable nasal congestion and consequently can serve as their own controls in a crossover study design. Patients with acute allergic or infectious rhinitis also represent a large proportion of the patient type likely to self-medicate with a nasal decongestant. Because of the relatively brief time course of these acute disorders and greater variation in stability of congestion, larger numbers of these patients would have to be studied by assigning them in random fashion to placebo or drug groups. Further, for comparative purposes these groups have to be matched by age, sex, and if possible, the degree of nasal congestion at the time of study. Smoking by test subjects should be prohibited 24 hours prior to and during the test.

c. *Methods of study.* Observation should include both the subjective response and objectively measured nasal airway resistance before the drug or placebo is administered, and at appropriate intervals thereafter to demonstrate time of onset, magnitude, and duration of response.

d. *Interpretation of data.* A recommended dose of the test drug should induce a statistically significant reduction in nasal airway resistance when compared with the placebo response.

Evidence of drug effectiveness is required from a minimum of two positive studies based on the results of two different investigators or laboratories.

All data submitted to the Food and Drug Administration must present both favorable and any unfavorable results.

e. *Evaluation of safety.* Tests of safety should involve the usual tests for toxicity relevant to the known possible adverse effects of the drugs under testing. Tests should be done in the form of dose response curves up to a maximum therapeutic effectiveness.

IX. MISCELLANEOUS INGREDIENTS

A. GENERAL COMMENT

The action of several drugs considered by the Panel do not fall within the main pharmacologic groups, i.e., antitussives, expectorants, bronchodilators, anticholinergics, antihistamines, and nasal decongestants reviewed by the Panel. However, these miscellaneous ingredients are found in many OTC CCABA products. Because of the differences in their intended action in CCABA products, they are discussed individually below.

B. CATEGORIZATION OF DATA

The miscellaneous ingredients and/or labeling have been reviewed and classified as follows:

1. *Conditions under which CCABA products are not generally recognized as safe and effective or are misbranded.* The use of certain conditions are unsupported by scientific data, and in some instances by sound theoretical reasoning. The Panel concludes that the following ingredients and/or labeling should be removed from the market until scientific testing supports their use.

a. *Antihistamines in combination CCABA products exclusively for sedation.* The Panel concludes that the combining of an antihistamine in a CCABA combination product for the exclusive purpose of sedation is irrational. The Panel is aware that CCABA combination products are currently available for use at bedtime and promoted for such various claims as "for restful sleep". However, the duration of drug effects in "nighttime cold preparations" which are recommended to be taken once at bedtime is not fully documented. Although antihistamines produce sedation as a side effect depending upon the dosage, the addition of an antihistamine for the primary purpose of sedation is not rational. The Panel has recommended the use of antihistamines in CCABA combination products only for the relief of symptoms of allergic rhinitis. (See part II. paragraph C.5.b. above—Combination products containing antihistamines with sleep-aid claims.)

Certain antihistamines are generally considered safe for OTC use. The Panel has recommended specific doses for each of these antihistamines after a consideration of the scientific data available for these ingredients. The Panel concluded that the antihistamines reviewed by the Panel and classified as Category I are both safe and effective for the treatment of the symptoms of allergic rhinitis when administered as labeled. (See part VII. paragraph B.1. above—Category I conditions under which antihistamine ingredients are generally recognized as safe and effective and are not misbranded.) However, the Panel does not recommend the addition of another antihistamine to a CCABA combination product for the exclusive purpose of sedation. The rationale for the use of an additional antihistamine in CCABA combination products for the exclusive purpose of sedation has not been demonstrated.

b. *Vitamins used alone or in combination CCABA products with labeling claims for the prevention or treatment of the "common cold".* The Panel is unaware of any well-controlled studies documenting the safety or effectiveness

of vitamins for use in the prevention or treatment of the "common cold". In addition, the Panel concludes that the use of any vitamin in CCABA combination products for the prevention of colds is irrational since such products should only be used when the symptoms of the "common cold" are present. It would, therefore, be irrational for a consumer to take a cold combination product containing vitamins to prevent a cold. The Panel has discussed this issue earlier in this document. (See part II. paragraph C.5.a. above—Combination products containing vitamins.)

The Panel is aware of the popular use of vitamin C for treatment of the symptoms of the "common cold." However, the Panel has reviewed the available data which is discussed below and concludes that no drug labeling claims should be made for vitamin C for the prevention or treatment of the symptoms of the "common cold" until adequate data are available to substantiate such claims. (See part IX. paragraph B.2.b. below—Ascorbic acid (vitamin C).)

2. *Conditions for which the available data are insufficient to permit final classification at this time.* The Panel concludes that adequate and reliable scientific evidence is not available at this time to permit final classification of the claimed active ingredients for the conditions listed below. The Panel believes it reasonable to provide 3 years for vitamin C, 2 years for phenobarbital and caffeine, and 3 years for antihistamines for the development and review of evidence to substantiate the conditions specified below. Marketing need not cease during this time if adequate testing is undertaken. If adequate effectiveness data are not obtained within the time period provided, the ingredients listed in this category should no longer be marketed as over-the-counter products. The ingredients considered in this category are:

Antihistamines in combination CCABA products with sleep-aid claims

Ascorbic acid (vitamin C)
Caffeine
Phenobarbital

a. *Antihistamines in combination CCABA products with sleep-aid claims.* The Panel concludes that there are insufficient data to permit final classification of the safety and effectiveness for OTC use of sleep-aid claims for antihistamines in combination CCABA products in which their primary claim is for the relief of the symptoms of allergic disorders. The Panel is aware that antihistamines may have several activities, e.g., antitussive, antihistamine or sedative activity, depending on the dosage level used. The Panel has discussed this issue earlier in this document. (See part II. paragraph C.5.b. above—Combination products containing antihistamines with sleep-aid claims.)

(1) *Safety.* Clinical experience has confirmed that antihistamines are safe in the dosage ranges used in combination CCABA products with sleep-aid claims.

The Panel concludes that the antihistamines reviewed by the Panel and classified as Category I are both safe and effective for the treatment of the symptoms of allergic rhinitis when administered as labeled. (See part VII. paragraph B.1. above—Category I conditions under which antihistamine ingredients are generally recognized as safe and effective and are not misbranded.) However, the Panel was unable to make a final definition as to the safe and effective use of antihistamines as sleep-aids in CCABA products.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of antihistamines in combination CCABA products as sleep-aids. Although sedation may be a side effect, the effectiveness of antihistamines in CCABA combination products as sleep-aids, is not fully understood.

(3) *Proposed dosage.* The Panel is unable to determine a proposed dosage. The Panel concludes that the pharmaceutical industry should consult with the Food and Drug Administration as to a suitable proposed dosage for testing. Otherwise, the Panel recommends that each drug manufacturer evaluate the dosage as labeled on the manufacturer's marketed product(s).

(4) *Labeling.* The Panel recommends that labeling claims contained in each drug manufacturer's currently marketed product, i.e., "for restful sleep", should be used.

(5) *Evaluation.* Data to demonstrate effectiveness will be required to be completed in 3 years. The Panel recommends a testing protocol in conformance with the requirements specified by the OTC Sedative, Tranquilizer and Sleep-Aid Drug Products Panel as published in the FEDERAL REGISTER of December 8, 1975 (40 FR 57292).

b. *Ascorbic acid (vitamin C).* The Panel concludes that there are insufficient data to permit final classification of ascorbic acid as safe and effective for OTC use in the prevention or treatment of the "common cold." The use of vitamin C in CCABA combination products has been discussed earlier in this document. (See part II. paragraph C.5.a. above—Combination products containing vitamins.)

(1) *Safety.* Long experience and innumerable studies attest to the fact that ascorbic acid, in doses preventing scurvy, is entirely safe. The daily requirement of ascorbic acid for the adult man is 30 mg and the National Academy of Sciences-National Research Council has therefore set the daily dietary allowance for ascorbic acid at 45 mg (Ref. 1). Ascorbic acid is probably safe in the dosage used for the treatment of acute catarrhal conditions of the nasal mucous membranes which is usually accompanied with profuse discharge from the nostrils, referred to as coryza. Dosages recommended for prevention or treatment of coryza range from 1 to 3 gm or more daily raising blood levels above the renal threshold with consequent rapid excretion by the kidney. Change from a high to a low level of ascorbic acid in the diet appears to predispose to the development of scurvy (Ref. 2).

In humans, massive doses of vitamin C, from 1 to 10 or more gm per day, have not caused toxic symptoms. Diarrhea is the only symptom reported. High levels of urinary ascorbic acid may give false positive tests for sugar in diabetic patients (Ref. 3). Also, theoretically, large doses of ascorbic acid increase the level of uric and oxalic acid in the urine, a possible hazard in patients with a tendency to gout or oxalate renal stones (Ref. 2). Large doses of vitamin C in laboratory animals have been reported to reduce fertility (Ref. 3). In a large study in human subjects (Ref. 4) the administration of large daily doses of vitamin C caused a marked but transitory fall in the vitamin C content of the blood when the vitamin C was discontinued.

(2) *Effectiveness.* There are no well-controlled studies documenting the effectiveness of vitamin C in the prevention or treatment of the "common cold."

Ten or more studies have left the matter of effectiveness in doubt. None of the studies done to date have shown ascorbic acid in any of the dosage schedules used to be unequivocally effective, although trends in favor of effectiveness have been seen. The need for elimination of bias by careful design of clinical trials has been repeatedly stressed.

The claimed effects of large doses of vitamin C on the "common cold" include prevention of colds, more rapid recovery and reduced severity.

In reviews of the data, Pauling argued persuasively (Refs. 5 through 8) that the data favored a beneficial effect of large dosages of vitamin C in treating the "common cold." In another review of these data more caution is urged in accepting this interpretation (Ref. 3). In a third review (Ref. 9), data presented by the reviewer as well as data from many other studies are interpreted as favoring a beneficial effect of large dosages of vitamin C in treating the "common cold." However, an addendum citing data published in 1974 (Ref. 10) failed to support a beneficial effect in doses ranging from 50 to 1,000 mg of vitamin C daily.

In a double-blind study comprising 1,000 subjects (Ref. 11) receiving a placebo or vitamin C in a dose of 1,000 mg daily and 4,000 mg for each of the first 3 days of a cold, there were 30 percent fewer days of confinement to the house among those receiving vitamin C as compared with those receiving the placebo, a finding that was highly significant ($p=0.001$). A second study indicated that the effect observed was not ascribable to either a prophylactic or a therapeutic effect alone (Ref. 4). A dosage level of 2,000 mg/day was not significantly different in its effects from one of 250 mg/day.

In the third of a series of large-scale double-blind studies on the effect of vitamin C on the "common cold" also recently published, the data indicated that subjects receiving vitamin C either in regular or sustained release forms in a dose of 500 mg each week, 1,500 mg on the first day of a cold and 1,000 mg daily for the next 4 days, had a significantly

milder illness than those receiving a placebo (Ref. 12). These findings indicate that very large daily doses of vitamin C may be unnecessary.

In a recent study (Ref. 13), a random sample of employees in the National Institutes of Health comprising 190 subjects were given prophylactic daily ascorbic acid (3,000 mg) or a placebo and with the onset of a "cold" were given 3,000 mg or 6,000 mg ascorbic acid or a placebo. The study was well-designed with the exception that the placebo differed in taste from the active drug thus leading the investigators to question whether the observed result of "minor influence on the duration and severity of colds" was attributable to this flaw in the study design rather than to a beneficial effect of ascorbic acid.

One means by which vitamin C might favorably influence the "common cold" is suggested by recent in vitro studies showing that in the presence of 250 mcg/ml vitamin C and glutathione, the growth of one of the causes of the "common cold," rhinovirus, was markedly suppressed. This concentration of vitamin C was without an adverse effect on the cells (Ref. 14). In contrast to the implication that vitamin C has a specific antiviral effect, one of the recent clinical studies indicates that vitamin C has a beneficial effect on various types of illnesses and not only the syndrome referred to as the "common cold" (Ref. 11).

The Panel concludes that the published data support a beneficial effect of vitamin C on the severity and perhaps frequency of the "common cold" when given in dosages exceeding the daily requirement. However, it is not yet clear that this effect is clinically significant. The magnitude of the dosages needed and the optimum schedule for prophylaxis and therapy remain to be determined.

(3) *Proposed dosage.* The Panel is unable to determine a proposed dosage. The Panel concludes that the pharmaceutical industry should consult with the Food and Drug Administration as to a suitable proposed dosage for testing.

(4) *Labeling.* The Panel is unable to determine suitable labeling. The Panel concludes that no drug labeling claims should be made for vitamin C for the prevention or treatment of the symptoms of the "common cold" until adequate data are available to substantiate such claims. The Panel has discussed such labeling claims above. (See part IX. paragraph B.1.b. above—Vitamins used alone or in combination CCABA products with labeling claims for the prevention or treatment of the "common cold.") The Panel recognizes that vitamin C is readily available as a food supplement to any consumer who so selects to treat the symptoms of the "common cold."

(5) *Evaluation.* Data to demonstrate effectiveness will be required to be completed in 3 years.

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(14) Schwerdt, P. R. and C. E. Schwerdt, "Effect of Ascorbic Acid on Rhinovirus Replication in WI-38 Cells (38724)," *Proceedings of the Society for Experimental Biology and Medicine*, 148:1237–1243, 1975.

c. *Caffeine.* The Panel concludes that there are insufficient data to permit final classification of caffeine as safe and effective as a "stimulant corrective" for OTC use in combination CCABA products containing central nervous system sedating drugs, such as the antihistamines. The Panel presumes that caffeine has been added as a "stimulant corrective" rather than as an active ingredient. The Panel has discussed this issue earlier in this document. (See part II. paragraph C.5.e. above—Combination products containing correctives (stimulants and sedatives).)

(1) *Safety.* Clinical experience has confirmed that caffeine is generally considered safe in the doses (15 to 30 mg) commonly contained in CCABA combination products.

The Panel is aware of the OTC Sedative, Tranquilizer and Sleep-Aid Drug Product Panel's findings regarding caffeine which were published in the FEDERAL REGISTER of December 8, 1975 (40 FR 57292). That Panel concluded that caffeine when used alone and not in a combination drug product is safe and effective for use as a stimulant at a recommended dose of 100 to 200 mg not more often than every 3 to 4 hours.

(2) *Effectiveness.* There are no well-controlled studies demonstrating the effectiveness of caffeine as a "stimulant corrective" in combination CCABA products. The Panel is unaware of any data that support such use in combination products.

(3) *Proposed dosage.* The Panel is unable to determine a proposed dosage. The Panel concludes that the pharmaceutical industry should consult with the Food and Drug Administration as to a suitable proposed dosage for testing. Otherwise, the Panel recommends that each drug manufacturer evaluate the dosage as labeled on the manufacturer's marketed product(s).

(4) *Labeling.* The Panel recommends the labeling claims contained in each drug manufacturer's currently marketed products. In addition, the Panel recommends the activity of caffeine should be identified on the label as "an ingredient added to counteract drowsiness caused by other drugs in this product."

(5) *Evaluation.* Data to demonstrate effectiveness as a stimulant corrective will be required to be completed in 2 years. An acceptable test procedure will be one in which the combination with and without the corrective is evaluated to assess the effectiveness of the corrective to significantly decrease the incidence and/or intensity of the undesirable side effect and the safety of this combination.

d. *Phenobarbital.* The Panel concludes that there are insufficient data to permit final classification of phenobarbital as safe and effective for OTC use as a "stimulant corrective" in combination products with central nervous system stimulant drugs, such as the theophyllines and ephedrine. The Panel presumes that phenobarbital has been added as a "sedative corrective" rather than as a CCABA active ingredient. The Panel has discussed this issue earlier in this document. (See part II. paragraph C.5.e. above—Combination products containing correctives (stimulants and sedatives).)

(1) *Safety.* Clinical experience has confirmed that phenobarbital is generally considered safe in the doses recommended for sedative effect.

The generally recognized dose of phenobarbital as a sedative is 15 to 30 mg given 2 to 4 times daily (Refs. 1 through 3). An official compedium gives a range of 50 to 200 mg daily (Ref. 4). Adverse reactions are infrequent. Effective sedation is usually accompanied by lengthened reaction time (Ref. 5). There are occasional reports of megaloblastic anemia on prolonged use (Ref. 3). Phenobarbital stimulates the synthesis of drug-metabolizing enzymes in the liver, which may increase the metabolism (biotransformation) of other drugs administered at the same time. This type of interaction interferes with obtaining a predictable intensity and/or duration of action of other drugs administered during the period of phenobarbital administration (Refs. 1 through 3). Barbiturates, as a class, are subject to abuse. In patients with acute intermittent porphyria, phenobarbital may precipitate a dangerous rise in the level of porphyrins.

(2) *Effectiveness.* Phenobarbital is used in combination products containing

theophyllines and ephedrine, at a dose of 8 mg, to counteract the central nervous stimulant effect of these drugs. However, the effectiveness of phenobarbital as a "sedative corrective" at a dose of 8 mg has not been established.

The generally recognized dose of phenobarbital as a sedative is 15 to 30 mg given 2 to 4 times daily (Refs. 1 through 3). It would be reasonable to expect that if there is stimulation from other drugs such as ephedrine, the dose to antagonize the stimulation should be at least the minimum effective sedation dose. All the citations in the various volumes submitted state only that a barbiturate is useful in counteracting the stimulant effects of drugs like ephedrine. None suggest a dose. Phenobarbital stimulates hepatic enzymes which may increase the metabolism of other drugs and thereby reduce their expected activity (Refs. 1 and 2). It would seem that the only way to determine the effectiveness of an 8 mg dose of phenobarbital and whether it contributes to the combination of antiasthmatic preparations is by conducting controlled clinical trials.

(3) *Proposed dosage.* Adult oral dosage is 8 to 16 mg every 4 hours.

(4) *Labeling.* The Panel recommends the following: (i) *Indications.* The activity of phenobarbital should be identified on the label as "an ingredient added to counteract nervousness caused by other drugs in this product".

(ii) *Warnings.* (*a*) *"Caution:* May cause drowsiness. Avoid driving a motor vehicle or operating heavy machinery".

(*b*) "Do not take this product if you are presently taking other drugs except under the advice and supervision of a rective":

(*c*) "May be habit-forming".

(5) *Evaluation.* Effectiveness at 8 mg has not been established. Further studies must be completed in 2 years. The Panel recommends the following guidelines to establish effectiveness as a "sedative corrective".

a. *General principles.* Sympathomimetic drugs and theophyllines may cause central nervous system stimulation in some patients. To counteract this a small dose of sedative has been added to some combinations. An experimental protocol should be designed to evaluate the effectiveness of the sedative under the above circumstances and, in addition, it is necessary to show whether the sedative has any additional beneficial or adverse effects on bronchospasm.

b. *Selection of patients.* Testing should be based on the diagnosis of asthma. There should be generalized airway obstruction whose severity varies greatly over a short period of time and this should be demonstrated by pulmonary function tests with significant improvement occurring after the use of a Category I bronchodilator drug.

c. *Methods of study.* The study should consist of testing the bronchodilator drug or drugs without the sedative and in combination with a Category I sedative. The trial should be double-blind and crossover in design. The preparations should probably be given ½ hour before meals to be sure of good absorption. It is suggested that the preparation be given at the manufacturer's suggested dosage 4 times daily for 5 days, and then a crossover alternate be given for a similar period.

Two methods of evaluating the preparation should be involved:

(1) There should be a questionnaire with questions related to nervousness, insomnia, irritability, and tremor. There should also be questions related to the patient's assessment of change in his asthmatic condition. The questionnaire might best be developed in the form of a diary.

(2) Pulmonary function tests and blood gas estimations: The latter are important to determine if the sedative is producing any respiratory depressant effect. These determinations should be done at the beginning of the trial and at the end of the trial before taking the first dose and 1 hour after taking the first dose. Therefore, there should be sets of pulmonary function tests as follows:

(i) First preparation (bronchodilator alone or with a sedative): One half hour before taking the first dose of the first preparation and 1 hour after taking the first dose of the first preparation.

(ii) As above at the end of the 5 days when the last dose of the first preparation is taken.

Evidence of drug effectiveness is required from a minimum of two positive studies based on the results of two different investigators or laboratories.

All data submitted to the Food and Drug Administration must present both favorable and any unfavorable results.

(iii) Second preparation (crossover alternate with bronchodilator alone or with a sedative): After an appropriate washout period, the second preparation is given. Determinations are made ½ hour before taking the first dose of the second preparation and 1 hour after taking the first dose of the second preparation.

(iv) As above at the end of the second 5-day series when the last dose of the second preparation is taken.

(v) If possible, repeated estimations of peak expiratory flow rates should be done each day of the 5-day periods, for example, 1 hour after taking the medication.

To obtain sufficient data it will probably be necessary to test about 30 patients.

If the sedative is to be combined with a theophylline it would probably be useful to test for theophylline blood levels at intervals after an oral dose of the theophylline and after an oral dose of the theophylline plus the sedative. This is to determine whether there are any abnormalities of absorption produced. These tests need not be done on asthmatics and could probably be done on volunteers. Probably only 15 individuals need be tested.

From a safety point of view it is assumed that the bronchodilators and sedatives are all in Category I.

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(3) "AMA Drug Evaluations—1973," 2d Ed., American Medical Association, Chicago, pp. 305 and 348, 1973.

(4) The Pharmacopeia of the United States of America, 18th Rev., The Mack Publishing Co., Easton, Pa., 1970.

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Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371)) and the Administrative Procedure Act (secs. 4, 5, 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)) and under authority delegated to him (21 CFR 5.1), (recodification published in the FEDERAL REGISTER of June 15, 1976 (41 FR 24268)) the Commissioner of Food and Drugs proposes that Subchapter D be amended by adding a new Part 341 to read as follows:

PART 341—COLD, COUGH, ALLERGY, BRONCHODILATOR AND ANTIASTHMATIC PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Sec.
341.1 Scope.
341.3 Definitions.

Subpart B—Active Ingredients

341.12 Antihistamines.
341.14 Antitussives.
341.16 Bronchodilators.
341.20 Nasal decongestants.
341.40 Permitted combinations of active ingredients.

Subpart C—Testing Procedures

341.45 Theophylline tablet dissolution testing.

Subpart D—Labeling

341.50 Labeling of cold, cough, allergy, bronchodilator and antiasthmatic products.
341.70 Products containing anticholinergics.
341.72 Products containing antihistamines.
341.74 Products containing antitussives.
341.76 Products containing bronchodilators.
341.78 Products containing expectorants.
341.80 Products containing nasal decongestants.
341.85 Labeling of combinations of active ingredients.
341.90 Professional labeling.

AUTHORITY: Secs. 201, 502, 505, 701, 52 Stat. 1040–42 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371); (5 U.S.C. 553, 554, 702, 703, 704).

Subpart A—General Provisions

§ 341.1 Scope.

An over-the-counter cold, cough, allergy, bronchodilator or antiasthmatic product in a form suitable for oral, inhalant, or topical administration is generally recognized as safe and effective and is not misbranded if it meets each of the following conditions and each of the general conditions established in § 330.1 of this chapter.

§ 341.3 **Definitions.**

As used in this part:

(a) *Age (dosage) range.* Infant or baby (under 2 years), child (2 years to under 12 years), and adult (12 years and over).

(b) *Allergy product.* A drug product used for the relief of the symptoms of allergic rhinitis (such as hay fever).

(c) *Antiasthmatic drug.* A drug product used for the control of the symptoms of bronchial asthma.

(d) *Anticholinergic drug.* A drug used for the relief of excessive secretions of the nose and eyes, symptoms commonly associated with hay fever, allergy, rhinitis, and the "common cold" (cold).

(e) *Antihistaminic drug.* A drug used for the relief of the symptoms of mild allergic rhinitis (such as hay fever) (seasonal allergic rhinitis) and perennial allergic rhinitis.

(f) *Antitussive drug.* A drug which inhibits, controls or suppresses the act of coughing.

(g) *Asthma product.* A drug product used for the control of the symptoms of bronchial asthma.

(h) *Bronchodilator drug.* A drug used to overcome spasms that cause narrowing of the bronchial air tubes, such as in the symptomatic treatment of the wheezing and shortness of breath of asthma.

(i) *Cough product.* A drug product used to inhibit, control or suppress the act of coughing.

(j) *Expectorant drug.* A drug used to promote or facilitate the removal of secretions from the respiratory airways.

(k) *Hay fever product.* A drug product used for the relief of the symptoms of allergic rhinitis (such as hay fever).

(l) *Inhalant dosage.* The dosage range that is generally recognized as safe and effective inhaled nasally or by mouth.

(m) *Nasal decongestant drug.* A drug which reduces nasal congestion caused by acute or chronic rhinitis.

(n) *Oral dosage.* The dosage range that is generally recognized as safe and effective by mouth.

(o) *Topical dosage.* The dosage range that is generally recognized as safe and effective applied topically, such as by external rub for inhalation, as a lozenge for local application by mouth, or as drops or sprays for local application intranasally.

Subpart B—Active Ingredients

§ 341.12 **Antihistamines.**

The active ingredients of the product consist of the following within the dosage limit established for each ingredient:

(a) *Brompheniramine maleate.* Adult oral dosage is 4 mg every 4 to 6 hours not to exceed 24 mg in 24 hours. Children 6 to under 12 years oral dosage is 2 mg every 4 to 6 hours not to exceed 12 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(a). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(b) *Chlorpheniramine maleate.* Adult oral dosage is 4 mg every 4 to 6 hours not to exceed 24 mg in 24 hours. Children 6 to under 12 years oral dosage is 2 mg every 4 to 6 hours not to exceed 12 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(b). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(c) *Diphenhydramine hydrochloride.* Adult oral dosage is 25 to 50 mg every 4 to 6 hours not to exceed 300 mg in 24 hours. Children 6 to under 12 years oral dosage is 12.5 to 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(c). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(d) *Doxylamine succinate.* Adult oral dosage is 7.5 to 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours. Children 6 to under 12 years oral dosage is 3.75 to 6.25 mg every 4 to 6 hours not to exceed 37.5 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(d). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(e) *Methapyrilene preparations.* Adult oral dosage is 50 mg every 4 to 6 hours not to exceed 300 mg in 24 hours. Children 6 to under 12 years oral dosage is 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90 (f). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(f) *Phenindamine tartrate.* Adult oral dosage is 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours. Children 6 to under 12 years oral dosage is 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(g). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(g) *Pheniramine maleate.* Adult oral dosage is 12.5 to 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours. Children 6 to under 12 years oral dosage is 6.25 to 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(h). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(h) *Promethazine hydrochloride.* Adult oral dosage is 6.25 to 12.5 mg every 8 to 12 hours not to exceed 37.5 mg in 24 hours. Children 6 to under 12 years oral dosage is 3.125 to 6.25 mg every 8 to 12 hours not to exceed 18.75 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(i). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(i) *Pyrilamine maleate.* Adult oral dosage is 25 to 50 mg every 6 to 8 hours not to exceed 200 mg in 24 hours. Children 6 to under 12 years oral dosage is 12.5 to 25 mg every 6 to 8 hours not to exceed 100 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(j). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(j) *Thonzylamine hydrochloride.* Adult oral dosage is 50 to 100 mg every 4 to 6 hours not to exceed 600 mg in 24 hours. Children 6 to 12 years oral dosage is 25 to 50 mg every 4 to 6 hours not to exceed 300 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(1). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

§ 341.14 **Antitussives.**

The active ingredients of the product consist of the following within the dosage limit established for each ingredient:

(a) *Codeine preparations (codeine, codeine alkaloid, codeine phosphate, codeine sulfate).* (1) Adult oral dosage is 10 to 20 mg every 4 to 6 hours not to exceed 120 mg in 24 hours. Children 6 to under 12 years oral dosage is 5 to 10 mg every 4 to 6 hours not to exceed 60 mg in 24 hours. Children 2 to under 6 years oral dosage is 2.5 to 5 mg every 4 to 6 hours not to exceed 30 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(2) Shall apply to products pursuant to the requirements identified in § 329.20(a) and § 1308.15(b) of this chapter.

(b) *Dextromethorphan, dextromethorphan hydrobromide.* Adult oral dosage is 10 to 20 mg every 4 hours or 30 mg every 6 to 8 hours not to exceed 120 mg in 24 hours. Children 6 to under 12 years oral dosage is 5 to 10 mg every 4 hours or 15 mg every 6 to 8 hours not to exceed 60 mg in 24 hours. Children 2 to under 6 years oral dosage is 2.5 to 5 mg every 4 hours or 7.5 mg every 6 to 8 hours not to exceed 30 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(c) *Diphenhydramine hydrochloride.* Adult oral dosage is 25 mg every 4 hours not to exceed 150 mg in 24 hours. Children 6 to under 12 years oral dosage is 12.5 mg every 4 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is identified in § 341.90(c). For children under 2 years, there is no recomended dosage except under the advice and supervision of a physician.

§ 341.16 **Bronchodilators.**

The active ingredients of the product consist of the following within the dosage limit established for each ingredient:

(a) *Ephedrine preparations, (ephedrine, ephedrine hydrochloride, ephedrine sulfate, racephedrine hydrochloride).* Adult oral dosage is 12.5 to 25 mg not more often than every 4 hours not to exceed 150 mg in 24 hours. Children 2 to under 12 years oral dosage is identified in § 341.90(e). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(b) *Epinephrine preparations (epinephrine, epinephrine bitartrate, epi-*

nephrine hydrochloride (racemic) (inhalant)). Adults and children 4 years and above inhalation dosage is 1 to 3 inhalations of a 1 percent aqueous solution of 1-epinephrine or the equivalent in a pressurized preparation not more often than every 3 hours, except under the advice and supervision of a physician. For children under 4 years, there is no recommended dosage except under the advice and supervision of a physician.

Children and adolescents should not have unsupervised access to this inhaler. There is the possibility of abuse of this material and possible adverse effects on the heart if excessively used.

(c) *Methoxyphenamine hydrochloride.* Adult oral dosage is 100 mg every 4 to 6 hours not to exceed 600 mg in 24 hours. For children under 12 years, there is no recommended dosage except under the advice and supervision of a physician.

(d) *Theophylline preparations (aminophylline, theophylline anhydrous, theophylline calcium salicylate, theophylline sodium glycinate).* Adult oral dosage based on the anhydrous theophylline equivalent is 100 to 200 mg every 6 hours not to exceed 800 mg in 24 hours. Children 2 to under 12 years oral dosage is identified in § 341.90(k). For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

§ 341.20 Nasal decongestants.

The active ingredients of the product consist of the following within the dosage limit established for each ingredient:

(a) *Ephedrine preparations (ephedrine, ephedrine hydrochloride, ephedrine sulfate, racephedrine hydrochloride) (topical).* Adult topical dosage is 2 to 3 drops or sprays in each nostril of a 0.5 percent aqueous solution not more frequently than every 4 hours. Children 6 to under 12 years topical dosage is 1 or 2 drops or sprays of a 0.5 percent solution not more frequently than every 4 hours. For children under 6 years, there is no recommended dosage except under the advice and supervision of a physician.

(b) *Naphazoline hydrochloride (topical).* Adult topical dosage is 1 to 2 drops or sprays of a 0.05 percent aqueous solution in each nostril not more frequently than every 6 hours. Children 6 to under 12 years topical dosage is 1 to 2 drops or sprays of a 0.025 percent aqueous solution in each nostril not more frequently than every 6 hours. For children under 6 years, there is no recommended dosage except under the advice and supervision of a physician.

(c) *Oxymetazoline hydrochloride (topical).* Adults and children 6 to under 12 years topical dosage is 2 to 3 drops or sprays of a 0.05 percent aqueous solution in each nostril 2 times daily (in the morning and evening). Children 2 to under 6 years topical dosage is 2 to 3 drops of a 0.025 percent aqueous solution in each nostril 2 times daily (in the morning and evening). Only drops should be used in children 2 to under 6 years since the spray is difficult to use in the small nostril. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(d) *Phenylephrine hydrochloride (oral/topical*—(1) *As an oral nasal decongestant.* Adult oral dosage is 10 mg every 4 hours not to exceed 60 mg in 24 hours. Children 6 to under 12 years oral dosage is 5 mg every 4 hours not to exceed 30 mg in 24 hours. Children 2 to under 6 years oral dosage is 2.5 mg every 4 hours not to exceed 15 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(2) *As a topical nasal decongestant.* Adult topical dosage is 2 to 3 drops or sprays in each nostril of a 0.25 to 0.5 percent aqueous solution not more frequently than every 4 hours. Children 6 to under 12 years topical dosage is 2 to 3 drops or sprays in each nostril of a 0.25 percent aqueous solution not more frequently than every 4 hours. Children 2 to under 6 years topical dosage is 2 to 3 drops in each nostril of a 0.125 percent aqueous solution not more frequently than every 4 hours. Only drops should be used in children 2 to under 6 years since the spray is difficult to use in the small nostril. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(e) *Phenylpropanolamine preparations (phenylpropanolamine bitartrate, phenylpropanolamine hydrochloride, phenylpropanolamine maleate) (oral).* Dosages are based on the phenylpropanolamine hydrochloride equivalent. Adult oral dosage is 25 mg every 4 hours or 50 mg every 8 hours not to exceed 150 mg in 24 hours. Children 6 to under 12 years oral dosage is 12.5 mg every 4 hours or 25 mg every 8 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is 6.25 mg every 4 hours or 12.5 mg every 8 hours not to exceed 37.5 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(f) *Propylhexedrine (inhalant).* Adults and children 6 to under 12 years inhalant dosage from an inhaler that shall deliver in each 800 ml of air 0.40 to 0.50 mg of propylhexedrine is 2 inhalations in each nostril not more frequently than every 2 hours. For children under 6 years, there is no recommended dosage except under the advice and supervision of a physician. The inhaler should retain effectiveness for a minimum of 2 to 3 months.

(g) *Pseudoephedrine preparations (pseudoephedrine hydrochloride, pseudoephedrine sulfate) (oral).* Adult oral dosage is 60 mg every 4 hours not to exceed a maximum of 360 mg in 24 hours. Children 6 to under 12 years oral dosage is 30 mg every 4 hours not to exceed 180 mg in 24 hours. Children 2 to under 6 years oral dosage is 15 mg every 4 hours not to exceed 90 mg in 24 hours. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

(h) *Xylometazoline hydrochloride (topical).* Adult topical dosage is 2 to 3 drops or sprays in each nostril of a 0.1 percent aqueous solution every 8 to 10 hours. Children 2 to under 12 years topical dosage is 2 to 3 drops or sprays in each nostril of a 0.05 percent aqueous solution every 8 to 10 hours. Only drops should be used in children 2 to under 6 years since the spray is difficult to use in the small nostril. For children under 2 years, there is no recommended dosage except under the advice and supervision of a physician.

§ 341.40 Permitted combinations of active ingredients.

(a) Any single antihistamine active ingredient identified in § 341.12 may be combined with any single generally recognized as safe and effective analgesic-antipyretic active ingredient: *Provided,* That the combination contains any applicable labeling identified in § 341.85(d).

(b) Any single antihistamine active ingredient identified in § 341.12 may be combined with any single oral nasal decongestant active ingredient identified in § 341.20.

(c) Any single antihistamine active ingredient identified in § 341.12 may be combined with any single oral nasal decongestant active ingredient identified in § 341.20 with any single generally recognized as safe and effective analgesic-antipyretic active ingredient: *Provided,* That the combination contains the labeling identified in § 341.85(d).

(d) Any single antihistamine active ingredient identified in § 341.12 may be combined with any single antitussive active ingredient identified in § 341.14: *Provided,* That the combination contains the labeling identified in § 341.85(a).

(e) Any single antihistamine active ingredient identified in § 341.12 may be combined with any single oral nasal decongestant active ingredient identified in § 341.20 with any single antitussive active ingredient identified in § 341.14.

(f) Any single antitussive active ingredient identified in § 341.14 may be combined with any single oral bronchodilator active ingredient identified in § 341.16: *Provided,* That the combination contains the labeling identified in § 341.85(b).

(g) Any single antitussive active ingredient identified in § 341.14 may be combined with any single generally recognized as safe and effective expectorant active ingredient.

(h) Any single antitussive active ingredient identified in § 341.14 may be combined with any single oral nasal decongestant active ingredient identified in § 341.20.

(i) Any single antitussive active ingredient identified in § 413.14 may be combined with any single generally recognized as safe and effective expectorant active ingredient with any single oral nasal decongestant active ingredient identified in § 341.20.

(j) Any single antitussive active ingredient identified in § 341.14 may be combined with any single generally recognized as safe and effective local anesthetic or local analgesic active in-

gredient: *Provided,* That the product is available only as a lozenge.

(k) Any single bronchodilator active ingredient identified in § 341.16(a) may be combined with any single bronchodilator active ingredient identified in § 341.16(d).

(l) Any single oral bronchodilator active ingredient identified in § 341.16 may be combined with any single generally recognized as safe and effective expectorant active ingredient: *Provided,* That the combination contains the labeling identified in § 341.85(c).

(m) Any single oral nasal decongestant active ingredient identified in § 341.20 may be combined with any single generally recognized as safe and effective analgesic-antipyretic active ingredient: *Provided,* That the combination contains the labeling identified in § 341.85(d).

(n) Any single oral nasal decongestant active ingredient identified in § 341.20 may be combined with any single generally recognized as safe and effective expectorant active ingredient.

(o) Any single nasal decongestant active ingredient identified in § 341.20 may be combined with any single generally recognized as safe and effective local anesthetic or local analgesic active ingredient: *Provided,* That the product is available only as a lozenge.

Subpart C—Testing Procedures

§ 341.45 Theophylline tablet dissolution testing.

All tablet product formulations containing theophylline preparation(s) identified in § 341.16(d) shall be tested according to the procedures described in the United States Pharmacopeia XIX (page 651). The tablets shall be suitable for OTC use if the quantity of theophylline dissolved within 15 minutes is not less than 50 percent of the labeled amount, based on the anhydrous theophylline, equivalent content, and the quantity of theoplylline dissolved within 30 minutes is not less than 90 percent of the labeled amount of theophylline, based on the anhydrous theophylline equivalent content, for each of the tablets tested. The resulting data shall be submitted by petition to the Food and Drug Administration for approval prior to use. The petition and the data contained therein shall be maintained in a permanent file for public review by the office of the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20852.

Subpart D—Labeling

§ 341.50 Labeling of cold, cough, allergy, bronchodilator, and antiasthmatic products.

(a) *Indications.* (1) The labeling shall identify the product pursuant to the appropriate definition(s) established in § 341.3 and shall contain the applicable labeling for the active ingredient(s) as set forth in §§ 341.70, 341.72, 341.74, 341.76, 341.78, and 341.80.

(2) In addition, labeling may also contain the following indication(s): *Provided,* That such phrase(s) is combined and contiguous with the indications required as set forth in § 341.50(a)(i):

(i) "as may be associated with the common cold (cold)."

(ii) "as may occur in the common cold (cold)."

(b) *Directions for use.* The labeling of the product contains the recommended dosage and appropriate directions identified under §§ 341.12, 341.14, 341.16, or 341.20 under the heading "Directions," per time interval, e.g., every 4 hours, or other time period, e.g., 3 times daily, broken down by age groups, if appropriate, followed by "or as directed by a physician."

(c) *Warnings.* The labeling of the product contains the appropriate warning(s) under §§ 341.70, 341.72, 341.74, 341.76, 341.78, or 341.80 and, if applicable, the following general warning under the heading "Warning," which may be combined to eliminate duplicative words or phrases so the resulting warning is clear and understandable. For products containing an alcoholic content greater than 10 percent (weight/weight) "Do not give this product to children under 6 years except under the advice and supervision of a physician".

(d) *Drug interaction precautions.* The labeling of the product, where appropriate under § 341.76 or § 341.80, contains drug interaction precautions, under the heading "Drug Interaction Precautions".

§ 341.70 Products containing anticholinergics.

(a) *Indications.* The labeling of the product shall contain any of the following indications, under the heading "Indications":

(1) "For temporary relief of watery nasal discharge and watering eyes as may occur in certain allergic conditions and infections of the upper respiratory tract".

(2) "Temporarily suppresses watery nasal discharge".

(3) "Temporary relief from excessive nasal secretions".

(4) "Temporary relief from running nose".

(5) "Temporarily suppresses watering of eyes".

(b) *Warnings.* The labeling of the product contains the following warnings, under the heading "Warning":

(1) "Do not exceed recommended dosage except under the advice and supervision of a physician".

(2) "Do not continue to take this product if constipation, excessive dryness of the mouth, insomnia, excitement, confusion, rapid pulse, or blurring of vision occur".

(3) *"Caution:* Do not take this product if you have asthma, glaucoma or have difficulty in urination due to enlargement of the prostate gland except under the advice and supervision of a physician".

(4) "Do not give this product to children under 12 years except under the advice and supervision of a physician".

§ 341.72 Products containing antihistamines.

(a) *Indications.* The labeling of the product shall contain any of the following indications, under the heading "Indications":

(1) "Alleviates, decreases, or for temporary relief of, running nose, sneezing, itching of the nose or throat and itchy and watery eyes as may occur in allergic rhinitis (such as hay fever)".

(2) "Alleviates, decreases, or for temporary relief of, running nose as may occur in allergic rhinitis (such as hay fever)".

(3) "Alleviates, decreases, or for temporary relief of, sneezing as may occur in allergic rhinitis (such as hay fever)".

(4) "Alleviates, decreases, or for temporary relief of, itching of the nose or throat as may occur in allergic rhinitis (such as hay fever)".

(5) "Alleviates, decreases, or for temporary relief of, itchy and watery eyes as may occur in allergic rhinitis (such as hay fever)".

(6) "Dries running nose as may occur in allergic rhinitis (such as hay fever)".

(b) *Warnings.* The labeling of the product contains the following warnings, under the heading "Warnings":

(1) "May cause excitability especially in children".

(2) "Do not take this product if you have asthma, glaucoma or difficulty in urination due to enlargement of the prostrate gland except under the advice and supervision of a physician".

(3) *"Caution:* Avoid driving a motor vehicle or operating heavy machinery".

(4) *"Caution:* Avoid alcoholic beverages while taking this product".

(5) "Do not give this product to children under 6 years except under the advice and supervision of a physician".

(6) For products containing the active ingredients identified in paragraphs (a), (b), (f), (i), and (j) of § 341.12: "May cause drowsiness".

(7) For products containing the active ingredients identified in paragraphs (c), (d), (e), (g), and (h) of § 341.12: "May cause marked drowsiness".

(8) For products containing an active ingredient identified in § 341.12(f): *"Caution:* May cause nervousness and insomnia in some individuals".

§ 341.74 Products containing antitussives.

(a) *Indications.* The labeling of the product may contain any of the following indications, under the heading "Indications": (1) "Cough suppressant which temporarily reduces the impulse to cough".

(2) "For the temporary relief of cough due to minor throat and bronchial irritation as may occur with the common cold (cold) or with inhaled irritants".

(3) "Temporarily quiets coughing by its antitussive action".

(4) "Temporarily helps you cough less".

(5) "Temporarily helps to quiet the cough reflex that causes coughing".

(6) For products containing an ingredient identified in § 341.14(a): "Calms the cough control center and relieves coughing".

(7) For products containing an ingredient identified in § 341.14 (b) and (c):

(i) "Calms the cough control center and relieves coughing".

(ii) "Non-narcotic cough suppressant for the temporary control of coughs".

(iii) "Calms cough impulses without narcotics".

(b) *Warnings.* The labeling of the product contains the following warnings, under the heading "Warnings": (1) "Do not give this product to children under 2 years except under the advice and supervision of a physician".

(2) "Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, or emphysema, or where cough is accompanied by excessive secretions except under the advice and supervision of a physician".

(3) *"Caution:* A persistent cough may be a sign of a serious condition. If cough persists for more than 1 week, tends to recur or is accompanied by high fever, rash or persistent headache, consult a physician".

(4) For products containing an ingredient identified in § 341.14(a):

(i) "May cause or aggravate constipation".

(ii) "Do not give this product to children taking other drugs except under the advice and supervision of a physician".

(iii) "Do not take this product if you have a chronic pulmonary disease or shortness of breath except under the advice and supervision of a physician".

(5) For products containing an ingredient identified in § 341.14(c): (i) May cause marked drowsiness".

(ii) "May cause excitability especially in children".

(iii) "Do not take this product if you have glaucoma or have difficulty in urination due to enlargement of the prostate gland except under the advice and supervision of a physician".

(iv) "Caution: Avoid driving a motor vehicle or operating heavy machinery".

(v) "Do not give this product to children under 6 years except under the advice and supervision of a physician".

§ 341.76 Products containing bronchodilators.

(a) *Indications.* (1) The labeling of a product to be taken by inhalation may contain under the heading "Indications" the time to onset of action expressed in minutes.

(2) The labeling of the product shall contain any of the following indications, under the heading "Indications":

(i) "For temporary relief of bronchial asthma".

(ii) "For symptomatic control of bronchial asthma".

(iii) "Provides temporary relief from acute symptoms of bronchial asthma".

(iv) "Relaxes tense bronchial muscles to ease breathing for asthma patients".

(v) "For temporary relief of wheezing (attacks and distress) of bronchial asthma".

(b) *Warnings.* The labeling of the product contains the following warning, under the heading "Warnings": (1) "Caution: Do not take this product unless a diagnosis of asthma has been made by a physician".

(2) For products containing an ingredient identified in § 341.16 (a) and (c):

(i) *"Caution:* Do not continue to take this product but seek medical assistance immediately if symptoms are not relieved within 1 hour or become worse".

(ii) "Nervousness, tremor, sleeplessness, nausea and loss of appetite may occur".

(iii) "Do not take this product if you have heart disease, high blood pressure, thyroid disease, diabetes or difficulty in urination due to enlargement of the prostate gland".

(iv) *Drug interaction precaution.* "Do not take this product if you are presently taking a prescription antihypertensive or antidepressant drug containing a monoamine oxidase inhibitor".

(v) "Do not give this product to children under 12 years except under the advice and supervision of a physician".

(3) For products containing an ingredient identified in § 341.16(b):

(i) "Do not take this product at higher than recommended doses except under the advice and supervision of a physician for it may cause nervousness and rapid heart beat".

(ii) *"Caution:* Do not continue to take this product but seek medical assistance immediately if symptoms are not relieved within 20 minutes or become worse".

(iii) "Do not take this product if you have heart disease or high blood pressure except under the advice and supervision of a physician".

(iv) *Drug interaction precaution.* "Do not take this product of you are presently taking a prescription antihypertensive or antidepressant drug containing a monamine oxidase inhibitor".

(v) "Keep this product out of reach of children and adolescents because unsupervised access may cause abuse or possible adverse effects on the heart if excessively used".

(vi) "Do not give this product to children under 4 years except under the advice and supervision of a physician".

(4) For products containing an ingredient identified in § 341.16(d):

(i) "Do not exceed recommended dosage except under the advice and supervision of a physician".

(ii) "Do not take this product if nausea, vomiting or restlessness occurs".

(iii) *"Caution:* Do not continue to take this product but seek medical assistance immediately if symptoms are not relieved within 1 hour or become worse".

(iv) "Do not take this product if you are presently taking a drug or suppository containing any form of theophylline except under the advice and supervision of a physician".

(v) "Do not give this product to children under 12 years except under the advice and supervision of a physician. Excessive use may cause toxic effects and even death in children".

§ 341.78 Products containing expectorants.

(a) *Indication.* The labeling of the product may contain any of the following indications, under the heading "Indications":

(1) "Helps loosen phlegm (sputum)".

(2) "Helps rid the passageways of bothersome mucus".

(3) "Expectorant action to help loosen phlegm (sputum) and bronchial secretions".

(4) "Helps drainage of bronchial tubes by thinning the mucus".

(5) "Relieves irritated membranes in the respiratory passageways by preventing dryness through increased mucus flow".

(b) *Warnings.* The labeling of the product contains the following warnings, under the heading, "Warnings":

(1) "Do not give this product to children under 2 years except under the advice and supervision of a physician".

(2) "Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, or emphysema, or where cough is accompanied by excessive secretions except under the advice and supervision of a physician".

(3) *"Caution:* A persistent cough may be a sign of a serious condition. If cough persists for more than 1 week, tends to recur or is accompanied by high fever, rash or persistent headache, consult a physician".

§ 341.80 Products containing nasal decongestants.

(a) *Indications.* The labeling of the product shall contain any of the following indications, under the heading "Indications":

(1) "For temporary relief of nasal congestion due to the common cold (cold)".

(2) "For temporary relief of nasal congestion due to hay fever or other upper respiratory allergies".

(3) "For temporary relief of nasal congestion associated with sinusitus".

(4) "For the temporary relief of stuffy nose (stopped up nose, nasal stuffiness, clogged up nose)".

(5) "Reduces swelling of nasal passages; shrinks swollen membranes".

(6) "Decongest nasal passages".

(7) "Temporarily restores freer breathing through the nose".

(8) "Helps clear nasal passages".

(9) "Helps decongest sinus openings, sinus passages".

(10) "Promotes nasal and/or sinus drainage".

(11) For products with claims for duration of effect: Statements as to duration of effect must be substantiated and accompanied by a specific time period expressed in minutes or hours, as appropriate.

(12) For products to be used as topical nasal decongestants with claims for rapid onset of action: Statements relating to time to onset of action, such as, "fast" or "quick", must be accompanied by a specific time period expressed in minutes.

(13) For products to be used as topical nasal decongestants which can demonstrate a cooling sensation:

(i) "Provides cooling sensation".

(ii) "Cooling".

(iii) "Cools nasal passages".

(b) *Warnings.* The label of the product contains the following warnings, under the heading "Warnings".

(1) For products containing topical nasal decongestants:

(i) "Do not exceed recommended dosage because symptoms may occur such as burning, stinging, sneezing, or increase of nasal discharge.

(ii) "Do not use this product for more than 3 days. If symptoms persist, consult a physician".

(iii) "The use of this dispenser by more than one person may spread infection".

(2) For products used as oral nasal decongestants:

(i) "Do not exceed recommended dosage because at higher doses nervousness, dizziness, or sleeplessness may occur".

(ii) "If symptoms do not improve within 7 days or are accompanied by high fever, consult a physician before continuing use".

(iii) "Do not take this preparation if you have high blood pressure, heart disease, diabetes, or thyroid disease except under the advice and supervision of a physician".

(iv) *"Drug interaction precaution:* Do not take this product if you are presently taking a prescription antihypertensive or antidepressant drug containing a monoamine oxidase inhibitor except under the advice and supervision of a physician".

(3) For products used as inhalant nasal decongestants:

(i) "This inhaler should be warmed in the hand before use to increase effectiveness".

(ii) "Do not give this product to children under 6 years except under the advice and supervision of a physician".

(iii) "Children should not have unsupervised access to this inhaler".

(iv) *"Caution:* Not for use by mouth".

(4) For products containing the active ingredient identified in § 341.20(a) at a concentration of 0.5 percent: "Do not give this product to children under 6 years except under the advice and supervision of a physician".

(5) For products containing the active ingredient identified in § 341.20(b) at a concentration of 0.025 percent: "Do not give this product to children under 6 years except under the advice and supervision of a physician".

(6) For products containing the active ingredient identified in § 341.20(b) at a concentration of 0.05 percent: "For adult use only. Do not give this product to children under 6 years since it may cause sedation if swallowed".

(7) For products containing the active ingredient identified in § 341.20(d) (2) at a concentration of 0.125 percent: "Do not give this product to children under 2 years except under the advice and supervision of a physician".

(8) For products containing the active ingredient identified in § 341.20(d) (2) at a concentration of 0.25 percent: "Do not give this product to children under 6 years except under the advice and supervision of a physician".

(9) For products containing the active ingredient identified in § 341.20(d) (2) at a concentration of 0.5 percent: "For adult use only. Do not give this product to children under 12 years except under the advice and supervision of a physician".

(10) For products containing the active ingredient identified in § 341.20(h) at a concentration of 0.05 percent: "Do not give this product to children under 2 years except under the advice and supervision of a physician".

(11) For products containing the active ingredient identified in § 341.20(h) at a concentration of 0.1 percent: "For adult use only. Do not give this product to children under 12 years except under the advice and supervision of a physician".

§ 341.85 Labeling of combinations of active ingredients.

(a) *Antihistamine combined with an antitussive.* A combination identified in § 341.40(d) shall contain the following warning under the heading "Warning": "Caution: May cause marked drowsiness". The Food and Drug Administration will grant an exemption to the labeling term "marked", which may be removed from the warning statement upon petition if adequate data are submitted to demonstrate that the combination product does not cause a significant increase in drowsiness as compared with each active ingredient when tested alone. The petition and the data contained therein shall be maintained in a permanent file for public review by the office of the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20852.

(b) *Antitussive combined with a bronchodilator.* A combination identified in § 341.40(f) shall contain the following warning, under the heading "Warning": "This product should be used only for cough associated with asthma".

(c) *Bronchodilator combined with an expectorant.* A combination identified in § 341.40(1) shall contain the following warning, under the heading "Warning": "This product should be used only for cough associated with asthma".

(d) *Aspirin (acetylsalicylic acid) containing combinations.* Any combination identified in § 341.40 (a), (c), or (m) containing aspirin (acetylsalicylic acid) shall contain the following warning, under the heading "Warning": "This product contains aspirin and should not be taken by individuals who are sensitive to aspirin".

§ 341.90 Professional labeling.

The labeling of the product provided to health professionals (but not to the general public) may contain the following additional dosage information for products containing the active ingredients identified below:

(a) For products containing brompheniramine maleate: Children 2 to under 6 years oral dosage is 1 mg every 4 to 6 hours not to exceed 6 mg in 24 hours.

(b) For products containing chlorpheniramine maleate: Children 2 to under 6 years oral dosage is 1 mg every 4 to 6 hours not to exceed 6 mg in 24 hours.

(c) For products containing diphenhydramine hydrochloride:

(1) *For use as an antihistamine:* Children 2 to under 6 years oral dosage is 6.25 mg every 4 to 6 hours not to exceed 37.5 mg in 24 hours.

(2) *For use as an antitussive:* Children 2 to under 6 years oral dosage is 6.25 mg every 4 hours not to exceed 37.5 mg in 24 hours.

(d) *For products containing doxylamine succinate:* Children 2 to under 6 years oral dosage is 1.9 to 3.125 mg every 4 to 6 hours not to exceed 18.75 mg in 24 hours.

(e) *For products containing ephedrine preparations for use as a bronchodilator (ephedrine, ephedrine hydrochloride, ephedrine sulfate, racephedrine hydrochloride):* Children 6 to under 12 years oral dosage is 6.25 to 12.5 mg not more often than every 4 hours not to exceed 75 mg in 24 hours. Children 2 to under 6 years oral dosage is 0.3 to 0.5 mg/kg of body weight not more often than every 4 hours not to exceed 2 mg/kg of body weight in 24 hours.

(f) *For products containing methapyrilene preparations (methapyrilene fumarate, methapyrilene hydrochloride):* Children 2 to under 6 years oral dosage is 12.5 mg every 4 to 6 hours not to exceed 75 mg in 24 hours.

(g) *For products containing phenindamine tartrate:* Children 2 to under 6 years oral dosage is 6.25 mg every 4 to 6 hours not to exceed 37.5 mg in 24 hours.

(h) *For products containing pheniramine maleate:* Children 2 to under 6 years oral dosage is 3.125 to 6.25 mg every 4 to 6 hours not to exceed 37.5 mg in 24 hours.

(i) *For products containing promethazine hydrochloride:* Children 2 to under 6 years oral dosage is 1.56 to 3.125 mg every 8 to 12 hours not to exceed 9.375 mg in 24 hours.

(j) *For products containing pyrilamine maleate:* Children 2 to under 6 years oral dosage is 6.25 to 12.5 mg every 6 to 8 hours not to exceed 50 mg in 24 hours.

(k) *For products containing theophylline preparations (aminophylline, theophylline anhydrous, theophylline calcium salicylate, theophylline sodium glycinate):* Children 2 to under 12 years oral dosage based on the anhydrous theophylline equivalent is 3.33 mg/kg of body weight 3 times daily every 8 hours not to exceed 10 mg/kg in 24 hours.

(l) For products containing thonzylamine hydrochloride: Children 2 to under 6 years oral dosage is 12.5 to 25 mg every 4 to 6 hours not to exceed 150 mg in 24 hours.

Interested persons are invited to submit their comments in writing (preferably in quintuplicate and identified with the Hearing Clerk docket number found in brackets in the heading of this document) regarding this proposal on or before December 8, 1976. Such comments should be addressed to the office of the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20852, and may be accompanied by a memorandum or brief in support thereof. Additional comments replying to any comments so filed may also be submitted on or before January 7, 1977. Received comments may be seen in the above office during working hours, Monday through Friday.

Dated: July 30, 1976.

SHERWIN GARDNER,
Acting Commissioner of Food and Drugs.

[FR Doc.76–22710 Filed 9–8–76;8:45 am]

federal register

THURSDAY, SEPTEMBER 9, 1976



PART III:

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

National Institutes of Health

■

RECOMBINANT DNA RESEARCH GUIDELINES

Draft Environmental Impact Statement

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

National Institutes of Health

RECOMBINANT DNA RESEARCH GUIDELINES

Draft Environmental Impact Statement

On Wednesday, June 23, 1976, the Director of the National Institutes of Health, with the concurrence of the Secretary of Health, Education, and Welfare and the Assistant Secretary for Health, issued Guidelines that will govern the conduct of NIH-supported research on recombinant DNA molecules.

The decision by the NIH Director to release the Guidelines was reached after extensive scientific and public airing of the issues. The issues were discussed at public meetings of the Recombinant DNA Molecule Program Advisory Committee (Recombinant Advisory Committee) and the Advisory Committee to the NIH Director. The Recombinant Advisory Committee debated three different versions of the Guidelines during this period, and made detailed recommendations to the NIH Director on how this line of research could proceed effectively with maximum protection of workers and the environment against possible hazards.

The Advisory Committee to the NIH Director, augmented with consultants representing law, ethics, consumer affairs, and the environment, was asked to advise on whether the proposed Guidelines balanced responsibility to protect the public with the potential benefits through the pursuit of new knowledge. The many points of view expressed at an open meeting of the Committee on February 9 and 10, 1976, and in subsequent correspondence, were taken into consideration in the Director's decision.

A number of public commentators urged NIH to consider preparing an environmental impact statement on recombinant DNA research activity. They evoked the possibility that organisms containing recombinant DNA molecules might escape and affect the environment in potentially harmful ways. It should be noted that the development of the guidelines was in large part tantamount to conducting an environmental impact assessment. For example, the objectives of recombinant DNA research were considered and the potential hazards and risks analyzed. Possible alternative approaches to the objectives were thoroughly explored, to maximize safety and minimize potential risks. And an elaborate review structure to ensure safety has been created.

The Guidelines are premised on physical and biological containment to prevent the release or propagation of DNA recombinants outside the laboratory. Deliberate release of organisms into the environment is prohibited. The stipulated physical and biological containment ensures that this research will proceed with a high degree of safety and precaution.

With a view to promoting public understanding of its issuance of the Guidelines, NIH conducted an environmental impact assessment and prepared the present draft environmental impact statement in accordance with the National Environmental Policy Act of 1969. Notice of the availability of this document appeared in the FEDERAL REGISTER of September 2.

In order to extend the opportunity for public comment and consideration, the present draft environmental impact statement is offered for general comment. Please address any comments on this draft statement to the Director, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20014. All comments should be submitted by October 18, 1976.

Additional copies of this draft are available from Dr. Rudolf G. Wanner, Associate Director for Environmental Health and Safety, Building 12A, Room 4051, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20014.

Dated: August 26, 1976.

DONALD S. FREDRICKSON,
Director,
National Institutes of Health.

DRAFT ENVIRONMENTAL IMPACT STATEMENT

GUIDELINES FOR RESEARCH INVOLVING RECOMBINANT DNA MOLECULES

NATIONAL INSTITUTES OF HEALTH
BETHESDA, MARYLAND

August 19, 1976

GUIDELINES FOR RESEARCH INVOLVING RECOMBINANT DNA MOLECULES

National Institutes of Health, Public Health Service, DHEW, Bethesda, Maryland

(X) Draft ( ) Final Environmental Impact Statement.

Name of Action

(X) Administrative ( ) Legislative Action.

Additional Information

Additional information on the proposed action, including technical documents pertinent to this statement may be obtained from:

Dr. Donald S. Fredrickson, Director, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20014, Telephone: (301) 496-2433.

A copy of the "Guidelines for Research Involving Recombinant DNA Molecules" is attached. (Appendix D)

COMMENTS

The Department, in issuing this draft, is requesting comments on the accuracy of the factual information (including the absence of relevant material) and projections contained therein. Comments shall be submitted by October 18, 1976, the Council on Environmental Quality weekly notice in the FEDERAL REGISTER. Address comments to Dr. Donald S. Fredrickson.

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FOREWORD

Recent developments in molecular genetics, particularly in the last 4 years, open avenues to science that were previously inaccessible. In the "recombinant DNA" experiments considered here, genes—deoxyribonucleic acid (DNA) molecules—from virtually any living organism can be transferred to cells of certain completely unrelated organisms. For example, the genes from one species of bacteria have been transferred to bacteria of another species. And genes from toads and from fruit flies have been introduced into the bacterium *Escherichia coli*.

If the recipient bacterium is then allowed to multiply, it will propagate these newly acquired genes as part of its own genetic complement. It appears likely that any kind of gene from any kind of organism could be introduced into *E. coli* and certain other organisms.

This ability to join together genetic material from two different sources and to propagate these hybrid elements in bacterial and animal cells has resulted in a profound and qualitative change in the field of genetics. Now, for the first time, there is a methodology for crossing very large evolutionary boundaries, and for moving genes between organisms that are believed to have previously had little genetic contact.

The promise of recombinant DNA research for better understanding and improved treatment of human disease is great. There is also a possible risk that microorganisms with foreign genes might cause disease or alter the environment should they escape from the laboratory and infect human beings, animals, or plants. However, in the absence of further experimental data neither the benefits nor the risks can be precisely identified or assessed.

On June 23, 1976, the Director of the National Institutes of Health released Guidelines governing the conduct of NIH-supported research on recombinant DNA molecules (See Appendix D). Promulgation of these Guidelines followed 2 years of intensive discussion and debate within the scientific community and NIH itself, with public participation, concerning the possible hazards of such research and the best means for averting them, although the possible hazards remain speculative. The Guidelines prohibit certain kinds of recombinant DNA experiments and, for those experiments that are permitted, they specify safety precautions and conditions designed to protect the health of laboratory workers, the general public, and the environment should the putative hazards prove real.

The issuance of Guidelines establishing conditions and precautions with respect to such experiments is viewed by NIH as a Federal action that may significantly affect the quality of the human environment, and NIH Director Dr. Donald S. Fredrickson ordered the preparation of this statement pursuant to the National Environmental Policy Act.

Although NEPA assumes that such Federal actions will not be taken until the NEPA procedures are completed, the Director of NIH concluded that the public interest required immediate issuance of the Guidelines, rather than deferral for the months that would be required for completion of the NEPA process. This was because the escape of potentially hazardous organisms was more likely in the absence of NIH action. Further, prompt issuance of the Guidelines was believed necessary in order to promote their acceptance by scientists in the United States and abroad who do not come under the purview of NIH.

Issuance of and compliance with the Guidelines is, in itself, expected to decrease the chance of any detrimental environmental impact. However, since there has been little actual experience to date with recombinant DNA experiments, the indicated confidence in the Guidelines rests essentially upon the judgment of scientists. Their confidence is based on two premises. First, it is believed that the containment measures specified in the Guidelines make the escape of potentially harmful recombinant organisms into the environment highly improbable. Second, it is believed that, even if an experiment performed in accordance with the Guidelines does result in accidental release of recombinant organisms, adverse effects will either not occur or not be serious.

In the absence of an adequate base of data derived from either experiments or experience, it must be recognized that future events may not conform to these judgments. There is some statistical probability that recombinant organisms will find their way into the environment either from experiments under NIH auspices or from the activities of others. It is not difficult to construct scenarios in which injury could result. Although the possibility of significant environmental consequences is entirely speculative, the chance of an event that could cause severe injury, however low the probability, must be treated as an environmental impact.

The NIH Guidelines, in addition to ensuring the safety of NIH-supported researchers, the general public and the environment, are serving as a model for other laboratories throughout the world, thereby promoting environmental protection beyond that achievable through other actions available to the Federal Government. And the experiments themselves may be expected ultimately to lead to an increase of knowledge and the advancement of medicine and other sciences.

Although the action in question—that is, issuance of the Guidelines—has already been taken, the Director of NIH believes that the NEPA review will further enlighten the public and focus attention on the important issues involved, in the interest of gaining the understanding and views of the broadest possible segment of the American people. In issuing the Guidelines, the NIH Director pointed out that they will be subject to continuous review and modification in the light of changing circumstances. Constructive modification could result from information received during the NEPA process.

II. Authority

The Federal action discussed in this document is taken under the authority of Title III of the Public Health Service Act—General Powers and Duties of Public Health Service; Part A—Research and Investigation; sections 301 and 307 (42 U.S.C. 241 and 242*l*).

III. Objective of the NIH Action

The objective of the proposed action—release of the NIH Guidelines—is the protection of laboratory workers, the general public, and the environment from infection by possibly hazardous agents that may result from recombinant DNA research. The Guidelines are meant to ensure that experiments involving recombinant DNA molecules and which are supported by NIH, are carried out under conditions and safeguards that minimize the possibility of the harmful exposure of any human being or other component of the environment to these possibly hazardous agents.

It is NIH policy that all work supported by NIH, either in its own laboratories or through grants or contracts to various organizations, must be carried out according to the Guidelines. As part of this objective, the Guidelines describe procedures that will be used to ensure implementation. A further objective of establishing the Guidelines is to influence, to the extent possible, other Federal, non-Federal, and foreign organizations in their efforts to assure that recombinant DNA experiments will be carried out with minimal risk to laboratory workers, the general public, and the environment.

IV. Background

A. Description of the Recombinant DNA Experimental Process

All living things, from subcellular particles to higher organisms, require specific information for their reproduction and functions. The basic source of this information is deoxyribonucleic acid (DNA), which is the principal substance of the genes, the units of heredity (1). Each cell of an organism is composed of various organized structures, several of which contain DNA. Figure IV–1 illustrates a typical cell.

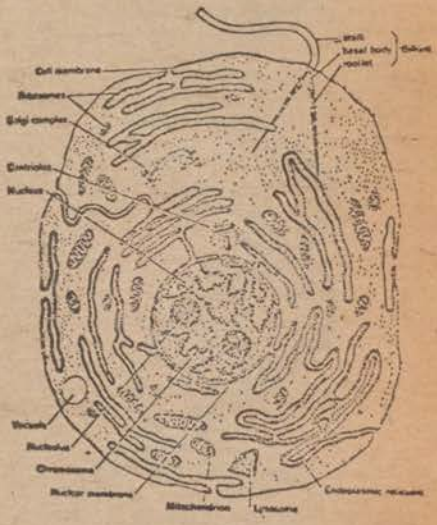

Figure IV–1

DNA plays two roles: (1) Provides information for the reproduction, growth, and functions of the cell, and (2) preserves and directs replication of this information and transfers it to the offspring. These two roles of DNA are common to animals, plants, single-cell organisms, and many viruses. The DNA of cells is mainly found in organized structures called chromosomes.

Intracellular DNA also occurs outside of the chromosomes as separately replicating molecules. Such DNA molecules include the plasmids, found in bacteria; the DNA of chloroplasts, common to green plants; and the DNA of mitochondria, the energy-producing units of the cells of complex organisms. These DNAs, while not strictly part of the inherent genetic make-up of a cell, help define the cell's functional capability. Another type of DNA commonly found in cells is the DNA of infecting viruses.

In the past 30 years the structure of the DNA molecule has been studied in-

tensively, and it can now be described in much detail. The molecule may be compared to a very long, but twisted stepladder with thousands to millions of rungs (shown in Figure IV–2). The sides of the ladder are formed of sugar molecules (deoxyribose) attached end to end through phosphate groups. At right angles to each sugar molecule is one of four possible bases—adenine, guanine, thymine, and cytosine. The precise sequence of these bases, the rungs of the ladder, codes the information content. The "reading" of the code contained in the sequence of bases results in the formation of proteins which in turn permit the essential functions of the cell.

A gene is a portion of the DNA molecule which codes for the manufacture of a single protein. In higher organisms, much of the DNA may not serve as genes in this sense, but may regulate the activity of nearby genes. It is possible to break open cells and isolate DNA, free of other cellular constituents.



FIGURE IV–2

In recombinant DNA experiments, DNA is first isolated from two different cell types. Each DNA is then broken into segments. Each segment may contain one or more genes, or it may contain a portion of the DNA that lacks functional genes. The breaking is accomplished by means of bacterial enzymes (restriction endonucleases), which cut the DNA in such a way that the chemical structure at the ends of the segments permits interchangeable rejoining when the two different DNAs are mixed. In this way single DNA molecules containing portions of the two different DNAs are constructed. The DNA recombined in these experiments can be derived from widely divergent sources. The DNA from one of the sources serves as a carrier, or vector, for the insertion of the recombined DNA into a cell, or host. The vector may be DNA from a virus or a plasmid, usually derived from the same species as will serve as the host of the recombinant DNA. From a growth culture of the host cells, those containing the DNA fragment of particular interest are selected and allowed to multiply. The resulting population of identical cells is called a "clone." In some experiments the DNA will be extracted from the cells for study; in others, the properties of the cells themselves will be investigated.

In the experiments discussed in the Guidelines, the host cells are generally single-cell microorganisms such as bacteria, or animal or plant cells that were originally obtained from living tissue but are grown as single cells under special laboratory conditions.

The process of producing recombinant DNA molecules and introducing them into cells is illustrated in Figure IV–3.

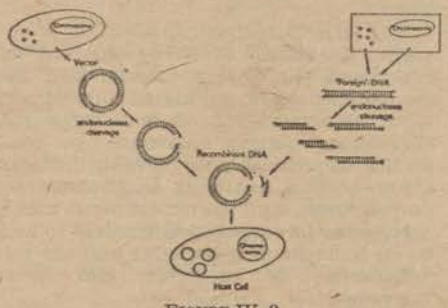

FIGURE IV–3

The cell represented at the upper left contains chromosomal DNA and several separately replicating DNA molecules. The nonchromosomal DNA molecules can be isolated from the cell and manipulated to serve as vectors (carriers) for DNA from a foreign cell. Most DNA molecules used as vectors are circular. They can be cleaved, as shown, by enzymes (restriction endonucleases) to yield linear molecules with rejoinable ends.

At the upper right is another cell, represented here as a rectangle. It serves as the source of the foreign DNA to be inserted in the vector. This DNA can also be cleaved by enzymes. The rectangular cell could be derived from any living species, and the foreign DNA might contain chromosomal or nonchromosomal DNA, or both.

In the next steps, the foreign DNA fragment is mixed and combined with the vector DNA, and the recombinant DNA is reinserted into a host cell. In most experiments this host cell will be of the same species as the source of the vector. The recipient cells are then placed under conditions where they grow and multiply by division. Each new cell will contain recombinant DNA.

B. EVENTS LEADING TO DEVELOPMENT OF GUIDELINES

On June 23, 1976, the Director, NIH, released "National Institutes of Health Guidelines for Research Involving Recombinant DNA Molecules" (see Appendix D). This action was approved by the Secretary of Health, Education, and Welfare and the Assistant Secretary for Health. The Guidelines established carefully controlled conditions for the conduct of experiments involving the insertion of recombinatn genes into organisms, such as bacteria. The chronology leading to the present Guidelines and the decision to release them are outlined below.

It was some of the scientists engaged in recombinant DNA research who called for a moratorium on certain kinds of experiments in order to assess the risks and devise appropriate guidelines. The capability to perform DNA recombinations, and the potential hazards, had become apparent at the Gordon Research Conference on Nucleic Acids in July 1973. Those in attendance voted to send an open letter to Dr. Philip Handler, President of the National Academy of Sciences, and to Dr. John R. Hogness, President of the Institute of Medicine, NAS. The letter, appearing in "Science" (2), suggested that the Academy "establish a study committee to consider this problem and to recommend specific actions or guidelines, should that seem appropriate."

In response, NAS formed a committee, and its members published another letter in "Science" in July of 1974 (3). Under the title "Potential Biohazards of Recombinant DNA Molecules," the letter proposed:

> First, and most important, that until the potential hazards of such recombinant DNA molecules have been better evaluated or until adequate methods are developed for preventing their spread, scientists throughout the world join with the members of this committee in voluntarily deferring * * * [certain] experiments * * *.
>
> Second, plans to link fragments of animal DNAs to bacterial plasmid DNA or bacteriophage DNA should be carefully weighed * * *.
>
> Third, the Director of the National Institutes of Health is requested to give immediate consideration to establishing an advisory committee charged with (i) overseeing an experimental program to evaluate the potential biological and ecological hazards of the above types of recombinant DNA molecules; (ii) developing procedures which will minimize the spread of such molecules within human and other populations; and (iii) devising guidelines to be followed by investigators working with potentially hazardous recombinant DNA molecules.
>
> Fourth, an international meeting of involved scientists from all over the world should be convened early in the coming year to review scientific progress in this area and to further discuss appropriate ways to deal with the potential biohazards of recombinant DNA molecules.

On October 7, 1974, the NIH Recombinant DNA Molecule Program Advisory Committee (hereafter "Recombinant Advisory Committee") was established to advise the Secretary of HEW, the Assistant Secretary for Health, and the Director of NIH, concerning a program for developing procedures which will minimize the spread of such molecules within human and other populations, and for devising guidelines to be followed by investigators working with potentially hazardous recombinants."

The international meeting proposed in the "Science" article (2) was held in February 1975 at the Asilomar Conference Center, Pacific Grove, California. It was sponsored by the National Academy of Sciences and supported by the National Institutes of Health and the National Science Foundation. One hundred and fifty people attended, including 52 foreign scientists from 15 countries, 16 representatives of the press, and 4 attorneys.

The conference reviewed progress in research on recombinant DNA molecules and discussed ways to deal with the potential biohazards of the work. Participants felt that experiments on con-

struction of recombinant DNA molecules should proceed: *Provided*, that appropriate containment is utilized. The conference made recommendations for matching levels of containment with levels of possible hazard for various types of experiments. Certain experiments were judged to pose such serious potential dangers that the conference recommended against their being conducted at the present time.

A report on the conference was submitted to the Assembly of Life Sciences, National Research Council, NAS, and approved by its Executive Committee on May 20, 1975. A summary statement of the report (4) was published in "Science, Nature," and the "Proceedings of the National Academy of Sciences." The report noted that "in many countries steps are already being taken by national bodies to formulate codes of practice for the conduct of experiments with known or potential biohazards. Until these are established, we urge individual scientists to use the proposals in this document as a guide."

The NIH Recombinant Advisory Committee held its first meeting in San Francisco immediately after the Asilomar conference. It proposed that NIH use the recommendations of the Asilomar conference as guidelines for research until the committee had an opportunity to elaborate more specific guidelines, and that NIH establish a newsletter for informal distribution of information. NIH accepted these recommendations.

At the second meeting, held on May 12–13, 1975, in Bethesda, Maryland, the committee received a report on biohazard-containment facilities in the United States and reviewed a proposed NIH contract program for the construction and testing of microorganisms that would have very limited ability to survive in natural environments and would thereby limit any possible hazards. A subcommittee chaired by Dr. David Hogness was appointed to draft guidelines for research involving recombinant DNA molecules, to be discussed at the next meeting.

The NIH committee, beginning with the draft guidelines prepared by the Hogness subcommittee, prepared proposed guidelines for research with recombinant DNA molecules at its third meeting, held on July 18–19, 1975, in Woods Hole, Massachusetts.

Following this meeting, many letters were received which were critical of the guidelines. The majority of critics felt that they were too lax, others that they were too strict. The committee reviewed all letters, and a new subcommittee, chaired by Dr. Elizabeth Kutter, was appointed to revise the guidelines.

A fourth committee meeting was held on December 4–5, 1975, in La Jolla, California. For this meeting a "variorum edition" had been prepared, comparing line-for-line the Hogness, Woods Hole, and Kutter guidelines. The committee reviewed these, voting item-by-item for their preference among the three variations and, in many cases, adding new material. The result was the "Proposed Guidelines for Research Involving Recombinant DNA Molecules," which were referred to the Director, NIH, for a final decision in December 1975.

The Director of the National Institutes of Health called a special meeting of the Advisory Committee to the Director to review these proposed guidelines. The meeting was held at NIH, Bethesda, on February 9–10, 1976. The Advisory Committee is charged to advise the Director, NIH, on matters relating to the broad setting—scientific, technological, and socioeconomic—in which the continuing development of the biomedical sciences, education for the health professions, and biomedical communications must take place, and to advise on their implications for NIH policy, program development, resource allocation, and administration. The members of the committee are knowledgeable in the fields of basic and clinical biomedical sciences, the social sciences, physical sciences, research, education, and communications. In addition to current members of the committee, the Director, NIH, invited a number of former committee members as well as other scientific and public representatives to participate in the special February session.

The purpose of the meeting was to seek the committee's advice on the guidelines proposed by the Recombinant Advisory Committee. The Advisory Committee to the Director was asked whether, in their judgment, the guidelines balanced scientific responsibility to the public with scientific freedom to pursue new knowledge.

Public responsibility weighs heavily in this genetic research area. The scientific community must have the public's confidence that the goals of this profoundly important research accord respect to important ethical, legal, and social values of our society. A key element in achieving and maintaining this public trust is for the scientific community to ensure an openness and candor in its proceedings. Representatives of the international press were invited to the Asilomar conference, and the proceedings received extensive coverage. The meetings of the Director's Advisory Committee and the Recombinant Advisory Committee have also reflected the intent of science to be an open community in considering the conduct of recombinant DNA experiments. Notification of all the meetings was published in the FEDERAL REGISTER and all the meetings were attended and reported by representatives of the press. At the Director's Advisory Committee meeting, there was ample opportunity for comment and an airing of the issues, not only by the committee members but by public witnesses as well. All major points of view were broadly represented.

The guidelines were reviewed in light of the comments and suggestions made by participants at that meeting, as well as the written comments received afterward. As part of that review the Recombinant Advisory Committee was asked to consider at its meeting of April 1–2, 1976, a number of selected issues raised by the commentators. Those issues and the response of the Recombinant Advisory Committee were taken into account in arriving at the final decision on the Guidelines.

The history of the events and discussions leading to the development of the Guidelines are described in greater detail in the "Decision of the Director, NIH," published as a preamble to the Guidelines in the FEDERAL REGISTER, Part II, July 7, 1976 (See Appendix D).

C. DESCRIPTION OF ISSUES RAISED BY RECOMBINANT DNA RESEARCH

1. *Possible hazardous situations.* The stable insertion of DNA derived from a different species into a cell or virus (and therefore the progeny thereof) may change certain properties of the host. The changes may be advantageous, detrimental, or neutral with regard to (a) the survival of the recipient species, (b) other forms of life that come in contact with the recipient and (c) aspects of the nonliving environment. Current knowledge does not permit accurate assessment of whether such changes will be advantageous, detrimental or neutral, and to what degree, when considering a particular recombinant DNA experiment. At present it is only possible to speculate on ways in which the presence of recombinant DNA in a cell or virus could bring about these effects. It should be emphasized that there is no known instance in which a hazardous agent has been created by recombinant DNA technology. The following discussion is speculative and consider ways in which hazardous agents might be produced.

a. *The effect of foreign DNA on the survival of recipient species (host cells or viruses).* The effect of foreign DNA on the survival of recipient species is important to the discussion of possible hazards of recombinant DNA experiments because although a recipient species may acquire a potential for harmful effects as a result of the foreign DNA, the possibility that the harmful effect will occur will depend on the survival of the recipient and its ability to multiply. If acquisition of foreign DNA increases the probability of survival and multiplication the possibility of harmful effects will increase. Similarly, if acquisition of foreign DNA decreases the probability of survival or multiplication, the possibility of harmful effects will decrease. It is important to recognize, in evaluating the potential for harmful effects, that significant infections of animals and plants by bacteria or viruses may require contact with either a large or small number of the infectious agent, depending on the agent.

There are various indications that bacteria and viruses containing inserted foreign DNA are less likely to survive and multiply than are the original organisms. Natural evolution results in the survival of well-balanced and efficient organisms. Essential functions are carefully controlled, and can be switched on and off as needed. It is unlikely that uncontrolled, nonessential properties such as might be introduced by foreign genes would result in any advantage to the survival and multiplication of an other-

wise well-balanced organisms. It is more likely that the new properties accompanying insertion of foreign genes will confer some relative disability to the recipient organisms. Therefore it is likely that bacterial cells containing inserted foreign DNA will multiply more slowly than the same cells without foreign DNA. Thus, in a natural competitive environment, bacteria containing recombinant DNA would generally be expected to disappear. The rate of disappearance will depend on the relative rate of growth compared to other, competing bacteria. The following calculation demonstrates this point.

Assume that a new organism constitutes 90 percent of a population, but grows 10 percent less rapidly than its natural counterpart. The new organism will drop from a concentration of 90 percent to a concentration of 0.0001 percent (1 part in 1,000,000) in 207 generations. If the generation time of the natural organism is one hour, this amounts to about 8½ days.

One example of a situation in which the capability of recipient bacterial host cells to survive may be significantly increased as the result of the presence of a foreign DNA is the case of resistance to antibiotics and drugs. It is well known that such resistance is often genetically determined and genes specifying resistance have been described. Furthermore it is well known that such genes may be transferred, by natural DNA recombination, from one species of microorganism to another. Such natural events are in fact responsible for the rapid and wide spread of resistance to clinically important drugs that has been observed during the last 20 years.

The ability of recipient bacterial host cells to survive and multiply might also be enhanced by acquisiton and expression of a foreign gene conferring the ability to metabolize particular nutrients. In an environmental niche containing the metabolite, such a recombinant might compete succesfully against organisms native to the niche. This could result in destruction of an environmental component—that is, the metabolite. Also, if the native organisms were performing beneficial functions, those functions could be lost upon the successful establishment of the recombinant in the niche.

b. *The effect of bacteria and viruses containing recombined DNA on other forms of life.* The analysis leading to the Guidelines centered on the possibility of deleterious effects, since the concern was the health and safety of living organisms, including humans, and the environment. Agents constructed by recombinant DNA technology could prove hazardous to other forms of life by becoming pathogenic (disease-producing) or toxigenic (toxin-producing), or by becoming more pathogenic or toxigenic than the original agent.

There are two basic mechanisms by which a recipient microorganism might be altered with regard to its pathogenicity or toxicity as a result of a resident recombinant:

(1) *The recombinant DNA may result in formation of a protein that has undesirable effects.* The case in which bacterial cells are used as carriers of foreign DNA is discussed first. A foreign protein, specified by the foreign DNA, might act after being liberated from the microorganism, or it could function within the microorganism and alter, secondarily, normal microbial cell function in such a way that the cell is rendered harmful to other living things. Either means depends on the expression of the foreign genes; that is, the information in the foreign genes must be used by the recipient bacterium to produce a foreign protein. Examples of protein that might prove harmful to other organisms are hormones, enzymes and toxins.

The weight of present evidence suggests that foreign DNA from bacteria of one species, when inserted into bacteria of another species, may be expressed in the recipient. For example, if the donor of the foreign DNA produces a toxic substance, then the recipient call may produce such a substance if the gene for the toxic substance is present in the recombinant. The recipient may or may not be more hazardous than the original donor organism, depending on the relative ability of the two organisms to grow and infect an animal or plant species at risk.

The evidence available at present is insufficient to predict whether or not foreign genes derived from a complex organism (animals, plants, yeasts, and fungi) will be expressed in a bacterium in any particular instance. It may be that specific manipulations will be required to permit bacteria to express information of a foreign DNA efficiently. Faithful expression of a gene requires accurate functioning of the complex bacterial machinery involved in protein synthesis. At each step, specific signals originating in the foreign gene must be recognized by the bacterial machinery. Evolutionary divergence has resulted in different signals in bacteria and complex organisms.

Attempts to translate animal virus and animal cell genes into portein, using cell-free systems containing the protein-synthesizing machinery isolated from bacteria such as *E. coli* yield some protein-like products. The protein products characterized to date were not faithful products of the information in the genes.

In a few cases, intact bacteria containing recombined genes from complex organisms have been tested for evidence of expression of the inserted gene. By and large, accurate expression of the genes has not yet been demonstrated, although it may occur at a low frequency. In some instances, a new protein has been found, replacing one encoded by a bacterial gene. This result is expected if a bacterial gene is interrupted by insertion of the new DNA sequence within it, and does not necessarily indicate expression of the foreign gene. DNA fragments from yeast have been inserted into a strain of the bacterium *E. coli* which cannot manufacture the amino acid histidine (5). (Histidine is a component of most proteins and therefore is required for the growth of all organisms.) After insertion, some cells no longer required histidine; thus, the presence of the yeast DNA overcame the requirement for histidine. This is the first suggestion that a foreign gene from an organism more complex than bacteria may actually function in a bacterial cell. (Although yeast is a single-cell organism, it contains an organized nucleus like cells of higher organisms.) However, the detailed mechanism explaining this observation is unknown.

Analogous issues must be considered for the case in which animal viruses are the carriers of foreign DNA. Many viruses are simply described as DNA molecules enclosed and protected by coats of protein molecules. The protein coat protects the DNA from environmental effects, thus increasing the ability of the viral DNA to infect a cell. If viral DNAs are recombined with foreign DNAs in such a way that necessary viral genes remain intact, then the recombinant DNA may in turn be able to produce, and be packaged in, the coat of the virus. Inadvertent dispersal of such a viral particle outside of the laboratory might then result in entry of the recombinant DNA into cells of living organisms. The foreign genes may be expressed, resulting in the formation of a protein foreign to the infected cell, or the uncontrolled synthesis of a normal protein. The likelihood of expression of the foreign genes will probably depend on the degree of relatedness between its source and the infected organism as well as its location in the viral DNA used as vector. Currently, few if any relevant experimental data are available so that estimates of the probability of expression are, in these instances, impossible.

(2) *The recombined DNA may itself cause pathogenic or toxic effects.* Foreign DNA inserted in a bacterial gene, might so alter the microbial cell's properties that it becomes harmful to other organisms. This might happen, for example, through a change in the growth rate and competitive advantage of the recipient microbial cell, resulting in increased virulence of a mildly pathogenic bacteria. In general, one would expect the inserted DNA to result in a reduced growth rate and a selective disadvantage to the organism, as discussed in "a" above. Similar issues arise where animal viruses serve as carriers of foreign DNA.

It is also necessary to consider situations in which DNA molecules themselves may escape from the laboratory or from the experimental host cell and enter cells of living organisms with which they come in contact. Although free DNA molecules are themselves relatively fragile (and the probability that they would survive, in a significant form or for a significant time, in air, water, or any other medium, is considered remote), they can be protected in nature in a variety of ways and be released either into, or close to, a living cell.

When a cell or virus dies, or comes close to or invades the tissue of another living organism, the recombinant DNA may effectively enter a new cell. A hazardous situation similar to that described above might ensue if foreign proteins were manufactured in this "secondary" recipient. The recombinant DNA might survive as an independent cellular component, or it could recombine by natural

process with the DNA of the secondary recipient. Various possible deleterious consequences of such a recombination may be considered.

If the secondary recipient is another microorganism, the same considerations described in IV–C–1–a apply. If the secondary recipient is one of the cells of an animal or plant, different considerations apply. The latter include alterations of normal cellular control mechanisms, synthesis of a foreign protein (such as a hormone), and insertion of genes involved in cancer production (if, for example, the foreign DNA were derived from a cancer-producing virus).

It should be pointed out that the likelihood of causing inheritable changes in the offspring of complex organisms by such a mechanism is extremely low in animals because of the protection afforded germ-line cells (eggs and sperm) by their location. Thus, the possibility that recombined foreign DNA would reach germ line cells at a time in the life of such cells when secondary recombination can occur is extremely remote. With one-celled organisms, plants, or simple multicellular organisms, the probability of causing heritable change by secondary recombination may be higher.

What is the probability of secondary recombination between prokaryotes and eukaryotes in nature? It is generally held that recombination in nature is more likely if similar or identical sequences of bases (rungs in the DNA ladder) occur in the two recombining DNAs. The greater the degree of similar sequences, the more likely is recombination. In general, the more closely two species are related, the more likely it is that similar sequences will be found in their DNAs. Thus, DNA from primates has more DNA sequences in common with human DNA than does DNA from mice, or fish, or plants. Recombination may also occur between DNAs not sharing sequences but at lower frequencies.

It is possible that the capacity for interspecies recombination between distantly related species exists in nature. For example, bacteria in animal intestines are constantly exposed to fragments of animal DNA released from dead intestinal cells. Significant recombination requires the uptake of intact segments of animal DNA and their subsequent incorporation into the bacterial DNA. The frequency of such events is unknown.

There are very few available data permitting assessment of the reverse process—namely, the incorporation of bacterial DNA into the cells, or DNA, of more complex organisms. Although there are reports of experiments in which bacterial DNA was inserted into animal and plant species and production of the bacterial protein followed, the process is very inefficient and many investigators have been unable to repeat these experiments (6–8).

There are certain well-documented instances in which the DNAs of different living things become more or less permanently recombined in nature. These instances involve recombination between the DNAs of nonchromosomal genes, such as those of viruses or plasmids, or recombination between the DNAs of viruses or plasmids and chromosomal genes. The former instance, for example, is the mechanism behind the rapid spread of resistance to antibiotics among different bacterial species (9, 10). This spread accompanied the prevalent use of antibiotics in medicine and agriculture. Some viral DNAs recombine into and persist in chromosomal DNA of cells of receptive organisms (11, 12). Some viral DNAs acquire, in stable form, DNA sequences derived from their host cells (13, 14). There is also strong evidence for recombination of the DNA form of RNA tumor virus genes with chromosomal genes (15–17).

2. *Expected benefits of DNA recombinant research.* Benefits may be divided into two broad categories: An increased understanding of basic biological processes, and practical applications for medicine, agriculture, and industry.

At this time the practical applications are, of course, speculative. It is important to stress that the most significant results of this work, as with any truly innovative endeavor, are likely to arise in unexpected ways and will almost certainly not follow a predictable path.

a. *Increased understanding of basic biological processes.* There are many important fundamental biomedical questions that can be answered or approached by DNA recombinant research. In order to advance against diseases in inheritance, we need to understand the structure of genes and how they work. The DNA recombinant methodology provides a simple and inexpensive way to prepare large quantities of specific genetic information in pure form. This should permit elucidation of the organization and function of the genetic information in higher organisms. For example, current estimates of the fraction of this information that codes for proteins are simply educated guesses. There are almost no clues about the function of the portions of DNA that do not code for proteins, although these DNA sequences are suspected of being involved in the regulation of gene expression.

The existing state of ignorance is largely attributable to our previous inability to isolate discrete segments of the DNA in a form that permits detailed molecular analysis. Recombinant DNA methodology remove this barrier. Furthermore, ancillary techniques have been developed whereby pure DNA segments that contain particular sequences of interest can be identified and selected. Of particular interest is the isolation of pure DNA segments that contain the genes for the variable and constant portions of the immunoglobin proteins. The analyses of such segments obtained from both germline and somatic cells should be of inestimable value in determining the mechanism of immunologic diversity.

A major problem in understanding the mechanism by which certain viruses cause cancer is how and where the infecting or endogenous viral genomes are integrated into the cell's chromosome. This bears on the question of how the expression of the integrated viral genes affects cellular regulation, thus leading to the abnormal growth characteristics of cancer cells. With the recombinant DNA techniques for isolation and purification of specific genes, this research problem is reduced to manageable proportions. It is possible to isolate the desired DNA segment in pure form. Large quantities can be obtained for detailed study by simply extracting a culture of the bacteria carrying the viral DNA segment in a plasmid.

b. *Potential practical applications for medicine, agriculture and industry.* Certain of the potential applications will only be realized if the reproduction of the recombined foreign DNA in a recipient host cell is followed by expression of the genetic information contained in the DNA in the form of synthesis of proteins. Since the efficient translation of eukaryote genes in bacterial (prokaryote) hosts has yet to be proved, these potential applications are speculative at this time. Applications that depend on the expression of foreign prokaryotic genes in prokaryotic recipient cells are presently more certain.

(1) *Synthesis of medically important proteins and other substances.* It has been suggested that genes coding for medically important substances be attached to bacterial vectors, and that the bacteria then be used to produce large quantities of the desired material. A number of costly and/or rare substances would be prime candidates for such synthesis:

Human insulin (a future shortage of currently used animal insulin appears to be likely);

Human growth hormone (presently available only from human cadavers and in short supply);

Clothing factor VIII (for treatment of hemophilia).

Specific antibodies and antigens (for preventing and treating infectious, allergic, and autoimmune disease, and perhaps even cancer);

Certain enzymes, such as fibrinolysin and urokinase (promising agents in the treatment of embolism) and lysosomal enzymes.

(2) *Endowment of plants with new synthesis capabilities.* Whole plants may be generated from a single cell, and thus insertion of recombinant DNA into such cells might make it possible to endow plant species with the capability of—

Improved photosynthetic fixation of carbon dioxide;

Nitrogen fixation by presently inept species (thereby reducing the need for costly chemical fertilizers that cause pollution—e.g., eutrophication);

Producing a higher quality or quantity of food protein.

(3) *Some industrial applications.* A number of industrial processes utilize microorganisms containing enzymes (which are proteins) to produce important chemicals (e.g., steroid hormones or other drugs, vitamins) or foodstuffs (e.g., cheese). Such processes could be improved through innovations effected by DNA recombinant research. Completely new biosynthetic reactions may thereby become available, permitting the synthesis of large amounts of complex and

valuable compounds with ease and at low cost.

Some highly speculative applications relate to the area of energy production and neutralization of pollutants—e.g., as in oil spills. Genetic modification through DNA recombination might it possible to devise microorganisms tailor-made for such important purposes.

3. *Long-range implications.* The experimental situations treated in the Guidelines are those that appear feasible either currently or in the near future. The experiments primarily involve insertion of recombined DNA into bacteria or into single cells derived from more complex organisms and maintained under special laboratory conditions. It is only in the case of plants that the Guidelines cover experiments involving insertion of DNA into cells capable of developing into complex, multicellular organisms. The Guidelines and the discussions leading to their development have focused on problems of safety.

It is possible that techniques similar to or derived from current recombinant DNA methodology may, in the future, be applicable to the deliberate modification of complex animals, including humans. Such modification might have as its aim correction of an inherited defect in an individual, or alteration of heritable characteristics in the offspring of individuals of a given species. The latter type of alteration has been successfully achieved in agriculture for centuries, by classical breeding techniques. It may be that recombinant DNA methods, should they develop in appropriate ways, may offer new opportunities for specificity and accuracy in animal breeding.

The deliberate application of such methods for the correction of individual genetic defects or the alteration of heritable characteristics in man raises complex and difficult problems. In addition to philosophical, moral, and ethical questions of concern to individuals, serious societal issues are involved. Broad discussion of these problems in a variety of forums will be required to inform both private and public decision-making.

4. *Possible deliberate misuse.* In the event that recombinant DNA technology can yield hazardous agents, such agents might be considered for deliberate perpetration of harm to animals (including humans), plants or the environment. The possibilities include biological warfare or sabotage. Because it is not known whether recombinant DNA technology can yield such agents, discussion of these problems such as theft by saboteurs is hypothetical and difficult. With regard to biological warfare, a July 3, 1975 letter to Dr. David Baltimore from James L. Malone, General Counsel of the United States Arms Control and Disarmament Agency says, "you raise the question as to whether the Biological Weapons Convention prohibits production of recombinant DNA molecules for purposes of constructing biological weapons. In our opinion the answer is in the affirmative. The use of recombinant DNA molecules for such purposes clearly falls within the scope of the Convention's provisions."

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V. DESCRIPTION OF THE PROPOSED ACTION

The Director, National Institutes of Health, has issued Guidelines that will govern the conduct of NIH-supported research on recombinant DNA molecules. The Guidelines will apply to all NIH-supported research on such molecules—that is, molecules which are made by combining segments of DNA from different organisms in a cell free-system and which can be inserted into some living cell, there to replicate. The objective of the Guidelines is the protection of the laboratory worker, the general public, and the environment from infection by possibly hazardous agents that may result from this research. The complete text of the Guidelines is found in the FEDERAL REGISTER, Part II, for Wednesday, July 7, 1976. As an integral part of this Draft Environmental Impact Statement the Guidelines are found in Appendix D.

The mechanisms by which the NIH will implement the application of the Guidelines are outlined in the Guidelines themselves and are specified in greater detail in Appendix C. Noncompliance with the Guidelines will result in termination of funding of research grants and contracts.

The Guidelines describe (1) safeguards that protect the laboratory worker, the general public, and the environment, (2) the criteria for assessing the possible dangers from experiments involving recombinant DNA molecules, (3) the criteria for matching the assessed possible dangers of individual experiments with the appropriate safeguards, and (4) the roles and responsibilities of principal investigators, their institutions, and NIH for ensuring the implementation of the requirements specified in these Guidelines. The emphasis on protection of laboratory workers from infection reflects the fact that laboratory workers are the persons at the greatest risk of infection and that the most likely route of escape of possibly hazardous agents from the laboratory is the laboratory worker.

The physical safeguards have been grouped into four levels providing increasing capability for containment. The four levels approximate those recommended by the Center for Disease Control for the control of known infectious agents that have been determined to be of (1) no or minimal, (2) ordinary, (3) special, or (4) extreme hazard to man and other living things. These correspond to the terms Minimal, Low, Moderate, and High risk, respectively, as used in the NIH Guidelines. The safeguards include usual and special microbiological safety practices, primary physical barriers that isolate the experiment from the laboratory worker, and facility installations that either markedly reduce or eliminate the potential for accidental dissemination of recombinant DNA molecules to the environment. The four levels, designated P1 to P4, provide increasing protection against contact with or accidental release of microorganisms containing recombinant DNA molecules.

Additional safeguards are provided by the use of host cells and vectors with demonstrably limited ability to survive in other than specially designed laboratory environments. This concept is called "biological containment" in the Guidelines. In the case of bacterial host cells and vectors, this means that particular strains of cells and vectors with genetically determined and fastidious survival requirements must be used. For those experiments judged to be of potentially moderate or high risk, the properties of the bacterial strains to be used

must be certified by the NIH Recombinant Advisory Committee prior to initiation of experiments. In the case of a vector derived from an animal virus, the virus itself must be a low risk agent (CDC or National Cancer Institute), and a strain of the virus that is defective in infection must serve as the source of the vector DNA.

The selection of containment (safeguard) levels is dependent on the assessed possible dangers of the experiment. The Guidelines provide standards for evaluating the conceivable dangers of particular experiments involving recombinant DNA molecules. In the absence of evidence of any hazard actually occurring, these standards are based on relevant current knowledge. Permissible experiments are placed into four classes of increasing possible danger which correspond to the four levels of increasing containment capability (safeguards). Certain experiments, judged to have the potential for extreme hazard, should they prove dangerous, are prohibited.

The possibility for danger depends on—

(1) The biohazard associated with the DNA of the cell or microorganism that serves as the DNA source (e.g., genes for toxin production),

(2) The degree to which the DNA segment has been purified away from other genes and shown to be free of harmful characteristics,

(3) The biohazard associated with the vector that serves to transmit the source DNA to a recipient host cell,

(4) The ability of the vector to survive in natural environments or habitats,

(5) The kinds and number of different organisms that are susceptible to infection by the recipient or vector,

(6) The biohazard of the recipient host cell that serves to replicate the recombinant DNA molecule,

(7) The ability of the recipient cell to survive in natural environments or habitats,

(8) The ability of the recipient cell to transmit the recombinant DNA molecule to other cells capable of surviving in natural environments or habitats,

(9) The potential of the recipient cell to obtain the source DNA by natural means, and

(10) The evolutionary relatedness of the DNA source to humans.

The Guidelines prohibit a number of types of experiments, including those in which an organism contributing DNA is itself a biohazard of greater than low risk as determined by conventional methods of risk assessment (low risk corresponds to class 2 agents as defined by the Center for Disease Control). The host cells and vectors are required to be of no or minimal risk. The potential dangers are considered to increase as the organism providing the source DNA approaches humans phylogenetically. Thus, source DNA from primate cells is considered to have greater potential dangers than source DNA from lower eukaryotes. In general, greater possible dangers are assigned to recombinants than are present in the most hazardous component used to construct the DNA.

The risk-assessment standards are specified in detail for one prokaryote host-vector system employing a variant of *E. coli* called strain K12, which is, by itself, of no or minimal risk. Eukaryote host-vector systems using defective viral vectors are also described. The descriptions of these systems provide principles by which the potential dangers of recombinant DNA experiments with other host-vector systems can be assessed.

The Guidelines also establish an administrative framework for assigning the responsibility for ensuring safety in recombinant DNA research supported by NIH. This responsibility is shared among the principal investigators, their institutions, and NIH. The principal investigators have the primary responsibility for hazard assessment and for implementation of appropriate safeguards. The institutions are responsible for ensuring that the principal investigators have the capabilities for meeting the requirements stipulated in the Guidelines. NIH is responsible for securing an independent assessment of the potential dangers of this research and for ensuring that no research is supported unless it conforms to the requirements stipulated in the Guidelines.

The Guidelines require that the institutions establish biohazard committees to carry out the institutional responsibility, and stipulate the qualifications and expertise of the committee membership. NIH responsibilities are detailed in the Guidelines and are divided among (1) NIH Initial Review Groups, (2) the NIH Recombinant DNA Molecule Program Advisory Committee, and (3) the NIH staff.

Physical containment requirements

The safeguards in the Guidelines require the use of procedures and physical containment systems to protect laboratory workers and the environment from exposure to potentially harmful organisms. The requirements include procedures and equipment in which work is to be done and special laboratory room and building features, as well as appropriate training of workers. The systems are grouped into four levels of containment—P1, P2, P3, and P4—each providing a level of containment greater than the one preceding it. The level of containment that must be provided by a laboratory in which an experiment is to be done is based on an assessment of the degree of hazard involved.

The following description of the physical containment levels is presented to outline these requirements. A complete description may be found in the Guidelines (Appendix B).

P1 Level (Minimal). A laboratory suitable for experiments involving recombinant DNA molecules requiring physical containment at the P1 level is shown in Figure V–1. Such a laboratory possesses no special engineering design features. Work in this laboratory is generally conducted on open bench tops. Special containment equipment is neither required nor generally available. The laboratory is not separated from the general traffic patterns of the building, and public access is permitted. Control of biohazards is provided by standard microbiological practices.

P2 Level (Low). A laboratory suitable for experiments involving recombinant DNA molecules requiring physical containment at the P2 level (see Figure V–2) is similar in construction and design to the P1 laboratory. The P2 laboratory must have access to an autoclave within the building, and it may have a biological safety cabinet. Work that does not produce a considerable aerosol is conducted on the open bench. However, when excessive aerosols may be produced, low-risk experiments must be conducted in special cabinets (biological safety cabinets) that provide physical barriers against possible release of organisms. Although this laboratory is not separated from the general traffic patterns of the building, access to it is limited when experiments requiring P2-level physical containment are being conducted.

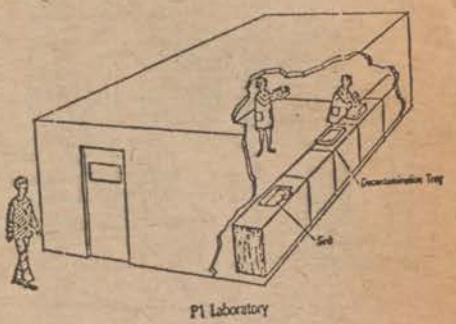

FIGURE V–1

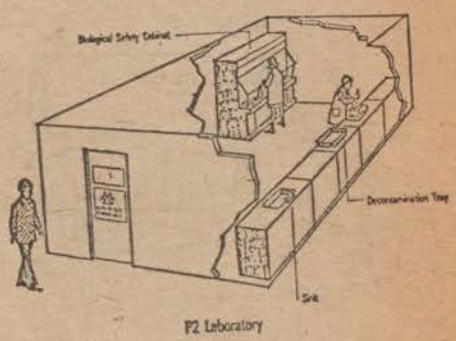

FIGURE V–2

P3 Level (Moderate). As shown in Figure V–3, a laboratory suitable for experiments involving recombinant DNA molecules requiring physical containment at the P3 level has special engineering design features and physical containment equipment. The laboratory is separated from areas that are open to the general public. Separation is generally achieved by controlled access corridors and air locks, locker rooms, or other double-doored facilities not available for use by the general public. Access to the laboratory is controlled. Biological safety cabinets are available within the controlled laboratory area. An autoclave shall be available within the building and preferably within the controlled laboratory area. Environmental protection is provided by waste sterilization techniques. The surfaces of walls, floors,

bench tops, and ceilings are easily cleanable to facilitate housekeeping and space decontamination. The laboratory ventilation system is balanced to provide for an inflow of supply air from the access corridor into the laboratory. No work in open vessels is conducted on the open bench; all such procedures are confined to biological safety cabinets.

P4 Level (High). As shown in Figure V–4, experiments involving recombinant DNA molecules requiring physical containment at the P4 level shall be confined to work areas in a maximum-security facility of the type designed to contain microorganisms that are extremely hazardous to man or may cause serious epidemic disease. The facility is either a separate building or a controlled interior area completely isolated from all other areas of a building. Access to the facility is under strict control. Class III biological safety cabinets are available.

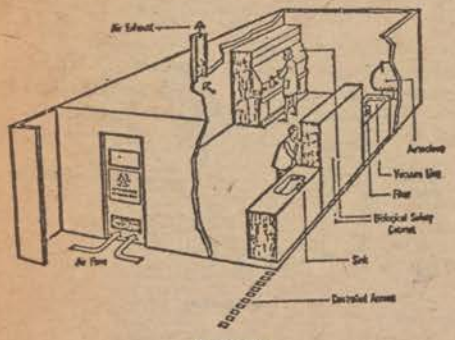

FIGURE V–3

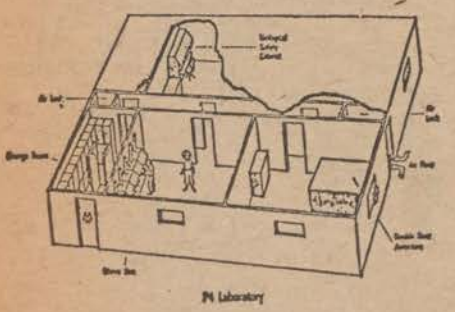

FIGURE V–4

A P4 facility has engineering features, shown in Figure V–5, designed to prevent the escape of microorganisms to the environment (1–4). The special features in a P4 facility include:

Monolithic walls, floors, and ceilings in which all penetrations such as for air ducts, electrical conduits, and utility pipes are sealed to ensure the physical isolation of the work area and to facilitate housekeeping and space decontamination.

Air locks through which supplies and materials can be brought safely into the facility.

Contiguous clothing change and shower rooms through which personnel enter into and exit from the facility.

Double-door autoclaves to sterilize and safely remove wastes and other materials from the facility.

A biowaste treatment system to sterilize liquid effluents if facility drains are installed.

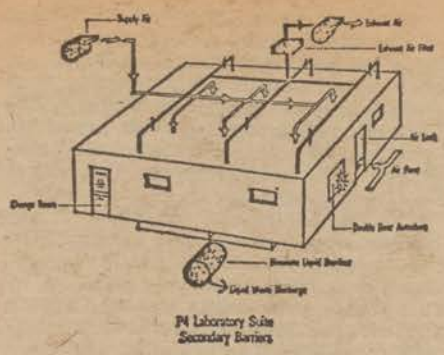

FIGURE V–5

A separate ventilation system that maintains negative air pressures and directional airflow within the facility.

A treatment system to decontaminate exhaust air before it is dispersed to the atmosphere. A central vacuum utility system is not encouraged; if one is installed, each branch line leading to a laboratory shall be protected by a high-efficiency particulate air filter.

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VI. DESCRIPTION OF ALTERNATIVES

The following general classes of action have been considered as alternatives to, or in addition to, the proposed action. The impact of each is described briefly, and reference is made to other portions of this document which have a more complete discussion of the particular impact in question.

A. NO ACTION

This alternative would perpetuate the situation existing prior to June 23, 1976. At that time the only restrictions on recombinant DNA research stemmed from voluntary compliance of the research community with the guidelines developed at the International Conference on Recombinant DNA Molecules, held at Asilomar, California, in February of 1975, which were published in scientific journals. The Asilomar guidelines differ in substance from the NIH Guidelines, and are considerably less stringent and less detailed in their requirements for containment of potentially hazardous organisms. For example, experiments that may be carried out with minimal containment according to the specific language of the Asilomar guidelines (e.g., the construction of an *E. coli* plasmid containing the noncancer-producing DNA segment of SV40) require P3 or P4 according to the NIH Guidelines. In addition, while the Asilomar guidelines recommend that certain experiments be deferred, the list of experiments to be deferred is expanded in the NIH Guidelines. Furthermore, disregard of the Asilomar guidelines carries no sanctions on investigators, and it could be expected that the currently high level of voluntary compliance would be eroded with time.

The "no action" alternative would greatly increase the probability that possibly hazardous organisms would be released into the environment. In addition, public concern would be increased in the absence of any Federal action. It is concluded that the "no action" alternative would not afford adequate protection of laboratory workers, the general public, and the environment from the possible hazards described in section IV–C–1.

The alternative of "no action" would essentially remove from the conduct of research the restrictions inherent in the NIH Guidelines. Experiments concerning basic biological processes, and the development of technology applicable to medical, agricultural, and industrial problems, would proceed at a faster rate. Moreover, the immediate cost of conducting research would be markedly decreased with the "no action" alternative, since the need for costly physical containment would be less.

B. NIH PROHIBITION OF FUNDING OF ALL EXPERIMENTS WITH RECOMBINANT DNA

NIH could refuse to fund any any recombinant DNA experiments. This would not necessarily result in the cessation of such research, since it may still be supported by non-NIH funds both in this country and abroad. Therefore a reduction of risks but not elimination of risks might be achieved by total NIH prohibition. Because the NIH funds a large proportion of the total biomedical research effort, a significant delay might be expected in the achievement of the goals and missions of programs designed to elucidate basic biological processes and, in turn, the mechanisms underlying various disease states. It is widely anticipated that a variety of research—impacting on health and other areas of human concern—will benefit from recombinant DNA technology (see Section IV–C–2).

American scientists have played a leading role in bringing the potential hazards of recombinant DNA research to the attention of scientists, governments, and international organizations. As a result, there is an effort to adopt safety procedures for the conduct of this reseearch in many countries. Although nations differ in their perceptions of the need to adopt safety measures, and of what the exact measures should be, the NIH Guidelines are being used as a model. NIH prohibition of the work would undermine American leadership in the establishment of worldwide standards for safety.

Finally, prohibition would be likely to have important impacts on American science, both in research and in development of technology. The leadership of

the United States in biological research would be threatened. Further, historical precedents indicate that measures which interfere with free inquiry in one area of interest, often inhibit the vitality of other aspects of society.

C. DEVELOPMENT OF DIFFERENT GUIDELINES

Each of the stipulations in the NIH Guidelines was made after assessment of the possible hazards associated with particular experiments. The available data, however, were limited, and different conclusions could have been reached. Some issues addressed in the preparation of the Guidelines which could have led to different specifications are as follows:

1. *Levels of physical containment.* For certain experiments in which the potential risk is controversial, the physical containment level could have been higher or lower. Examples of controversial issues are the recommendations with respect to containment levels for recombinant experiments involving bacterial cells and DNA derived from cold-blooded animals, and for experiments involving the use of DNA from animal viruses.

2. *Establishment of a few national P3 facilities openly available to all investigators, with the requirement that all experiments requiring P3 containment be conducted therein.* In effect, this will be the situation with respect to P4 facilities under the Guidelines. There are several advantages to working in regional centers:

a. It would be less expensive to construct and staff a few such regional centers than many such facilities.
b. Training would be centralized.
c. P3 facilities would be more uniformly accessible to qualified investigators from a variety of institutions.
d. There would be greater assurance that the facilities meet the specified requirements.
e. Banks of cells containing recombinant DNA could be maintained, with a view to decreasing the number of times the actual recombination process would be performed (such banks can also be maintained in the absence of centralized P3 facilities).
f. The sites could be placed away from population centers.

The disadvantages of establishing regional centers include:

a. Long-range planning would be necessary.
b. Scheduling would be a problem.
c. The investigator's independence would be diminished.
d. Competition for access might favor established investigators or established ideas.
e. The nature of the process, which might require only brief access of P3 facilities in a given day but over a lengthy period of time.
f. Access problems might unnecessarily discourage valuable research.

3. *All permissible recombinant DNA experiments be conducted in P4 facilities.* This alternative implies no distinction among experiments. It does not recognize that certain recombinant DNA experiments are widely agreed to pose little, if any, possible hazard. It is equivalent to a total prohibition on much recombinant DNA research because of the limited number of P4 facilities that are available and the high cost of construction. Because of access problems, interesting and important research of low or moderate possible hazard would be discouraged.

4. *Experiments prohibited at this time.* Certain types of experiments are prohibited by the Guidelines. Their selection was a matter of judgment, and depended on the assessment of the seriousness of the possible hazard. Alternative assessments would result in either an expansion or a contraction of the list of prohibited experiments and consequent decrease or increase in the possible risks. Some of the controversial recommendations are—

a. *The prohibition of experiments involving more than 10 liters of culture fluid containing recombinant DNAs known to make harmful products without the express approval of the NIH Recombinant Advisory Committee.* Controversy over this recommendation relates to the fact that some investigators and laboratories contend that larger volumes of culture fluid can be safety contained by special procedures and facilities. The recommendation places responsibility for evaluating the containment on the NIH Recombinant Advisory Committee.

b. *Sanction of the use of the bacterium Escherichia coli as a recipient for recombinant DNA molecules.* This organism has been studied extensively and is well suited to recombinant DNA research. It has been argued, however, that *E. coli* should not be used at the present time. This is because many *E. coli* strains are intimately associated with humans and other living things, and because they readily exchange DNA (genes) with certain other bacteria in nature.

Theoretically, the most desirable bacterial recipient of recombinant DNA would be a species uniquely adapted to carefully controlled laboratory environments and unable to survive or transmit DNA to other organisms in any natural environment. This means that the bacteria should be unable to survive in normal ecological niches, either in the laboratory or neighboring areas. It should be unable to colonize or survive in or on other living things, or in soil or water. In addition, these properties should not be significantly altered by the insertion into the bacterium of the recombined DNA. The bacteria must also be able to be manipulated for successful execution of the proposed experiment.

No bacteria is known to meet all these requirements. The guidelines permit the use of various forms of a particular strain of *E. coli* called K12. (The forms are called EK1, EK2 and EK3 in the Guidelines where they are discussed in detail.) Some of these forms already exist, others need to be constructed. Although related to other *E. coli* strains that do not in any way meet the definition of the ideal organism, these permissible strains of *E. coli* partially fulfill many of the criteria in the definition of the ideal strain. At present, no other bacterial species is known to approximate the definition as closely as *E. coli* K–12 and its derivatives. In the future, other bacteria, closer to the ideal, may become known, or the properties of already known species may be shown to approach the ideal more closely than *E. coli* strain K12 and its derivatives, as defined in the Guidelines.

c. *Sanction of the use of Simian Virus 40 (SV 40) as a carrier of a foreign DNA fragment.* It has been argued that SV40 should not be permitted, since it is known to cause cancer in laboratory animals. There is little evidence that SV40 results in disease in humans. However, SV40 infects humans, and demonstrable antibodies to SV40 indicate that infection has occurred in some members of the general population. Some of the infection may have resulted from the inadvertent inoculation of millions of individuals during the initial mass program of immunization aganist polio virus before SV40 was identified as a contaminant in the vaccine. The antibodies may have been formed against SV40-like viruses known to exist naturally in humans (1). It is possible that a recombined DNA carried by SV40 could infect humans and significantly affect their health (2). The Guidelines restrict the use of SV40 DNA to DNA from strains of the virus that are defective in the infection process. In addition, stringent physical containment is required.

d. *Sanction of experiments involving the transfer of uncharacterized mixtures of DNA segments derived from warm-blooded animals into bacteria.* Such experiments are believed to present a greater possible risk than others because they involve a conglomeration of undefined genes that might include DNA capable of causing disease.

e. *Sanction of the use of oncogenic viruses.* It has been argued that the introduction into *E. coli* of the whole DNA or any purified segment of the DNA of any virus oncogenic in any species should not be permitted.

D. *No guidelines but NIH consideration of each proposed project on an individual basis before funding.* With this alternative, individual investigators requesting NIH funds for projects involving recombinant DNA research would bring plans for proposed experiments to an NIH committee that would, without the use of formal guidelines, recommend suitable containment measures. Depending on the criteria used by the committee, this might result in lower or higher containment levels than are currently imposed by the Guidelines. The advantages of such a procedure would include constant reevaluation of potential hazards and containment measures, and up-to-date information for investigators. The disadvantages include the enormous time and resources required for review, given the size of the biological research enterprise in the United States, the problem of finding knowledgeable individuals to serve on such a committee—essentially a full-time occupation—the opportunity for arbitrary decisions, and the bypassing of local input in assessment of hazards.

It should be pointed out that under the present NIH Guidelines, local institutional biohazards committees must consider proposed research projects on an individuals basis and may impose more

stringent safeguards than those required by the Guidelines. The judgments of the investigator and his local committee will be reevaluated by the NIH Study Section reviewing the scientific merit of the proposal.

E. GENERAL FEDERAL REGULATION OF ALL SUCH RESEARCH

The NIH Guidelines control only recombinant DNA research supported by NIH. Nevertheless, NIH has assumed a real responsibility to work toward the promulgation of safety measures for all such research. Nationally, NIH has conducted and is continuing to conduct meetings with representatives of other Federal agencies and of private industry. In the case of the Federal Government, consideration is being given to the imposition of the Guidelines either by individual agency adoption or through an Executive Order. Non-Federal groups have indicated that they will voluntarily comply with reasonable guidelines designed to be applicable to their specific needs.

From the international standpoint, the NIH has been in communication with relevant national bodies, the World Health Organization, the European Molecular Biology Organization, and the International Council of Scientific Unions, among others, to encourage the widest possible application of the Guidelines.

A variety of administrative mechanisms could be employed to regulate recombinant DNA research. Relevant agencies are the Center for Disease Control (CDC), including the National Institute for Occupational Safety and Health (NIOSH), or the Occupational Safety and Health Administration, Department of Labor (OSHA). For example NIH could petition OSHA to enforce and monitor such research through its standard procedures. If OSHA concurred, the adopted guidelines could be extended to all facilities under OSHA's responsibility.

Legislation could be passed to impose procedures and specify containment for recombinant DNA experiments. Specific guidelines, as well as appropriate enforcement mechanisms and penalties, could be established as statute. The advantages of this approach would include uniformity in coverage and process. The disadvantages include the need for establishment of a new administrative mechanism and consequent costs, the long time generally required for enactment of legislation, and the relative inflexibility of law. Flexibility is desirable because presently recommended containment procedures will surely require timely revision as knowledge and experience are accumulated.

A body like the National Commission on the Protection of Human Subjects of Biomedical and Behavioral Research could be legislatively established. It should be noted that a bill (S. 2515) currently under consideration in the Congress would assign responsibility for consideration of recombinant DNA experiments to a permanent President's Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. A real concern would be the inability of a group with such a broad mandate to deal effectively with the highly specialized subject of recombinant DNA research.

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VII. ENVIRONMENTAL IMPACT OF THE GUIDELINES

A. IMPACT OF ISSUANCE OF NIH GUIDELINES

The primary impact of issuance of the Guidelines is to provide a mechanism for the protection of the laboratory worker, the general public, and the environment from the possible hazards that might result from recombinant DNA molecule research. These hazards are purely speculative at present; the speculations may prove to be wrong. Nevertheless the Guidelines take cognizance of the possibility of dangers to the laboratory worker, other persons, and the environment posed by the emergency research technology involving recombinant DNA molecules, and call for a number of measures aimed at reducing or eliminating human and environmental exposure to materials containing recombinant DNA molecules, in case they should prove hazardous. The Guidelines govern only work supported by the NIH, including NIH supported research at various institutions (grants and contracts) and research carried out within NIH intramural laboratories.

With regard to the anticipated but speculative benefits of recombinant DNA research, adherence to the Guidelines may postpone their realization. Certain experiments are prohibited; many permissible experiments will be delayed pending availability of suitable containment facilities and certification of appropriate hosts and vectors.

1. *Impact on the safety of laboratory personnel and on the spread of possibly hazardous agents by infected laboratory personnel.* The NIH Guidelines are directly concerned with reducing and eliminating exposures of laboratory personnel and all other persons to host cells and microorganisms containing recombinant DNA molecules. Because laboratory personnel would be the chief source of infection of other people, protection of personnel is of primary importance. Lack of knowledge about the real risks of such molecules makes it impossible to determine either the nature of the hazards or the extent to which laboratory personnel are endangered by exposures to the materials. Nevertheless present understanding of biology permits a ranking of the possible risks that may be associated with a given experiment.

Four levels of possible risk have been established: minimal, low, moderate, and high. Protection of personnel from minimal risk materials is provided by ordinary microbiological techniques. Since these procedures are generally performed on the open bench, exposures may occur. The avoidance of harmful effects depends more on the exceedingly low potential of these materials to cause a harmful infection than of the elimination of potential exposures. Potential harmful effects would require exposure to large numbers of organisms, e.g., due to accidental ingestion by poor pipetting techniques or self-inoculation by needle and syringe). Such exposures should be prevented by adherence to practices recommended for this risk level.

The safety of personnel handling materials of minimal risk in the prescribed manner is supported by the absence of any documented laboratory-acquired bacterial or viral infections involving known human etiologic agents that are customarily handled in the same fashion—i.e., CDC class 1 agents (see *Glossary*).

The protection of personnel from potential dangers associated with low- and moderate-risk materials is provided by a greater reliance on physical barriers separating the laboratory personnel from the experimental process as well as on safe microbiological practices. Accidental exposure by ingestion would be prevented by the adherence to the required use of mechanical pipetting for low- and moderate-risk materials. Potential exposure to low-risk materials through aerosols is reduced by the requirement that all processes that produce significant aerosols are to be confined to biological safety cabinets. Potential exposure to moderate-risk materials through aerosols is further reduced by the requirement to contain all processes that produce any aerosol. The use of Class I and Class II biological safety cabinets that comply with the standards specified in the Guidelines can reduce the potential exposure by a factor of 10,000 (1). Potential exposures of laboratory personnel not involved in these experiments are further controlled by the specified laboratory access procedures. These measures do not provide absolute protection from exposures, and the required primary barriers can be compromised by lack of attention to technique, poor placement of equipment, and human error. Experience demonstrates that the use of these measures reduces but does not prevent the potential for laboratory-acquired infections with relatively infectious agents such as class 2 and class 3 agents.

The nature of the harmful effects from exposures to low- and moderate-risk recombinant DNA materials cannot be determined. However, the ability for these materials to cause disease or injury, should they be hazardous can be estimated by comparison of their infectivity with that of known class 2 and class 3 agents. The requirement that recipient bacterial cells be class 1 agents (no or minimal risk) and that animal virus vectors be similarly low risk agents (in the absence of recombined DNA) reduces the likelihood that they will have the infectious properties of class 2 or 3 agents upon insertion of foreign DNA.

Recombinant DNA experiments assessed to have high-risk potential require special precautions designed to prevent exposures, as specified in the Guidelines. All such experimental procedures are required to be surrounded by absolute primary barriers that are gas-tight. These are barriers that physically isolate the experimental process from the laboratory worker. Research is conducted within these barriers through attached gloves. Materials are not removed from the barriers until they have been sterilized or put into hermetically sealed containers, which are then surface sterilized.

Experience with class 3 and 4 human etiologic agents demonstrates that the absolute primary barriers can be operated without exposure of the operators under standardized procedures, employing stable, well trained and well-disciplined personnel (2). This conclusion is based on those data in reference 2 that refer to the experience of recent years; the earlier experience is less relevant because of important recent developments in the design and availability of containment equipment. The procedures for combining segments of DNA and inserting them into recipient cells can be standardized, and the Guidelines require that research personnel be well trained and proficient in the necessary operational practices. Inspection and certification of all high-risk research facilities by NIH personnel provide additional assurances that these requirements will be met.

Thus, potentially harmful effects from research with high risk recombinant DNA molecules should be extremely unlikely given strict adherence to the NIH Guidelines.

Insofar as research sponsored by NIH is concerned, potentially harmful effects from experiments judged to present the possibility of very severe hazard should be prevented completely since those experiments are prohibited.

2. *Impact on the environmental spread of possibly hazardous agents.* The NIH guidelines are directly concerned with preventing the release of cells and microorganisms containing recombinant DNA molecules, or the release of recombinant DNA molecules themselves, into the environment, thus preventing potential exposures of humans, other animals and plant communities.

The Guidelines require decontamination of all liquid and solid wastes generated by low-, moderate-, or high-risk experiments. As the potential risk of these materials increases (low → high), further measures are required to increase the certainty of containment. The Guidelines recommend the decontamination of no- or minimal-risk materials before their disposal to the environment. This is standard microbiological practice.

The Guidelines prohibit the release of contaminated air under ordinary conditions. Procedures involving low- and moderate-risk materials that may produce aerosols are confined to primary barriers. Contaminants in the exhaust air from these barriers are removed by filtration.

The potential for accidental release of recombinant DNA materials into the atmosphere, however, increases with decreasing containment requirements (moderate → minimal). Harmful secondary effects from such accidental release of minimal-, low-, or moderate-risk materials are exceedingly remote. An analysis of 36 reported laboratory-acquired micro-epidemics in the period 1925–1975 involving over 1,000 infections with class 2, class 3, and class 4 human etiologic agents demonstrated no infections among persons who were never in the laboratory building or who were not associated in some way with the laboratory (2). Almost all of these outbreaks occurred in the absence of genuine efforts to control contaminated air, liquid wastes, refuse, and laundry.

Any potential release of high-risk materials to the environment should be prevented by adherence to the NIH Guidelines. All high-risk materials are required to be isolated in physically contained, absolute primary barriers. All effluents from these barriers are sterilized. The barriers themselves are located in maximum-security facilities, which are provided with additional barriers to prevent any accidental release. Air locks, negative air pressure, clothes-change rooms, filtration and incineration of all air exhausted from the facility, and the secondary sterilization of all liquid and solid wastes, provide additional protection to the environment.

The NIH Guidelines also define requirements for protecting the environment from potential dangers that may be associated with the shipment of recombinant DNA materials. Federal packaging standards appropriate for the shipment of class 4 human etiologic agents are required for the shipment of all recombinant materials.

3. *Cost impact.* The direct cost impact of the NIH guidelines is the cost of complying with their provisions. The costs will vary according to the level of potential risk of the research. There are no special facility requirements for work with minimal- and low-risk recombinant DNA materials (P1 and P2). There are equipment requirements for work involving low-risk recombinant DNA materials that will involve little cost impact. Low-risk research requires a biological safety cabinet for procedures that may produce significant aerosols and an autoclave for sterilizing waste materials. These items of equipment, however, are generally available within the existing facilities where such research is being conducted. The cost impact of the NIH guidelines on minimal- and low-risk research is therefore not significant.

Special equipment and facility requirements are specified for moderate-risk recombinant DNA research (P3). All work at this level of potential risk is to be conducted within biological safety cabinets (Class I or II). This requirement will necessitate the acquisition of many additional cabinets, the number being dependent on the scope of the research effort. It is estimated that one cabinet will be required for every three persons involved in the research. The cost of each cabinet is approximately $5,000.

Directional air flow, single-pass ventilation, and provisions for ensuring restricted access are facility requirements specified for moderate risk (P3) recombinant DNA research. While many new facilities (those constructed in the last decade) have been constructed with this capability, few older facilities can provide this capability without extensive renovation. Creating adequate access control by construction of architectural barriers (e.g., air locks, double-door alcove, etc.) is not expensive. However, th cost of renovation of air-handling systems to provide for single-pass, directional air flow may prevent some institutions from conducting moderate-risk research. It has been estimated that installation of air-handling systems that comply with the NIH Guidelines would cost approximately $200 per square foot of space serviced by the system.

The NIH Guidelines require that high-risk (P4) research involving recombinant DNA materials be conducted only in class III biological safety cabinets (glove boxes) that are installed in maximum security facilities. Fewer than 30 facilities within the United States have the potential for meeting the requirements specified in the Guidelines for such facilities. A smaller number may actually be available for this research. It is estimated that approximately $750,000 would be required to construct and equip a maximum-security facility having two 10-foot by 20-foot laboratory modules with class III cabinetry. This great cost is due to sophisticated mechanical support systems (e.g., negative pressure, exhaust air filtration, air waste treatment plant) and architectural barriers (e.g., clothes-change rooms, air locks, waste-staging areas, and monolithic walls, floors, and ceilings). The cost of class III cabinetry installed is approximately $3000 per linear foot. In addition, the cabinetry line and the facility each require a double-door autoclave, costing a minimum of $15,000 and $65,000 respectively.

4. *Secondary impacts.* There are three secondary impacts which further provide for environmental protection—i.e., reduce the potential risk to the environment from recombinant DNA research:

a. *Limited maximum-security containment capability.* The small number of facilities available to support high-risk research greatly restricts the number of such experiments that can be conducted. The reduction in the number of experiments minimizes the probability of accidental exposure of laboratory workers and subsequent secondary environmental impacts.

b. *Safety awareness.* The safe performance of biomedical research is dependent on an awareness of the risks and the safeguards required to control the risks. Issuance of the NIH Guidelines should strengthen safety performance in general by providing safety information and increasing the awareness of the laboratory worker to the potential hazards associated with biomedical research.

c. *Early recognition of potential hazards.* The Guidelines require that the principal investigator notify NIH of any serious or extended illness or accident that may result in serious exposure to man or to the environment. This monitoring procedure will provide an early warning of possible unforeseen hazard. For example, if a laboratory infection from exposure to a recombinant DNA molecule is confirmed, indicating a real hazard, an increase in safeguards or cessation of experiments can be required to minimize the hazard to other investigators conducing similar studies. This upgrading will also reduce any potential for environmental effects.

B. IMPACT OF EXPERIMENTS CONDUCTED UNDER THE GUIDELINES

1. *Possible undesirable impact*—a. *Dispersion of potentially hazardous agents.* The hypothetical mechanisms by which insertion of foreign genes into cells or viruses might result in the formation of hazardous agents are described in Section IV–C. There is, as stated before, no known instance in which a hazardous agent has been created by recombinant DNA technology. Current knowledge permits no more than speculation that such agents may be produced and an equally speculative assessment of the nature and extent of hazards that may follow upon a particulr recombinant DNA experiment. This is the underlying reason that the thrust of the Guidelines is to minimize contact of organisms containing recombinant DNA with other organisms or the environment. Therefore the following analysis of possible undesirable impacts due to dispersion of potentially hazardous agents emphasizes the likelihood of significant dispersion rather than the nature of the hazard itself. The analysis given does not apply in detail to all the possible situations, but can serve as a model for analyzing different situations.

In order that any potential hazard be realized, it is necessary that each of a number of sequential events occur. Each event in the sequence is possible only if the earlier events have occurred. The organism must—

(a) Contain foreign genes,
(b) Escape from the experimental situation,
(c) Survive after escape,
(d) Become established in an environment permitting its growth and multiplication,
(e) Contact other living organisms ih a significant manner, including contact by a sufficient number of organisms to ensure survival and growth and to cause infection. (Note that the environment in (d) may be a living organism itself).

In those cases where the detrimental effect results from the formation of a harmful protein, the organism containing the recombinant DNA must—

(f) Contain a gene for a potentially harmful protein,
(g) Be able to express the foreign gene—that is, synthesize the foreign protein,
(h) Synthesize the protein in sufficient quantity to be deleterious to the infected organism.

In those cases where the foreign DNA itself may be the cause of undesirable effects, another set of events must be considered. In the case where the foreign DNA increases the pathogenicity of the initial host cell or virus, the inserted DNA must—

(i) Impart a selective advantage for growth to the carrier of the recombinant DNA as compared with the original cell or virus,
(j) Alter the metabolism of the carrier so that it becomes disease producing.

In the case where the foreign DNA causes undesirable effects by virtue of its transfer out of the original recipient and reinsertion into cells of another species, the DNA must—

(k) Leave the original recipient without being destroyed,
(l) Survive transfer to another cell,
(m) Become associated with the other cell in a stable manner, either as an independent element or by natural recombination.

For example, in a hypothetical experiment classified as low-risk and carried out according to the requirements of the Guidelines, events (a) through (h) might be required to yield a hazardous situation. Available data might permit assignment of probabilities of : 1 for (a); of 10^{-2} (1 in 100) for (b); of 10^{-4} (1 in 10,000) for (c); and of 10^{-4} (1 in a million) for (d). Lack of any pertinent knowledge concerning events (e) through (h) would make assignment of probabilities impossible. Even assuming a probability of one for each event (e) through (h), the overall probability of a deleterious effect on a member of a species at risk in this hypothetical situation would then be the product of all probabilities (a) through (h), namely 10^{-12} (one in a trillion). This probability then needs to be compared with the number of organisms grown for the experiment. Typically, bacteria are grown in liquid mixtures to a concentration of between 10^8 and 10^{10} organisms per ml. The probability will also need to be corrected for the length of time over which the experiment is to be conducted. In reality, it may frequently be difficult to assess the relevant probabilities.

It is currently impossible to assign specific probabilities for many experiments, although crude estimates can often be made from current knowledge of laboratory-acquired infections, from prototype experiments set up to measure bacterial or viral escape (4), and from knowledge concerning the stability of organisms and DNA. NIH is currently supporting research designed to improve the ability to evaluate certain of these probabilities.

b. *Other considerations.* The foregoing descriptions of the kinds of possibly hazardous situations that might arise from organisms obtained through recombinant DNA experiments must be considered in the light of certain more general issues.

(1) *Monitoring for release of organisms containing recombined DNA.* Control of the spread of any agent outside of an experimental situation to laboratory workers or the outside environment is greatly assisted by adequate means for monitoring the agent in question. A pertinent example is the monitoring for spillage and spread of radioisotopes. The presence of radioisotopes is readily measured, and the exposure of laboratory personnel or the environment to radiation can be quantified. The situation is fundamentally different in the case of organisms or viruses containing recombined DNA. No simple general procedure exists for identifying an organism released from the laboratory against the large background level of related and unrelated organisms occurring naturally.

It is possible, however, to devise special pertinent procedures for detection of some of the agents used in recombinant DNA experiments. For example, development of bacterial strains, phages, or plasmids carrying readily detectable genetic traits would enable the monitoring of laboratory personnel, people working in the area, and their families for the presence of those agents. This would be analogous to the examination of drinking water, lakes, etc., for fecal contamination with enteric organisms. Detection in such instances could be at levels as low as 10^{-7} (1 part in 10,000,000). The adequacy of such screening is not presently known.

Given the nature of the series of events that might characterize a hazardous situation, the time factors involved in those events become relevant. Certain possible types of organisms containing recombinant DNA might, if they escaped and if they were hazardous, be immediately perceived as such—e.g., production of toxic foreign proteins. We might therefore be aware of the potential problem soon after dispersal of the organism, and reasonable means for minimizing further dispersal could be undertaken. In other instances—e.g., a cancer-producing DNA fragment—evidence of harmful effects might not be apparent for many years. The connection between the causative organisms and the observed harmful effects could be difficult to establish. Further, dispersal of the hazardous agent might then be so widespread as to make control difficult or impossible.

(2) *Natural occurrence of DNA recombination between unrelated organisms.* Concern over the potential for hazard in organisms containing recombined DNA develops from the central idea that such recombinants will be unique types of organisms, not normally arising in nature, and that their properties will therefore be unknown and unpredictable. Natural environments provide many opportunities for recombination of DNA between unrelated species, as for example, in the intestines of animals. Whether, or at what frequency, such recombinations may occur is not known at present, but it is probably low given the very low extent of shared base sequences that can be detected in DNAs derived from distantly related organisms. It would appear that naturally occurring interspecies recombinants, if they occur in nature, may have been selected against in evolution. However tests for shared base sequences are of limited sensitivity.

(3) *Relative irreversibility of spread of organisms.* Should organisms containing recombined DNA be dispersed into the environment, they might, depending on their fitness relative to naturally occuring organisms, find a suitable ecological niche for their own reproduction, and a potentially dangerous organism could then multiply and possibly spread. Subsequent cessation of experiments would not stop the diffusion of the hazardous agent. While means to eradicate the organism might be found, as in the case of smallpox, it is also possible that such means will not be available, or that they will be available too late to prevent or stop untoward events.

As described earlier, the likelihood is that newly constructed organisms will be less fit than those occurring naturally and therefore will disappear over time.

2. *Beneficial impacts of recombinant DNA research.* Section IV–C–2 describes the various anticipated benefits of recombinant DNA research. As with the possible hazards, many of the proposed benefits are speculative. Assessment of the likelihood that they will be realized will depend on information acquired from future experimentation. For example, assessment of the category of anticipated benefits that depends on the synthesis of eukaryote proteins in prokaryote cells (see IV–C–1–b) awaits additional data on the expression of the foreign genes. Should these benefits be realized, it may be expected that the cost of manufacturing certain clinically important proteins can be markedly decreased. Other clinically important proteins that are either in short supply (e.g. human growth hormone) or unobtainable by existing techniques may be made readily available. Innovative approaches to immunization against infectious diseases can also be expected.

Some of the indicted benefits appear certain. These are the benefits to be derived from an increased understanding of both basic biological processes and the mechanisms underlying a variety of disease states.

Application of the restrictions imposed by the Guidelines will retard progress toward the realization of the possible benefits. In addition to the prohibitions on certain experiments, there are many permissible experiments which will need to be postponed until the requirements in the Guidelines can be met. The acquisition and installation of P3 facilities requires adequate funds, extensive planning and installation. P4 facilities are limited in number. Experiments that require hosts and vectors with demonstrably limited ability to survive in natural environments must await development of appropriate hosts and vectors, their testing, and finally their certification by the NIH Recombinant Advisory Committee. Time will also be required for the various review processes that are required.

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APPENDIX A

GLOSSARY

1. Aerosol: A colloid of liquid or solid particles suspended in a gas, usually air.

2. Antibody: A protein which is formed in the body as a result of the inoculation of an antigen.

3. Antigen: A substance which when injected into an animal causes the formation of antibodies.

4. Autoclave: An apparatus for effecting sterilization by steam under pressure. It is fitted with a gauge that automatically regulates the pressure, and therefore the degree of heat to which the contents are subjected.

5. Bacteriophage: A virus that infects only bacteria.

6. Bid: Bureaus, Institutes, and Divisions of NIH.

7. Biohazard: A contraction of the words biological hazard; infectious agents presenting a risk or potential risk to the well-being of man, or other animals, either directly through infection or indirectly through disruption of the environment.

8. Biohazardous Agent: Any microbial unit capable or potentially capable of presenting a biohazard.

9. Biohazard Area: Any area (a complete operating complex, a single facility, a single room within a facility, etc.) in which work has been, or is being performed with biohazardous agents or materials.

10. Biohazard Control: Any set of equipment and procedures utilized to prevent or minimize the exposure of man and his environment to biohazardous agents or materials.

11. Biohazardous Material: Any substance which contains or potentially contains biohazardous agents.

12. Biowaste: Liquid wastes from biological research procedures.

13. CDC: Center for Disease Control, United States Public Health Service, Atlanta, Georgia.

14. CDC Classification of etiologic agents on the basis of hazard: A system for evaluating the hazards associated with various etiologic agents, and definition of minimal safety conditions for their management in microbiological investigations. The basis for Agent Classification is as follows:

Class 1: Agents or no or minimal hazard under ordinary conditions of handling.

Class 2: Agents of ordinary potential hazard. This class includes agents which may produce disease of varying degrees of severity from accidental inoculation or injection or other means of cutaneous penetration but which are contained by ordinary laboratory techniques.

Class 3: Agents involving special hazard or agents derived from outside the United States which require a federal permit for importation unless they are specified for higher classification. This class includes pathogens which require special conditions for containment.

Class 4: Agents that require the most stringent conditions for their containment because they are extremely hazardous to laboratory personnel or may cause serious epidemic disease. This class includes Class 3 agents from outside the United States when they are employed in entomological experiments or when other entomological experiments are conducted in the same laboratory area.

Class 5: Foreign animal pathogens that are excluded from the United States by law or whose entry is restricted by USDA administrative policy.

NOTE: Federally licensed vaccines containing live bacteria or viruses are not subject to these classifications. These classifications are applicable, however, to cultures of the strains used for vaccine production, or further passages of the vaccine strains.

15. Class I biological safety cabinet: A ventilated cabinet for personnel protection only, having an open front with inward flow of air away from the operator. The cabinet exhaust air is filtered through a high efficiency particulate air (HEPA) filter before being discharged to the outside atmosphere. This cabinet can be used for work with low- to moderate-hazard risk agents where no product protection is required.

16. Class II biological safety cabinet: An open-front cabinet for personnel and product protection with mass recirculated airflow with HEPA filtered exhaust and HEPA filtered recirculated air. This cabinet can be used for work with low- to moderate-hazard risk agents. It is not suitable for use with explosive and flammable substances, toxic agents, or radioactive materials.

17. Class III biological safety cabinet: A gas-tight cabinet providing total isolation for personnel and product protection with a HEPA-filtered air supply and a HEPA-filtered exhaust. The cabinet is fitted with gloves and is maintained under negative air pressure. This cabinet provides the highest containment reliability and should be utilized for all activities involving high-hazard risk agents.

18. Clone: A population of cells derived, by asexual reproduction, from a single cell. Every cell in the population is presumed to be genetically identical. In recombinant DNA research, every cell in a clone contains the same recombinant DNA species.

19. Coding sequence: The orderly array of codons which are subunits of a gene.

20. Chromosome: One or more small rod-shaped body(s) in the nucleus of a cell that contains genetic information for that cell. A collection of genes.

21. Deoxyribonucleic acid, or DNA: A complex substance of which genes are composed.

22. Effluent: A liquid or gas flowing from a process.

23. Endogenous: Developing or originating within the organism, or arising from causes within the organism.

24. Escherichia coli: A bacterium commonly found in the intestinal tract of animals.

25. Etiologic agent: A viable microorganism or its toxin which causes, or may cause, human disease.

26. Eukaryotic cell: A cell that contains a nucleus with a nuclear membrane surrounding multiple chromosomes; also contains extranuclear organelles.

27. Gene: The smallest portion of a chromosome that contains the hereditary information for the production of a protein.

28. Genetic engineering: Directed intervention with the content and/or organization of an organism's genetic complement.

29. Genome: The complete set of hereditary information in a cell as the chromosomes in

a eukaryote or the single chromosome in a prokaryote.

30. HEPA filter: (High Efficiency Particulate Air Filter) A disposable, extended medium, dry type filter with a particle removal efficiency of no less than 99.97% for 0.3um particles.

31. Infectious: Capable of invading a susceptible host, replicating, and causing an altered host reaction commonly referred to as a disease.

32. Laminar air flow: Air flow in which the entire body of air within a designated space moves with uniform velocity in one direction along parallel flow lines.

33. Laboratory acquired infection: Any infection resulting from exposure to biohazardous materials in a laboratory environment. Exposure may be the result of a specific accident or inadequate biohazard control procedure or equipment.

34. Messenger ribonucleic acid (mRNA): A complex molecule that transmits the information from the gene to a template on which a protein is formed.

35. Mitochondrion: A DNA-containing structure present in all aerobic eukaryotic cells. The mitochrondia produce energy for the cell and divide by fission after cell division has occurred.

36. Nucleotide: A basic unit of the polymeric structure of DNA. Each unit contains a sugar (deoxyribose), phosphoric acid, and one of the following organic substances: adenine, guanine, thymine or cytosine.

37. Oncogenesis: The process of tumor formation.

38. Organelle: An independent structural body existing within cells, generally related to a particular cellular function, and containing a special group of genes within an extrachromosomal DNA molecule (e.g., mitochrondria and chloroplasts).

39. Pathogenic: Producing or capable of producing disease.

40. Phenotype: The visible traits of an organism as determined by the genome or genotype.

41. Plasmid: A genetic element outside of the cromosome that is capable of replicating independently of the chromosome.

42. Polymer: A large molecule composed of simpler repeating units. DNA is a polymer composed of nucleotides, while starch and cellulose are polymers composed of sugars.

43. Prokaryotic organism or Prokaryote: Cells of bacteria or blue-green algae which are characterized as being rather small, having a single chromosome that is not enclosed by a nuclear membrane, and lacking organelles.

44. Restriction endonuclease: An enzyme capable of breaking DNA at specific sites. The action of the enzyme is unique in that "sticky" ends are formed which can join with other fragments of DNA to form a recombinant DNA molecule. In nature, these bacterial enzymes restrict invasion of foreign DNA.

45. Reverse transcriptase: An enzyme found in certain viruses which reverses the normal synthesis of RNA from DNA. DNA is formed for the replication of viral RNA.

46. R plasmid: A plasmid that carries genetic information for resistance to antibiotics and/or other antibacterial drugs.

47. Shotgun experiment: An experiment in which all the DNA fragments cleaved by a restriction endonuclease are inserted into a vector DNA, which is then put into a cell. This is in contrast to other recombinant DNA experiments where only selected fragments of DNA are inserted into a vector DNA.

48. Sterilize: Any act which results in the absence of all life on or in an object.

49. Vector: A carrier of a recombinant DNA molecule; usually a plasmid or bacteriophage.

50. Viable: Literally, "capable of life." Generally refers to the ability of microbial cells to grow and multiply as evidenced by, for example, formation of colonies on an agar culture medium. Frequently organisms may be viable under one set of culture conditions and not under another set, making it extremely important to define precisely the conditions used for determining viability.

Appendix B

Suggested References for Additional Reading

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Appendix C

Documents Describing the Implementation of the Guidelines

Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health

June 18, 1976.

To: Director, NIH, Through: Director, NIGMS, NIH.

From: Executive Secretary, Recombinant DNA Molecule Program Advisory Committee.

Subject: Operation of the Office of Recombinant DNA Activities (ORDA).

The proposed structure and responsibilities of an Office of Recombinant DNA Activities (ORDA) were described in Dr. Kirschstein's memorandum to you of April 28, 1976. The purpose of this document is to present our views as to how such an office can function effectively at the NIH. Consequently, the following relationships and activities are discussed:

I. *Office of the Director, NIH (OD, NIH).* The Office of Recombinant DNA Activities (ORDA) will be responsible for keeping the Office of the Director, NIH, (OD, NIH) and

particularly the Deputy Director for Science informed concerning the activities of ORDA, the status of BID extramural programs and intramural research involving recombinant DNA molecules, and on scientific and public developments which may affect NIH policy decisions and procedures regarding recombinant DNA technology. ORDA will interact with the Deputy Director for Science and the Associate Director for Collaborative Research, NIH in their capacities as chairman and vice-chairman, respectively, of the Recombinant DNA Molecule Program Advisory Committee (Recombinant Advisory Committee).

OD, NIH, in turn, should involve ORDA in all major planning activities leading to formation of NIH policies and procedures. As is current practice, the Executive Secretariat, NIH will provide ORDA with information copies of all correspondence relating to recombinant DNA matters. OD, NIH should provide ORDA with copies of outgoing correspondence, responses to Congressional inquiries, etc., to ensure that the NIH maintains uniform positions on the various matters relating to this technology.

An Executive Recombinant DNA Committee (Executive Committee) should be established in the Office of the Director, NIH. Members of the Committee would be: Deputy Director for Science (Chairman); Associate Director for Extramural Research and Training; Associate Director for Collaborative Research; Associate Director for Program Planning and Evaluation; Director, Office of Research Safety, NCI; and Associate Director for Environmental Health and Safety, DRS. The Special Assistant for Intramural Affairs will serve as Executive Secretary of the Executive Committee. There will be representation on this committee of one or more of the BIDS most involved in the support of research utilizing this technology. Problems (such as suitability of institutional biohazards committees, adequacy of review of applications, appropriateness of proposed new initiatives by BIDs, etc.) which cannot be resolved at the level of ORDA will be referred to the Executive Committee. Problems which can not be resolved at the level of the Executive Committee will be referred to the Recombinant Advisory Committee or subcommittees thereof by telephone, mail or presentation at the next meeting. The Deputy Director for Science will have the ultimate responsibility for decisions and can make urgent decisions without consultation with the committees. (OD, NIH may wish to propose an alternative approach other than the establishment of an Executive Committee).

The Deputy Director for Science, NIH, will have the responsibility for assigning to the individual BIDs various projects developed by the Executive Committee or Recombinant Advisory Committee or solicited by ORDA.

The Office of the Director, NIH will be responsible for promulgation and enforcement of regulations, and for accountability to congressional committees, DHEW, and the public. ORDA will keep the Deputy Director for Science, NIH informed of any potential problems which may lead to regulatory activities and/or need for accountability and may make appropriate recommendations in these circumstances.

II. *Dissemination of information.* The Office of the Director, NIH will be responsible for the promulgation of "Guidelines for Research Involving Recombinant DNA Molecules" (Guidelines), and should undertake the initial mass distribution of Guidelines to institutions and research laboratories through its mailing keys and use of the appropriate instrument, such as the "NIH Guide for Grants and Contracts" (NIH Guide), NIH Manual Issuance (NIH Manual), etc. Thereafter, ORDA will be responsible for distributing Guidelines and responding to requests by institutions and investigators regarding NIH policies and procedures. Dissemination of major changes in the Guidelines should also be handled as above.

The NIAID will have responsibility for publication of the "Nucleic Acid Recombinant Scientific Memoranda" (NARSM). Major announcements in NARSM, such as distribution of Guidelines, statements of NIH policies and procedures, announcements of certified host-vector systems, training courses, workshops, conferences, etc. will be coordinated with ORDA.

III. *Division of research grants.* ORDA will work with the Associate Director for Scientific Review, DRG on procedures for the review of grant applications involving recombinant DNA technology. On request, ORDA will brief executive secretaries and study sections on NIH policies and procedures.

Involvement of DRG in the processing of grant applications is discussed in Appendix A.

IV. *Institutes and divisions.* Institutes and Divisions will be required to report to ORDA on all activities involving recombinant DNA technology, including: intramural research projects, extramural grants and contracts, workshops, training courses, conferences, etc. BIDs will provide ORDA with copies of all incoming and outgoing correspondence dealing with recombinant DNA activities. Awarding components must consult with ORDA prior issuing Requests for Proposals (RFPs) and Requests for Applications (RFAs) likely to result in projects utilizing recombinant DNA technology. Procedures for obtaining information on extramural research, and for the processing of applications are proposed in Appendix A. Procedures for monitoring intramural research are proposed in Appendix B.

ORDA will be a source of information for the Institutes and Divisions, and their initial review groups, regarding current NIH policies and procedures. ORDA may establish an inter-BID Recombinant DNA Coordinating Committee to facilitate interchange of information. Because of the procedures proposed, NIH awarding components may wish to consider naming specific staff for liaison with ORDA.

V. *Special NIH relationships.* ORDA will maintain close working relationships with the Director, Office of Research Safety, NCI, the Associate Director for Environmental Health and Safety, DRS and the NIH Biohazards Committee, and will coordinate their activities on matters relating to recombinant DNA technology. The Office of Research Safety, NCI will continue to have primary responsibility for matters relating to physical containment of recombinant DNA materials, and will continue to maintain a register of high containment facilities in this country and abroad. However, plans for site inspections of P4 physical containment facilities currently or envisaged to be engaged in recombinant DNA research, and of other facilities as deemed necessary, will be coordinated through ORDA, and copies of site visit reports will be filed with ORDA.

VI. *Federal relationships.* ORDA will develop interrelationships with other federal agencies concerned with recombinant DNA technology, including but not limited to the following: National Academy of Sciences, National Science Foundation, Energy Research and Development Administration, Department of Agriculture, Environmental Protection Agency, National Aeronautics and Space Administration, and the Occupational Safety and Health Administration.

Parenthetically, it should be mentioned that representatives of the National Academy of Sciences and National Science Foundation are already attending meetings of the Recombinant Advisory Committee on a regular basis, and the National Aeronautics and Space Administration and the Energy Research and Development Administration have sent a representative to several of the meetings.

VII. *Non-Federal and international relationships.* ORDA will attempt to develop interrelationships with private foundations, professional societies, scientific journals and industry, and to coordinate NIH policies with international bodies concerned with recombinant DNA technology. The Executive Secretary of the Recombinant Advisory Committee already has a working relationship with the European Molecular Biology Organization.

VIII. *Institutional Biohazards Committees.* ORDA will receive directly from each institution involved in recombinant DNA activities the roster of its institutional biohazards committee. The minimum information should include the names, addresses, occupations and qualifications of the chairman and members of the committee. Institutions will be notified by the appropriate instrument (NIH Guide, NIH Manual, etc.) of the necessity for filing this information with ORDA.

As stipulated in the Guidelines, ORDA will assist in the formation of area biohazards committees composed of members of a given institution and/or other organizations beyond its own staff. An area committee will be necessary when expertise from outside a given institution is necessary for the biohazards committee to fulfill its functions.

ORDA will review the composition of institutional biohazards committees for compliance with the recommendations stated in the Guidelines, and will maintain updated lists of such complying committees. Serious questions about the suitability of a committee will be brought to the attention of the Executive Committee.

IX. *Information on accidents, containment and innovations.* As stipulated by the Guidelines, investigators are required to report to ORDA and to their institutional biohazards committees any serious or extended illness of a worker, or any accidents of the type described in the Guidelines. The Guidelines also require that investigators report to ORDA and their biohazards committee any problems pertaining to operation and implementation of biological and physical containment safety practices and procedures, or equipment or facility failure.

ORDA will receive from investigators information on purported EK2 and EK3 systems, and information bearing on the Guidelines, such as technical information relating to hazards and new safety procedures or innovations.

ORDA will receive and file these reports and, as appropriate bring them to the attention of the Deputy Director for Science, NIH, the Office of Research Safety, NCI, and the Recombinant Advisory Committee or subcommittees thereof. ORDA may, after review, recommend appropirate action to the Deputy Director for Science, NIH.

X. *Recombinant DNA molecule program advisory committee.* ORDA will have the management responsibilities for the Recombinant Advisory Committee, will serve as its staff, and will provide the Executive Secretary. Staff functions will include the gathering, analysis and dissemination of information, the presentation of issues, etc.

XI. *Transition and implementation.* Proposals for initial gathering of information on NIH activities in this area and implementation of the Guidelines are discussed in this Appendix C.

The relationships, responsibilities and procedures proposed in this memorandum and its appendices are wide-ranging and complex. They are, however, an attempt to describe how NIH might administer the Guidelines governing this controversial technology responsibly and effectively. I look forward to

hearing your comments and those of your staff on these proposals.

WILLIAM J. GARTLAND, Jr., Ph. D.

APPENDIX A TO APPENDIX C

PROCESSING, REVIEW, AND MANAGEMENT OF EXTRAMURAL PROJECTS INVOLVING RECOMBINANT DNA TECHNOLOGY

I. *General.* The purpose of this appendix is to discuss procedures for the processing, review and management of NIH supported projects which involve the use of recombinant DNA technology. The term "application", as used here, refers to all contract proposals and grant applications for research projects, program projects, centers, training, fellowships, research career development, etc., as defined in NIH Manual Issuance 4101: "Activity Codes, Organizational Codes and Definitions used in Extramural Programs." The procedures would apply to applications reviewed by DRG study sections and Institute and Division initial review groups.

II. *Capture of information.* One of the primary functions of the Office of Recombinant DNA Activities (ORDA) is to maintain a central register of NIH supported projects which involve recombinant DNA technology so that the NIH will know where these projects are located and will have the capability of rapidly communicating with project directors should the need arise.

In order to maintain an updated central register of projects it will be necessary for the NIH to modify application forms to indicate on the face sheet whether or not recombinant DNA technology is involved in the project. This could be modeled after the statement currently in use regarding research involving human subjects. The information would be captured, as is the case for human experimentation, and permit sorting by different parameters such as awarding component, geographic location of projects, etc.

III. *Receipt of applications.* Through the use of appropriate instrument (NIH Guide, NIH Manual, etc.), the NIH will inform applicants of the necessity for assessing the physical and biological containment required for the proposed experiments as stipulated in the NIH guidelines. This assessment must be incorporated into the application.

All applications requesting support for projects involving recombinant DNA technology will be required to have on file two documents: A Memorandum of Understanding and Agreement (MUA) and a Certification Statement (Certification) from the institutional biohazards committee. The NIH must and will require that a properly executed MUA and Certification accompany all applications proposing to use recombinant DNA technology. This will eliminate the need for tracking these documents after the application is accepted for review. The originals of these documents will be placed in the official files of the NIH awarding components with copies on file in ORDA.

IV. *Review of applications.* The executive secretaries of initial review groups are responsible for identifying all applications involving recombinant DNA technology, and for placing on the first page of every summary statement the following special note:

RECOMBINANT DNA MOLECULES—POTENTIAL BIOHAZARD

The executive secretaries are responsible for ensuring that the initial review groups make an independent assessment of the biological and physical containment levels required for the proposed experiments, and for stating in the text of the summary statement the initial review group's determination as to whether the containment levels proposed by the investigator meet the levels stipulated in the NIH guidelines. If the proposed containment levels are inadequate, the initial review group should discuss, in as much detail as possible, the inadequacies of the proposed containment and under what circumstances, if at all, the application should be eligible for funding. Initial review groups should be encouraged to disapprove applications if the proposed containment levels are so inadequate as to be irresponsible. It will be the responsibility of the awarding unit to inform applicants directly as to the fact that this was the reason for disapproval.

Executive secretaries and members of relevant initial review groups will receive a copy of the Guidelines to permit them to make these judgments. Problems relating to assessment of biological and physical containment levels proposed by investigators versus those required by the Guidelines will be referred to ORDA.

As in the case of human experimentation, national advisory councils and boards and final review bodies are expected to carefully scrutinize proposals, involving recombinant DNA technology, and make appropriate recommendations.

V. *Award of new and competing renewal projects.* Prior to the award of any project involving recombinant DNA technology, the NIH awarding component will forward to ORDA one copy of each of the following documents: The application, summary statement, MUA, Certification, any comments of the final review body, and a request for clearance to award. In those cases in which the initial or final review group, or staff of an awarding BID finds that a project requires a higher level of containment than that originally proposed by the applicant or the institution, a properly executed revised MUA and Certification Statement will be required prior to a request for approval to award. ORDA will review the documents and indicate concurrence or non-concurrence with the request for clearance to award. In the latter case, ORDA will prepare a memorandum outlining the reasons for disapproval but emphasizing that the action is independent of scientific merit or other reasons. Such a memorandum should be forwarded to the applicant through the awarding unit. In those cases in which ORDA is not able to reach a decision, or in which the awarding component or applicant disputes the decision, the decision will be submitted to the Executive Committee, and, if necessary, to the Recombinant Advisory Committee, for review. The final decision will rest with the Deputy Director for Science, NIH.

BIDs will forward to ORDA a copy of all award statements involving these applications.

ORDA will retain in its files the documents cited above. In the event that the volume of filed documents becomes excessive, ORDA will retain a copy of the face sheet of a funded application rather than the entire application. In those cases in which the proposed project involving recombinant DNA technology is but one component of a multiproject application, ORDA will retain in its files the face sheet of the application and the section(s) describing the project(s) involving recombinant DNA technology.

It must be emphasized that the primary responsibility for ensuring that applications have been properly reviewed, and that required documents are properly executed lies with NIH staff involved with the initial review groups and program areas. The procedures proposed above are intended to serve as a final review prior to award. ORDA will be available to NIH staff for advice and consultation, but it can not be expected to make decisions for review units and awarding components.

VI. *Award of non-competing renewals and incrementally-funded contracts.* Each non-competing renewal of a grant and subsequent budget period of an incrementally-funded contract utilizing recombinant DNA technology must be accompanied by an updated Certification Statement from the institutional biohazards committee. Prior to any award of this type the program official in the awarding component has the responsibility for reviewing the application for conformity with the Guidelines, for determining whether the proposed protocols do or do not require a higher level of containment than was required in the application as reviewed by the initial review group, and for ensuring that the required documents are properly executed. The program official will then forward to ORDA one copy of the application and the certification statement, along with a request for clearance to award. The latter will include a statement to the effect that the program official has reviewed the application for conformity with the Guidelines, and that the proposed containment levels are adequate. Thereafter, the procedures described in V will be followed, and BIDs will forward to ORDA a copy of all award statements involving these projects.

If the investigator proposes to significantly alter an approved protocol at the time of the non-competing renewal or subsequent budget period of an incrementally-funded contract, then the procedures described in VII must be followed. It is the responsibility of the program official to ensure that all the information and properly executed documents required in VII are present in the application prior to forwarding the request to ORDA.

VII. *Changes in awarded projects.* Since in many cases the NIH supports projects for project periods longer than one year, a number of situations will arise in funded projects. One situation arises when an investigator makes a decision to utilize recombinant DNA technology after the project has been reviewed and awarded. Another situation arises when an investigator decides to close DNA segments other than those originally reviewed, and for which higher levels of containment may be required. In these cases, and in all cases in which an investigator wishes to significantly alter an approved protocol, the investigator must first apply to the NIH awarding component for permission before proceeding. This requirement should be stated in the appropriate NIH instrument (NIH Manual, NIH Guide, etc.) The investigator will be required to submit to the awarding component a proposed protocol, an assessment of the levels of physical and biological containment required by the Guidelines, an MUA, and a Certification Statement from the institutional biohazards committee. The program official in the awarding component has the responsibility for reviewing the request in light of the Guidelines, for ensuring that the required documents are properly executed, and for forwarding to ORDA a copy of all the documents along with a recommendation. The latter should include the program official's independent assessment of the levels of physical and biological containment required by the NIH Guidelines, and a recommendation as to how to proceed. ORDA will review the request, and, when appropriate, refer the request to the initial review group, the Recombinant Advisory Committee, or ad hoc consultants.

VIII. *Requests for lowering of containment levels.* Under "characterized clones of DNA recombinants derived from shotgun experiments," the Guidelines state:

*** * * before containment conditions lower than the ones used to clone the DNA can be adopted, the investigator must obtain approval from the granting agency. Such ap-**

proval would be contingent upon data concerning: (a) The absence of potentially harmful genes (e.g., sequences contained in indigenous tumor viruses or which code for toxic substances), (b) the relation between the recovered and desired segment (e.g., hybridization and restriction endonuclease fragmentation analysis where applicable), and (c) maintenance of the biological properties of the vector.

This stipulation for NIH approval may be one of the most difficult sections of the Guidelines to implement. This is because of the technical nature of the data to be evaluated, and because of the volume of requests which can be anticipated. Therefore, the following proposed procedures are especially viewed as a feasibility trial.

An investigator who wishes to use lower levels of containment for characterized clones derived from shotgun experiments must state, in writing, the justification for the request to the program official of the NIH awarding component. Such justification will provide data on (a), (b) and (c) as stated above. The program official will retain the original request in the awarding component's file, and forward a copy to ORDA which will submit the request to the Recombinant Advisory Committee or to a subcommittee thereof for evaluation, or, if a precedent has been established, will make a decision independently. The decision will be forwarded to the program official who may appeal. The final decision rests with the Deputy Director for Science, NIH.

IX. *Large-scale experiments.* The Guidelines state that:

* * * at this time large-scale experiments (e.g., more than 10 liters of culture) with recombinant DNAs known to make harmful products are not to be carried out * * *. However, specific experiments in this category may be exempted from this rule if special biological containment precautions and equipment designed for large-scale operations are used, and provided that these experiments are expressly approved by the Recombinant DNA Molecule Program Advisory Committee.

An investigator who wishes to conduct such experiments must submit a request, along with a properly executed MUA and Certification Statement from the institutional biohazards committee, to the program official of the NIH awarding component. The program official will retain the original request in the awarding component's file, and forward copies to ORDA. ORDA will bring the request to the attention of the Recombinant Advisory Committee or subcommittees thereof, by mail, telephone, or presentation at the next meeting or, if a precedent has been established, will make a decision independently.

Appendix B to Appendix C

NIH intramural research

Because NIH intramural research projects are reviewed in a very different fashion than extramural projects, different procedures are applicable than those proposed in Appendix A.

At present, the Chief of the Laboratory in which an investigator plans to utilize recombinant DNA technology requests approval through the Scientific Director of the relevant BID to the Deputy Director for Science, NIH with copies to the Associate Director for Environmental Health and Safety, DRS. The request for approval is in the form of a draft Memorandum of Understanding and Agreement (MUA) which describes the type of experiment, nature of host-vector system, assessment of potential risk, proposed safety measures, proposed training of personnel, etc. The Deputy Director for Science then requests the NIH Biohazards Committee to review the research plan and procedures proposed in the draft MUA. The recommendations of the NIH Biohazards Committee are forwarded to the Deputy Director for Science, NIH. Recommendations of the NIH Biohazards Committee must be included in a final MUA, and the Associate Director for Environmental Health and Safety, DRS must certify that the safety measures included in the final MUA are available. The research cannot proceed until the final MUA is fully approved. The original copy of the MUA is sent to the Associate Director for Environmental Health and Safety, DRS with copies to the requesting investigator, the Laboratory Chief, the Scientific Director and the Executive Secretary of the NIH Biohazards Committee.

It is proposed here that a copy of the final MUA be forwarded to ORDA for review. If ORDA does not concure with the recommendations of the NIH Biohazards Committee, it may request the Deputy Director for Science, NIH to bring the matter to the attention of the Executive Committee or the Recombinant Advisory Committee for resolution.

ORDA will assist the NIH Biohazards Committee with problems relating to assessment of biological and physical containment levels proposed by investigators versus those required by the Guidelines, with requests for the use of lower containment levels for characterized clones derived from shotgun experiments, and with requests for permission to do large-scale experiments with recombinants known to make harmful products. ORDA will also assist the NIH Biohazards Committee in periodic review and revisions of MUAs. If ORDA does not concur with the decisions of the NIH Biohazards Committee, it may request the Deputy Director for Science, NIH to bring the matter to the attention of the Executive Committee or the Recombinant Advisory Committee.

Appendix C to Appendix C

Transition and implementation

The procedures proposed in Appendices A and B should be implemented as soon as possible. However, clearly there will be an interim period after the Guidelines are issued and before all the procedures are functioning. It is the purpose of this Appendix to propose how the Office of Recombinant DNA Activities (ORDA) might initiate coordination and gathering of information during this period.

I. *Intramural research.* ORDA will brief the Scientific Directors of the BIDs who will be expected to assure ORDA and the Deputy Director for Science, NIH of present and future compliance by intramural research scientists with the Guidelines.

ORDA will request the Deputy Director for Science, NIH to provide a copy of the final MUA on all intramural projects, utilizing recomingant DNA technology, which are already in progress. After review of the MUAs, ORDA will report any concerns to the Deputy Director for Science, NIH.

II. *Extramural programs.* ORDA will brief the Executive Committee for Extramural Affairs on NIH policies and procedures.

BIDs will be required to report to ORDA all presents or planned workshops, training courses, conferences, etc., relating to recombinant DNA technology. BIDs must also report all present or planned RPFs and RFAs likely to result in projects utilizing recombinant DNA technology. After review of this information, ORDA will report any concerns to the Deputy Director for Science, NIH and/or the Executive Committee.

With regard to active grants and contracts, BIDs will be required to submit to ORDA a copy of the application, summary statement and award statement for each currently funded project involving recombinant DNA technology. NIH awarding components will be responsible for ensuring that this reporting is as complete as possible.

BIDs will send a letter to investigators identified in the paragraph above to determine whether active research projects are in compliance with the Guidelines. Responses to this query will be retained in BID' official files, and a copy will be forwarded to ORDA for review. If ORDA is satisfied that a project is in compliance with the Guidelines, no further action is required. If the investigator reports that the project is not in full compliance with the guidelines, those aspects of the project which are not in compliance will have to be terminated. However, investigators will have the opportunity to petition the Recombinant Advisory Committee to permit continued use of characterized clones already in existence and constructed under Asilomar guidelines. Presumably, the use of these clones will be permitted to continue until the Recombinant Advisory Committee or a subcommittee thereof, has rendered its opinion.

The above procedures assume that all investigators are already at least in compliance with Asilomar guidelines. If projects are identified which appear not to be in compliance with Asilomar guidelines, they will be brought to the immediate attention of the Deputy Director for Science, NIH and the Recombinant Advisory Committee.

Appendix D

Recombinant DNA Research

Guidelines
as published in the
Federal Register, Part II,
July 7, 1976

On Wednesday, June 23, 1976, the Director, National Institutes of Health, with the concurrence of the Secretary of Health, Education, and Welfare, and the Assistant Secretary for Health, issued guidelines that will govern the conduct of NIH-supported research on recombinant DNA molecules. The NIH is also undertaking an environmental impact assessment of these guidelines for recombinant DNA research in accordance with the National Environmental Policy Act of 1969.

The NIH Guidelines establish carefully controlled conditions for the conduct of experiments involving the production of such molecules and their insertion into organisms such as bacteria. These Guidelines replace the recommendations contained in the 1975 "Summary Statement of the Asilomar Conference on Recombinant DNA Molecules." The latter would have permitted research under less strict conditions than the NIH Guidelines.

The chronology leading to the present Guidelines is described in detail in the NIH Director's decision document that follows. In summary, scientists engaged in this research called, in 1974, for a moratorium on certain kinds of experiments until an international meeting could be convened to consider the potential hazards of recombinant DNA molecules. They also called upon the NIH to establish a committee to provide advice on recombinant DNA technology.

The international meeting was held at the Asilomar Conference Center, Pacific Grove, California, in February 1975. The consensus of this meeting was that certain experiments should not be done at the present time, but that most of the work on construction of recombinant DNA molecules should proceed with appropriate physical and biological barriers. The Asilomar Conference report also

made interim assignments of the potential risks associated with different types of experiments. The NIH then assumed responsibility for translating the broadly based Asilomar recommendations into detailed guidelines for research.

The decision by the NIH Director on these Guidelines was reached after extensive scientific and public airing of the issues during the sixteen months which have elapsed since the Asilomar Conference. The issues were discussed at public meetings of the Recombinant DNA Molecule Program Advisory Committee (Recombinant Advisory Committee) and the Advisory Committee to the NIH Director. The Recombinant Advisory Committee extensively debated three different versions of the Guidelines during this period.

The Advisory Committee to the NIH Director, augmented with consultants representing law, ethics, consumer affairs and the environment, was asked to advise as to whether the proposed Guidelines balanced responsibility to protect the public with the potential benefits through the pursuit of new knowledge. The many different points of view expressed at this meeting were taken into consideration in the decision.

The NIH recognizes a special obligation to disseminate information on these guidelines as widely as possible. Accordingly, the Guidelines will be sent to all of the approximately 25,000 NIH grantees and contractors. Major professional societies which represent scientists working in this area will also be asked to endorse the Guidelines. The Guidelines will be sent to medical and scientific journals and editors of these journals will be asked to request that investigators include a description of the physical and biological containment procedures used in any recombinant research they report on. International health and scientific organizations will also receive copies of the guidelines for their review.

Filing of an environmental impact statement will provide opportunity for the scientific community, Federal, State and local agencies and the general public to address the potential benefits and hazards of this research area. In order for there to be further opportunity for public comment and consideration, these guidelines are being offered for general comment in the FEDERAL REGISTER. It must be clearly understood by the reader that the material that follows is not proposed rulemaking in the technical sense, but is a document on which early public comment and participation is invited.

Please address any comments on these draft policies and procedures to the Director, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20014. All comments should be received by November 1, 1976.

Additional copies of this notice are available from the Acting Director, Office of Recombinant DNA Activities, National Institute of General Medical Sciences, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20014.

DONALD S. FREDRICKSON, M.D.,
Director,
National Institutes of Health.

JUNE 25, 1976.

DECISION OF THE DIRECTOR, NATIONAL INSTITUTES OF HEALTH TO RELEASE GUIDELINES FOR RESEARCH ON RECOMBINANT DNA MOLECULES

JUNE 23, 1976.

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INTRODUCTION

Today, with the concurrence of the Secretary of Health, Education, and Welfare and the Assistant Secretary for Health, I am releasing guidelines that will govern the conduct of NIH-supported research on recombinant DNA molecules (molecules resulting from the recombination in cell-free systems of segments of deoxyribonucleic acid, the material that determines the hereditary characteristics of all known cells). These guidelines establish carefully controlled conditions for the conduct of experiments involving the insertion of such recombinant genes into organisms, such as bacteria. The chronology leading to the present guidelines and the decision to release them are outlined in this introduction.

In addition to developing these guidelines, NIH has undertaken an environmental impact assessment of these guidelines for recombinant DNA research in accordance with the National Environmental Policy Act of 1969 (NEPA). The guidelines are being released prior to completion of this assessment. They will replace the current Asilomar guidelines, discussed below, which in many instances allow research to proceed under less strict conditions. Because the NIH guidelines will afford a greater degree of scrutiny and protection, they are being released today, and will be effective while the environmental impact assessment is under way.

Recombinant DNA research brings to the fore certain problems in assessing the potential impact of basic science on society as a whole, including the manner of providing public participation in those assessments. The field of research involved is a rapidly moving one, at the leading edge of biological science. The experiments are extremely technical and complex. Molecular biologists active in this research have means of keeping informed, but even they may fail to keep abreast of the newest developments. It is not surprising that scientists in other fields and the general public have difficulty in understanding advances in recombinant DNA research. Yet public awareness and understanding of this line of investigation is vital.

It was the scientists engaged in recombinant DNA research who called for a moratorium on certain kinds of experiments in order to assess the risks and devise appropriate guidelines. The capability to perform DNA recombinations, and the potential hazards, had become apparent at the Gordon Research Conference on Nucleic Acids in July 1973. Those in attendance voted to send an open letter to Dr. Philip Handler, President of the National Academy of Sciences, and to Dr. John R. Hogness, President of the Institute of Medicine, NAS. The letter, appearing in "Science 181," 1114, (1973), suggested "that the Academies [*sic*] establish a study committee to consider this problem and to recommend specific actions or guidelines, should that seem appropriate."

In response, NAS formed a committee, and its members published another letter in "Science 185," 303, (1974). Entitled "Potential Biohazards of Recombinant DNA Molecules," the letter proposed:

First, and most important, that until the potential hazards of such recombinant DNA molecules have been better evaluated or until adequate methods are developed for preventing their spread, scientists throughout the world join with the members of this committee in voluntarily deferring * * * [certain] experiments * * *.

Second, plans to link fragments of animal DNAs to bacterial plasmid DNA or bacteriophage DNA should be carefully weighed * * *.

Third, the Director of the National Institutes of Health is requested to give immediate consideration to establishing an advisory committee charged with (i) overseeing an experimental program to evaluate the potential biological and ecological hazards of the above types of recombinant DNA molecules; (ii) developing procedures which will minimize the spread of such molecules within human and other populations; and (iii) devising guidelines to be followed by investigators working with potentially hazardous recombinant DNA molecules.

Fourth, an international meeting of involved scientists from all over the world should be convened early in the coming year to review scientific progress in this area and to further discuss appropriate ways to deal with the potential biohazards of recombinant DNA molecules.

On October 7, 1974, the NIH Recombinant DNA Molecule Program Advisory Committee (hereafter "Recombinant Advisory Committee") was established to advise the Secretary, HEW, the Assistant Secretary for Health, and the Director, NIH, "concerning a program for developing procedures which will minimize the spread of such molecules within human and other populations, and for devising guidelines to be followed by investigators working with potentially hazardous recombinants."

The international meeting proposed in the "Science" article (*185*, 303, 1974) was held in February 1975 at the Asilomar Conference Center, Pacific Grove, California. It was sponsored by the National Academy of Sciences and supported by the National Institutes of Health and the National Science Foundation. One hundred and fifty people attended, including 52 foreign scientists from 15 countries, 16 representatives of the press, and 4 attorneys.

The conference reviewed progress in research on recombinant DNA molecules and discussed ways to deal with the potential biohazards of the work. Participants felt that experiments on construction of recombinant DNA molecules should proceed, provided that appropriate biological and physical containment is utilized. The conference made recommendations for matching levels of containment with levels of possible hazard for various types of experiments. Certain experiments were judged to pose such serious potential dangers that the conference recommended against their being conducted at the present time.

A report on the conference was submitted to the Assembly of Life Sciences, National Research Council, NAS, and approved by its Executive Committee on May 20, 1975. A summary statement of the report was published in "Science 188," 991 (1975), "Nature 225," 442, (1975), and the "Proceedings of the National Academy of Sciences 72," 1981, (1975). The report noted that "in many countries steps are already being taken by national bodies to formulate codes of practice for the conduct of experiments with known or potential biohazard. Until these are

established, we urge individual scientists to use the proposals in this document as a guide."

The NIH Recombinant Advisory Committee held its first meeting in San Francisco immediately after the Asilomar conference. It proposed that NIH use the recommendations of the Asilomar conference as guidelines for research until the committee had an opportunity to elaborate more specific guidelines, and that NIH establish a newsletter for informal distribution of information. NIH accepted these recommendations.

At the second meeting, held on May 12–13, 1975, in Bethesda, Maryland, the committee received a report on biohazard-containment facilities in the United States and reviewed a proposed NIH contract program for the construction and testing of microorganisms that would have very limited ability to survive in natural environments and would thereby limit the potential hazards. A subcommittee chaired by Dr. David Hogness was appointed to draft guidelines for research involving recombinant DNA molecules, to be discussed at the next meeting.

The NIH committee, beginning with the draft guidelines prepared by the Hogness subcommittee, prepared proposed guidelines for research with recombinant DNA molecules at its third meeting, held on July 18–19, 1975, in Woods Hole, Massachusetts.

Following this meeting, many letters were received which were critical of the guidelines. The majority of critics felt that they were too lax, others that they were too strict. All letters were reviewed by the committee, and a new subcommittee, chaired by Dr. Elizabeth Kutter, was appointed to revise the guidelines.

A fourth committee meeting was held on December 4–5, 1975, in La Jolla, California. For this meeting a "variorum edition" had been prepared, comparing line-for-line the Hogness, Woods Hole, and Kutter guidelines. The committee reviewed these, voting item-by-item for their preference among the three variations and, in many cases, adding new material. The result was the "Proposed Guidelines for Research Involving Recombinant DNA Molecules," which were referred to the Director, NIH, for a final decision in December 1975.

As Director of the National Institutes of Health, I called a special meeting of the Advisory Committee to the Director to review these proposed guidelines. The meeting was held at NIH, Bethesda, on February 9–10, 1976. The Advisory Committee is charged to advise the Director, NIH, on matters relating to the broad setting—scientific, technological, and socioeconomic—in which the continuing development of the biomedical sciences, education for the health professions, and biomedical communications must take place, and to advise on their implications for NIH policy, program development, resource allocation, and administration. The members of the committee are knowledgeable in the fields of basic and clinical biomedical sciences, the social sciences, physical sciences, research, education, and communications. In addition to current members of the committee, I invited a number of former committee members as well as other scientific and public representatives to participate in the special February session.

The purpose of the meeting was to seek the committee's advice on the guidelines proposed by the Recombinant Advisory Committee. The Advisory Committee to the Director was asked to determine whether, in their judgment, the guidelines balanced scientific responsibility to the public with scientific freedom to pursue new knowledge.

Public responsibility weighs heavily in this genetic research area. The scientific community must have the public's confidence that the goals of this profoundly important research accord respect to important ethical, legal, and social values of our society. A key element in achieving and maintaining this public trust is for the scientific community to ensure an openness and candor in its proceedings. The meetings of the Director's Advisory Committee, the Asilomar group, and the Recombinant Advisory Committee have reflected the intent of science to be an open community in considering the conduct of recombinant DNA experiments. At the Director's Advisory Committee meeting, there was ample opportunity for comment and an airing of the issues, not only by the committee members but by public witnesses as well. All major points of view were broadly represented.

I have been reviewing the guidelines in light of the comments and suggestions made by participants at that meeting, as well as the written comments received afterward. As part of that review I asked the Recombinant Advisory Committee to consider at their meeting of April 1–2, 1976, a number of selected issues raised by the commentators. I have taken those issues and the response of the Recombinant Advisory Committee into account in arriving at my decision on the guidelines. An analysis of the issues and the basis for my decision follow:

I. General Policy Considerations

A word of explanation might be interjected at this point as to the nature of the studies in question. Within the past decade, enzymes capable of breaking DNA strands at specific sites and of coupling the broken fragments in new combinations were discovered, thus making possible the insertion of foreign genes into viruses or certain cell particles (plasmids). These, in turn, can be used as vectors to introduce the foreign genes into bacteria or into cells of plants or animals in test tubes. Thus transplanted, the genes may impart their hereditary properties to new hosts. These cells can be isolated and cloned—that is, bred into a geneticaly homogeneous culture. In general, there are two potential uses for the clones so produced: as a tool for studying the transferred genes, and as a new useful agent, say for the production of a scarce hormone.

Recombinant DNA research offers great promise, particularly for improving the understanding and possibly the treatment of various diseases. There is also a potential risk—that microorganisms with transplanted genes may prove hazardous to man or other forms of life. Thus special provisions are necessary for their containment.

All commentators acknowledged the exemplary responsibility of the scientific community in dealing publicly with the potential risks in DNA recombinant research and in calling for a self-imposed moratorium on certain experiments in order to assess potential hazards and devise appropriate guidelines. Most commentators agreed that the process leading to the formulation of the proposed guidelines was a most responsible and responsive one. Suggestions by the commentators on broad policy considerations are presented below. They relate to the science policy aspects of the guidelines, the implementation of the guidelines for NIH grantees and contractors, and the scope and impact of the guidelines nationally and internationally.

A. Science Policy Considerations

Commentators were divided on how best to steer a course between stifling research through excessive regulation and allowing it to continue with sufficient controls. Several emphasized that the public must have assurance that the controls afford adequate protection against potential hazards. In the views of these commentators, the burden is on the scientific community to show that the danger is minimal and that the benefits are substantial and far outweigh the risks.

Opinion differed on whether the proposed guidelines were an appropriate response to the potential benefits and hazards. Several found the guidelines to so exaggegrate safety procedures that inquiry would be unnecessarily retarded, while others found the guidelines weighted toward promoting research. The issue was how to strike a reasonable balance—in fact, a proper policy "bias"—between concerns to "go slow" and those to progress rapidly.

There was strong disagreement about the nature and level of the possible hazards of recombinant DNA research. Several commentators believed that the hazards posed were unique. In their view, the occurrence of an accident or the escape of a vector could initiate an irreversible process, with a potential for creating problems many times greater than those arising from the multitude of genetic recombinations that occur spontaneously in nature. These commentators stress the moral obligation on the part of the scientific community to do no harm.

Other commentators, however, found the guidelines to be adequate to the hazards posed. In their view, the guidelines struck an appropriate balance so that research could proceed cautiously. Still other commentators found the guidelines too onerous and restrictive in light of the potential benefits of this research for medicine, agriculture, and industry. Some felt that the guidelines are perhaps more stringent than necessary given the available evidence on the likelihood of hazards, but supported them as a compromise that would best serve the scientific community and the public at large. Many commentators urged that the guidelines be adopted as soon as possible to afford more specific direction to this research area.

I understand and appreciate the concerns of those who urge that this research proceed because of the benefits and of those who urge caution because of potential hazards. The guidelines issued today allow the research to go forward in a manner responsive and appropriate to hazards that may be realized in the future.

The object of these guidelines is to ensure that experimental DNA recombination will have no ill effects on those engaged in the work, on the general public, or on the environment. The essence of their construction is subdivision of potential experiments by class, decision as to which experiments should be permitted at present, and assignment to these of certain procedures for containment of recombinant organisms.

Containment is defined as physical and biological. Physical containment involves the isolation of the research by procedures which have evolved over many years of experience in laboratories studying infectious microorganisms. P1 containment—the first physical containment level—is that used in most routine bacteriology laboratories. P2 and P3 afford increasing isolation of the research from the environment. P4 represents the most extreme measures used for containing virulent pathogens, and permits no escape of contaminated air, wastes, or untreated materials. "Biological" containment is the use of vectors or hosts that are crippled by mutation so that the recombinant DNA is incapable of surviving under natural conditions.

The experiments now permitted under the guidelines involve no known additional haz-

ard to the workers or the environment beyond the relatively low risk known to be associated with the source materials. The additional hazards are speculative and therefore not quantifiable. In a real sense they are considerably less certain than are the benefits now clearly derivable from the projected research.

For example, the ability to produce, through "molecular cloning," relatively large amounts of pure DNA from the chromosomes of any living organism will have a profound effect in many areas of biology. No other procedure, not even chemical synthesis, can provide pure material corresponding to particular genes. DNA "probes," prepared from the clones will yield precise evidence on the presence or absence, the organization, and the expression of genes in health and disease.

Potential medical advances were outlined by scientists active in this research area who were present at the meeting of the Director's Advisory Committee. Of enormous importance, for example, is the opportunity to explore the malfunctioning of cells in complicated diseases. Our ability to understand a variety of hereditary defects may be significantly enhanced, with amelioration of their expression a real possibility. There is the potential to elucidate mechanisms in certain cancers, particularly those that might be caused by viruses.

Instead of mere propagation of foreign DNA, the expression of the genes of one organism by the cell machinery of another may alter the new host and open opportunities for manipulating the biological properties of cells. In certain prokaryotes (organisms with a poorly developed nucleus, like bacteria), this exchange of genetic information occurs in nature. Such exchange explains, for instance, an important mechanism for the changing and spreading of resistance to antibiotics in bacteria. Beneficial effects of this mechanism might be the production of medically important compounds for the treatment and control of disease. Examples frequently cited are the production of insulin, growth hormone, specific antibodies, and clotting factors absent in victims of hemophilia.

Aside from the potential medical benefits, a whole host of other applications in science and technology have been envisioned. Examples are the large-scale production of enzymes for industrial use and the development of bacteria that could ingest and destroy oil spills in the sea. Potential benefits in agriculture include the enhancement of nitrogen fixation in certain plants, permitting increased food production.

While the projected research offers the possibility of many benefits, it must proceed only with assurance that potential hazards can be controlled or prevented. Some commentators are concerned that nature may maintain a barrier to the exchange of DNA between prokaryotes and eukaryotes (higher organisms, with a well-formed nucleus)—a barrier that can now be crossed by experimentalists. They further argue that expression of the foreign DNA may alter the host in unpredictable and undesirable ways. Conceivable harm could result if the altered host has a competitive advantage that would foster its survival in some niche within the ecosystem. Other commentators believe that the endless experiments in recombination of DNA which nature has conducted since the beginning of life on the earth, and which have accounted in part for the evolution of species, have most likely involved exchange of DNA between widely disparate species. They argue that prokaryotes such as bacteria in the intestines of man do exchange DNA with this eukaryotic host and that the failure of the altered prokaryotes to be detected attests to a sharply limited capacity of such recombinants to survive. Thus nature, this argument runs, has already tested the probabilities of harmful recombination and any survivors of such are already in the ecosystem. The fact is that we do not know which of the above-stated propositions is correct.

The international scientific community, as exemplified by the Asilomar conference and the deliberations attendant upon preparation of the present guidelines, has indicated a desire to proceed with research in a conservative manner. And most of the considerable public commentary on the subject, while urging caution, has also favored proceeding. Three European groups have independently arrived at the opinion that recombinant DNA research should proceed with caution. These are the Working Party on Experimental Manipulation of the Genetic Composition of Micro-Organisms, whose "Ashby Report" was presented to Parliament in the United Kingdom by the Secretary of State for Education and Science in January 1975; the Advisory Committee on Medical Research of the World Health Organization, which issued a press release in July 1975; and the European Molecular Biology Organization Standing Committee on Recombinant DNA, meeting in February 1976.

There is no means for a flat proscription of such research throughout the world community of science. There is also no need to attempt it. It is likely that the evaluation engendered in the preparation and application of these guidelines will lead to beneficial review of some of the containment practices in other work that is not technically defined as recombinant DNA research.

Recombinant DNA research with which these guidelines are concerned involves microorganisms such as bacteria or viruses or cells of higher organisms growing in tissue culture. It is extremely important for the public to be aware that his research is not directed to altering of genes in humans although some of the techniques developed in this research may have relevance if this is attempted in the future.

NIH recognizes its responsibility to conduct and support research designed to determine the extent to which certain potentially harmful effects from recombinant DNA molecules may occur. Among these are experiments, to be conducted under maximum containment, that explore the capability of foreign genes to alter the character of host or vector, rendering it harmful, as through the production of toxic products.

Given the general desire that no rare and unexpected event arising from this research shall cause irreversible damage, it is obvious that merely to establish conservative rules of conduct for one group of scientists is not enough. The precautions must be uniformly and unanimously observed. Second, there must be full and timely exchange of experiences so that guidelines can be altered on the basis of new knowledge. The guidelines must also be implemented in a manner that protects all concerned—the scientific workers most likely to encounter unexpected hazards and all forms of life within our biosphere. The responsibility of the scientists involved is an inescapable and extreme as is their opportunity to beneficially enrich our understanding.

B. IMPLEMENTATION CONSIDERATIONS WITHIN THE NIH

All the commentators had suggestions concerning the structure and function of decision making as it relates to the principal investigator, the local biohazards committee, the peer review group, and the NIH Recombinant Advisory Committee. These comments and my response on the section of the guidelines relating to roles and responsibilities of investigators, their institutions, and the National Institutes of Health are presented below.

Of considerable concern to all commentators was the process by which NIH would proceed to implement the guidelines. The scientific community generally urged that there be no Federal regulations, while some of the public commentators recommended the regulatory process.

Many who opposed changing the proposed guidelines into Federal regulations expressed concern for flexibility and administrative efficiency, which could best be achieved, in their view, through voluntary compliance. Other commentators, however, believed it imperative to proceed toward regulation. In their view, the guidelines could be implemented for purposes of NIH funding and would govern the conduct of experiments until regulations were in effect. Another commentator who thought regulation would be harmful rather than helpful suggested that if there were to be regulations, they should be along lines similar to those that govern the sale, distribution, use, and disposal of radioisotopes.

The question of how best to proceed now that the guidelines have been released deserves careful attention. I share the concern of those who feel that the guidelines must remain flexible. It is especially important that there be opportunity to change them quickly, based on new information relating to scientific evidence, potential risks, or safety aspects of the research program.

The suggestions for regulation need further attention at this time. The process for regulation not only involves the Director of NIH, but also the Assistant Secretary for Health and the Secretary of Health, Education, and Welfare. These guidelines are being promulgated now in order to afford additional protection to all concerned. Consideration of their conversion to regulations can proceed with continuing review of their content and present and future implications. Meanwhile, the NIH shall continue to provide the opportunity for public comment and participation at least equivalent to that provided if steps towards regulations were to proceed immediately. The guidelines will be published in the FEDERAL REGISTER forthwith to allow for further public comment.

C. IMPLEMENTATION CONSIDERATIONS BEYOND THE PURVIEW OF NIH

Special concern has been expressed by many commentators regarding the application of the guidelines to research outside NIH by investigators other than its grantees or contractors. It has been urged that the guidelines be made applicable to recombinant DNA research conducted or supported by other agencies in HEW and by NSF, ERDA, DoD, and other governmental departments. Most commentators believe that these or similar guidelines should also govern research in the private sector, including industry, voluntary organizations, and foundations. Many feel that experiments conducted in colleges, universities, and even in high schools require some form of monitoring. And finally, all agree that in view of the potential hazards of recombinant DNA research to the biosphere, some form of international understanding on guidelines for the research is essential.

The committee, in the proposed guidelines, has suggested as one means of control that a description of the physical and biological containment procedures practiced in a research project be included in the publication of research results. In the scientific community this can be a powerful force for conformity, and we will undertake to present the recommendation to all appropriate journals. We are also prepared to take steps to disseminate the guidelines widely, and to arrange for a continual flow of information outward concerning the activities of the Re-

combinant Advisory Committee and the Advisory Committee to the Director, NIH, in the evolution of the guidelines and their implementation.

In response to these suggestions, I have already held a meeting with relevant HEW agencies and with representatives from other departments of the Federal Government. The purpose of the meeting was to exchange information on recombinant DNA research and to discuss the NIH guidelines. It served as an important beginning to address a common concern of these public institutions. A number of the representatives indicated that various departments might very well adopt the guideline for research conducted both in-house and supported outside. Following up, I have begun preliminary discussions with the Assistant Secretary for Health and the Secretary of HEW, to determine possible methods to ensure adoption of the guidelines by all Federal agencies. Encouraged by these efforts, we held a meeting on June 2 with representatives of industry to provide them with full information about the guidelines and to help determine the present and future interests of industrial laboratories in this type of research. The meeting provided one of the first opportunities for industry representatives to convene for a discussion of this research area, and an industry committee under the auspices of the Pharmaceutical Manufacturers Association will be formed to review the guidelines for potential application to the drug industry. Further meetings will be scheduled with other groups that have an active interest in recombinant DNA research.

It is my hope that the guidelines will be voluntarily adopted and honored by all who support or conduct such research throughout the United States, and that at least very similar guidelines will obtain throughout the rest of the world. NIH places the highest priority on efforts to inform and to work with international organizations, such as the World Health Organization and the International Council of Scientific Unions, with a review to achieving a consensus on safety standards in this most important research area.

There has been considerable international cooperation and activity in the past, and I expect it to continue in the future. The aforementioned Ashby Report, presented to Parliament in January 1975, describes the advances in knowledge and possible benefits to society of the experiments involving recombinant DNA molecules, and attempts to assess the hazards in these techniques. The Asilomar meeting also had a number of international representatives, as mentioned previously. The European Molecular Biology Organization (EMBO) has been involved in considering guidelines for recombinant DNA research. They have closely followed the activities of NIH, and will thus be encouraged, I believe, to monitor their research with augmented cooperation and coordination. For example, EMBO recently announced plans for a voluntary registry of recombinant DNA research in Europe. Following this EMBO initiative, NIH shall similarly maintain a voluntary registry of investigators and institutions engaged in such research in the United States. Plans for establishing this registry are under way.

D. ENVIRONMENTAL POLICY CONSIDERATIONS

A number of commentators urged NIH to consider preparing an environmental impact statement on recombinant DNA research activity. They evoked the possibility that organisms containing recombinant DNA molecules might escape and affect the environment in potentially harmful ways.

I am in full agreement that the potentially harmful effects of this research on the environment should be assessed. As discussed throughout this paper, the guidelines are premised on physical and biological containment to prevent the release or propagation of DNA recombinants outside the laboratory. Deliberate release of organisms into the environment is prohibited. In my view, the stipulated physical and biological containment ensures that this research will proceed with a high degree of safety and precaution. But I recognize the legitimate concern of those urging that an environmental impact assessment be done. In view of this concern and ensuing public debate, I have reviewed the appropriateness of such an assessment and have directed that one be undertaken.

The purpose of this assessment will be to review the environmental effects, if any, of research that may be conducted under the guidelines. The assessment will provide further opportunity for all concerned to address the potential benefits and hazards of this most important research activity. I expect a draft of the environmental impact statement should be completed by September 1 for comment by the scientific community, Federal and State agencies, and the general public.

It should be noted that the development of the guidelines was in large part tantamount to conducting an environmental impact assessment. For example, the objectives of recombinant DNA research, and alternate approaches to reach those objectives, have been considered. The potential hazards and risks have been analyzed. Alternative approaches have been thoroughly considered, to maximize safety and minimize potential risk. And an elaborate review structure has been created to achieve these safety objectives. From a public policy viewpoint, however, the environmental impact assessment will be yet another review that will provide further opportunity for the public to participate and comment on the conduct of this research.

II. METHODS OF CONTAINMENT

Comments on the containment provisions of the proposed guidelines were directed to the definitions of both physical and biological containment and to the safety and effectiveness of the prescribed levels. Several commentators found the concept of physical containment imprecise and too subject to the possibility for human error. Others questioned the concept of biological containment in terms of its safety and purported effectiveness in averting potential hazards. The commentators were divided on which method of containment would provide the most effective and safe system to avoid hazards. Several suggested that each of the physical containment levels be more fully explained.

W. Emmett Barkley, Ph.D., Director of the Office of Research Safety, National Cancer Institute, was asked to review the section on physical containment in light of these comments. Dr. Barkley convened a special committee of safety and health experts, who met to consider not only this section of the guidelines but also the section of the roles and responsibilities of researchers and their institutions. The committee thoroughly reviewed the section on physical containment and recommended a number of changes. The Recombinant Advisory Committee, meeting on April 1–2, 1976, reviewed the recommendations of the Barkley group. These are incorporated, with editorial revisions, in the final version of the guidelines.

The present section on physical containment is directly responsive to those commentators who asked for greater detail and explanation. Although different in detail, the four levels of containment approximate those given by the Center for Disease Control for human etiologic agents and by the National Cancer Institute for oncogenic viruses. For each of the proposed levels, optional items have been excluded, and only those items deemed absolutely necessary for safety are presented. Necessary facilities, practices, and equipment are specified. To give further guidance to investigators and their institutions, a supplement to the guidelines explains more fully safety practices appropriate to recombinant DNA research. And a new section has been added to ensure that shipment of recombinant DNA materials conforms, where appropriate, to the standards, prescribed by the U.S. Public Health Service, the Department of Transportation, and the Civil Aeronautics Board.

The section on physical containment is carefully designed to offer a constructive approach to meeting potential hazards for recombinant experiments at all levels of presumed risk. Certain commentators had suggested that the first level of physical containment (P1) be merged with the second level (P2). This suggestion, however, would tend to apply overly stringent standards for some experiments and might result in a lowering of standards necessary at the second level. I believe the level of control must be consistent with a reasonable estimate of the hazard; and the section on physical containment does provide this consistency. Accordingly, the first and second levels of physical containment remain as separate sections in the guidelines.

Because of the nature and operation of facilities required for experiments to be done at the fourth level of containment (P4), a provision has been included that the NIH shall review such facilities prior to funding them for recombinant DNA studies. The situation merits the special attention of experts who have maximum familiarity with the structure, operation, and potential problems of P4 installations. Several commentators advocated that NIH arrange for sharing of P4 facilities, both in the NIH intramural program and in institutions supported through NIH awards. In response to these suggestions, we are currently reviewing our facilities, including those at the Frederick Cancer Research Center (Fort Detrick), to determine how such a program can best be devised. It is most important that P4 facilities be made available to investigators. It should be noted that incidents of infection by even the most highly infectious and dangerous organisms are extremely infrequent at P4 facilities, and therefore the potential for hazard in certain complex experiments in recombinant DNA research is considerably reduced.

III. PROHIBITED EXPERIMENTS

1. Practically all commentators supported the present prohibition of certain experiments. There were suggestions for a clearer definition of the prohibition of certain experiments where increased antibiotic resistance may result. And it was urged by some that the prohibition be broadened to include experiments that result in resistance to any antibiotic, irrespective of its use in medicine or agriculture. Consideration of such a suggestion must take into account that antibiotic resistance occurs naturally among bacteria, and that resistance is a valuable marker in the study of microbial genetics in general and recombinants in particular.

In view of these concerns, however, the Recombinant Advisory Committee was asked to reconsider carefully the prohibition and related sections concerning antibiotic resistance. The committee noted that the prohibition relating to drug resistance was intended to ban those experiments that could compromise drug use in controlling disease agents in veterinary as well as human medicine and this is now clearly stated.

In the draft guidelines there were two statements concerning resistance to drugs which related to experiments with *E. coli*. The statements appeared to allow experi-

ments that would extend the range of resistance of this bacterium to therapeutically useful drugs and disinfectants, and thus seemed to be in conflict with the general prohibition on such research. There are numerous reports in the scientific literature indicating that E. coli can acquire resistance to all antibiotics known to act against it. Since E. coli acquires resistance naturally, the prohibition directed against increasing resistance does not apply. The ambiguous statements have been deleted from the present guidelines. On the other hand, new language has been inserted in the section dealing with other prokaryote species to set containment levels for permitted experiments.[1]

2. The Recombinant Advisory Committee was also asked to clarify whether the prohibition of use of DNA derived from pathogenic organisms (those classified as 3, 4, and 5 by the Center for Disease Control, USPHS) also included the DNA from any host infected with these organisms. The committee explained that this prohibition did extend to experiments with cells known to be so infected. To avoid misunderstanding, the prohibition as now worded includes such cells. In addition, the prohibitions have been extended to include moderate-risk oncogenic viruses, as defined by the National Cancer Institute, and cells known to be infected with them.

3. Two other issues relating to the section on prohibited experiments were raised by Roy Curtiss III, Ph.D., Professor, Department of Microbiology, University of Alabama School of Medicine, Birmingham, who is a member of the Recombinant Advisory Committee. Dr. Curtiss noted that for the class of experiments prohibited on the basis of production of highly toxic substances, only substances from microorganisms were cited as examples. He suggested that other examples be included, such as venoms from insects and snakes. The committee approved the suggestion and I concur.

In the proposed guidelines, release of organisms containing recombinant DNA molecules into the environment was prohibited unless a series of controlled tests had been done to leave no reasonable doubt of safety. Dr. Curtiss felt that the guidelines should provide greater specificity for testing and should include some form of review prior to release of the organism. I have decided that the guidelines should, for the present, prohibit any deliberate release of organisms containing recombinant DNA into the environment. With the present limited state of knowledge, it seems highly unlikely that there will be in the near future, any recombinant organism that is universally accepted as beig beneficial to introduce into the environment. When the scientific evidence becomes available that the potential benefits of recombinant organisms, particularly for agriculture, are about to be realized, then the guidelines can be altered to meet the need for release. It is most important that the potential environmental impact of the release be considered.

IV. Permissible Experiments: E. coli K–12 Host-Vector Systems

The continued use of E. coli as a host has drawn considerable comment, including some suggestions that its use be prohibited presently or within a specified time limit. It should be stressed that the use of E. coli as detailed in the guidelines is limited to E. coli K–12, a strain that has been carried in the laboratory for decades, and does not involve the use of any strain of E. coli that is freshly isolated from a natural source. E. coli K–12 does not usually colonize the normal bowel, even when given in large doses, and exhibits little if any muliplication while passing through the alimentary canal. For years it has been the subject of more intense investigation than any other single organism, and knowledge of its genetic markup and recombinant behavior exceeds greatly that pertaining to any other organism. I believe that because of this experience, E. coli K–12 will provide a host-vector system that is safer than other candidate microorganisms.

NIH recognizes the importance of supporting the development of alternative host-vector systems (such as B. subtilis, which has no ecological niche in man) and will encourage such development. It should be noted, however, that for each new host-vector system, the same questions of risk from altered properties attendant upon the presence of recombinant genes will apply as apply to E. coli. NIH does not believe it wise to set a time limit on replacement of E. coli systems by other organisms.

There were specific suggestions concerning the three levels of biological containment prescribed for use of E. coli K–12 vectors. Some commentators requested a more detailed explanation of the adequacy of protection for laboratory personnel with the first level of containment (EK1).[2] Sections of the guidelines dealing with physical containment and roles and responsibilities now specify the need for safety practices and accident plans.

For the second level of containment (EK2), it is required that a cloned DNA fragment be contained in a host-vector system that has no greater than a 10–8 probability of survival in a nonpermissive or natural environment. It was suggested that the selection of this level of biological containment and the appropriate tests for vertification be more fully explained in the guidelines. The committee, in responding to a request for further examination of this point, reviewed at considerable length the testing for an EK2 system and recommended certain modifications. We have accepted the committee's new language that better explains testing of survival of a genetic marker carried on the vector, preferably on an inserted DNA fragment.

Possible tests to determine the level of biological containment afforded by these altered host-vector systems are outlined in this section. Because this is such a new area of scientific research and development, however, it is inappropriate to standardize such testing at the present time. Standards will gradually be set as more experience with EK2 host-vector systems is acquired. The committee, for example, during its April 1976 meetings gave its first approval to an EK2 host-vector system. What is necessary is that new and more effective tests be devised by investigators, and this effort is very likely to occur under the present guidelines. For example, one task recognized by the committee is to clarify how survival of the organism and the cloned DNA should be defined in terms of temperature, medium, and other variables.

It is also very important to note here that the stringent requirements set by the committee for EK2 biological containment jeopardize considerably the capacity of such crippled organisms to survive and replicate even under permissive laboratory conditions. More experience will be required to determine whether EK2 containment will permit some lines of important research to be followed.

Several commentators suggested that methods and procedures to confirm an EK system at the third level of containment (EK3) be more fully explained. The Recombinant Advisory Committee was asked to consider this suggestion. After considerable discussion the committee declined to define the procedures more fully at this time, because development of an EK3 system is still far enough in the future not to warrant specific testing procedures. Further, it is not clear what tests are best suited. The language, therefore, remains general. The committee, however, is aware of the concerns for a more completely defined system of testing, and has considered the possibility of organizing a symposium for purposes of designating tests. In my view, more fully developed protocols for testing EK3 systems are warranted, and it is necessary that guidelines here be more fully developed before the committee proceeds to certify such a system. In this regard the NIH is prepared through the National Institute of Allergy and Infectious Diseases to support contracts to accomplish this task. We will seek the advice and assistance of the committee to define the scope of necessary work.

These guidelines also include a statement that for the time being no EK2 or EK3 host-vector system will be considered bona fide until the Recombinant Advisory Committee has certified it. I share the concern of the commentators that new host-vector systems require the highest quality of scientific review and scrutiny. At this early stage of development, it is most important that the committee provide that scrutiny. Further, I believe that until more experience has been gained, the committee should encourage and the NIH support research that will independently confirm and augment the data on which certification of EK2 host-vector systems are based.

V. Classification of Experiments Using the E. Coli K–12 Containment Systems

The guidelines assign different levels of containment for experiments in which DNA from different sources is to be introduced into an *E. coli* K–12 host-vector system. The variation is based on both facts and assumptions. There are some prokaryotes (bacteria) which constantly exchange DNA with *E. coli*. Here it is assumed that experimental conditions beyond those obtained in careful, routine microbiology laboratories are superfluous, because any exchange experiments have undoubtedly been performed already in nature.

In every instance of artificial recombination, consideration must be given to the possibility that foreign DNA may be translated into protein (expressed), and also to the possibility that normally repressed genes of the host may be expressed and thus change, undesirably, the characteristics of the cell. It is assumed that the more similar the DNAs of donor and host, the greater the probability of expression of foreign DNA, or of possible derepression of host genes. In those cases where the donor exchanges DNA with *E. coli* in nature, it is unlikely that recom-

[1] Specifically, experiments that would extend resistance to therapeutically useful drugs must use P3 physical containment plus a host-vector comparable to EK1, or P2 containment plus a host-vector comparable to EK2.

[2] The EK1 system presently consists of a battery of different vectors and of E. coli K–12 mutants, all of which afford a considerable degree of biological containment. The diversity of vectors and of host mutants in this battery has permitted a wide range of important scientific questions to be attacked. For example, the availability of different vectors with cleavage sites for different restriction endonucleases have increased the kind of DNA segments that can be cloned. By contrast, the first EK2 host-vector systems are only now being considered by the Recombinant Advisory Committee. While NIH is supporting the development of more EK2 host-vector systems, it is not expected that a battery equivalent to that available for the EK1 system will be certified by the Recombinant Advisory Committee in the near future.

bination experiments will create new genetic combinations. When prokaryote donors not known to exchange DNA with *E. coli* in nature are used, however, there is a greater potential for new genetic combinations to be formed and be expressed. Therefore, it is required that experiments involving prokaryotic DNA from a donor that is not known to exchange DNA with *E. coli* in nature be carried out at a higher level of containment. Recombination using prokaryotic DNA from an organism known to be highly pathogenic is prohibited.

There are only limited data available concerning the expression of DNA from higher forms of life (eukaryotes) in *E. coli* (or any other prokaryote). Therefore, the containment prescriptions for experiments inserting eukaryotic DNA into prokaryotes are based on risks having quite uncertain probabilities.

On the assumption that a prokaryote host might translate eukaryotic DNA, it is further presumed that the product of that foreign gene would be most harmful to man if it were an enzyme, hormone, or other protein that was similar (homologous) to proteins already produced by or active in man. An example is a bacterium that could produce insulin. Such a "rogue" bacterium could be of benefit if contained, a nuisance or possibly dangerous if capable of surviving in nature. This is one reason that the higher the phylogenetic order of the eukaryote, the higher the recommended containment, at least until the efficiency of expression of DNA from higher eukaryotes in prokaryotes can be determined.

There is a second, more concrete reason for scaling containment upward as the eukaryote host becomes similar to man. This is the concern that viruses capable of propagating in human tissue, and possibly causing diseases, can contaminate DNA, replicate in prokaryote hosts and infect the experimentalist. Such risks are greatest when total DNA from donor tissue is used in "shotgun" recombinant experiments; it diminishes to much lower levels when pure cloned DNA is used.

The commentators were clearly divided on the classification of containment criteria for different kinds of recombinant DNAs. Many commentators considered the guidelines too stringent and rigid. Others viewed the guidelines in certain instances as too permissive. And still others endorsed the guidelines as sensible and reasonable, affording the public an enormous degree of protection from the speculative risks. Several suggestions were made for the specific classes of experiments, and they follow:

1. Comment on the use of DNA from animals and plants in recombinant experiments varied widely. Some commentators suggested banning the use of DNA from primates, other mammals, and birds. Others suggested that higher levels of the containment be used for all such experiments. Still others believed that the guidelines were too strict for experiments of this class. I have carefully reviewed the issues raised by the commentators and the response of the committee to certain queries concerning use of animal and plant DNA in these experiments.

In my view, the classification for the use of DNA from primates, other mammals, and birds is appropriate to the potential hazards that might be posed. The physical and biological containment levels are very strict. For example, biological containment levels are at EK2 or EK3, and will effectively preclude experimentation until useful EK2 and EK3 systems are available. EK2 systems are still in the initial stages of development, and the first system was only certified at the most recent meeting of the Recombinant Advisory Committee. An EK3 host-vector system has yet to be tested, and its certification is far enough in the future to place a moratorium on those experiments requiring biological containment at an EK3 level. The physical containment levels of P3 or P4 themselves afford a very high degree of protection. I am satisfied that the guidelines demonstrate the caution and prudence that must govern the conduct of experiments in this category.

The guidelines allow reduced containment levels for primate DNA when it is derived from embryonic tissue or germ-line cells. This is based on evidence that embryonic material is less likely to contain viruses than is tissue from the adult. Obviously, the embryonic tissue must be free of adult tissue, and the present guidelines so indicate.

I have also carefully considered the special concerns arising from the use of DNA from cold-blooded vertebrates and other cold-blooded animals, because several commentators questioned the basis of lower physical and biological containment levels for DNA from these species. The Recombinant Advisory Committee has debated this extensively, and they were asked to do so once again in April.[a] The committee has now recommended high containment levels (P3+EK2) when the DNA is from a cold-blooded vertebrate known to produce a potent toxin. That recommendation is included in the present guidelines. Where no toxin is involved the committee supported lower containment levels. The guidelines specify P2+EK2 levels for such work. There was considerable discussion concerning the advisability of recommending lower containment (P2+EK1) when the DNA is isolated from embryonic tissue or germ-line cells from cold-blooded vertebrates. Those supporting lower containment levels argued that the justification for P2+EK2 was the possibility that cold-blooded vertebrates may carry viruses and that the distinction between adult and germ cell tissue is real. Others argued that, contrary to the situation with primate DNA, viruses are not a central problem with cold-blooded vertebrates and therefore no distinction should be made on the basis of tissue origin. Finally, the committee recommended, on a divided vote (8 to 4), to adopt P2+EK1 when the cold-blooded vertebrate DNA is isolated from embryonic tissue or germ-line cells. Upon reviewing these considerations, I have decided to retain the containment levels for embryonic or germ-line DNA from cold-blooded vertebrates as recommended by the committee.

In April the committee also reviewed, at our request, the classification of experiments where DNA is derived from other cold-blooded animals or lower eukaryotes. Several commentators, for example, had been concerned about the fact that insects are known to carry agents pathogenic to man. In the committee review, it was noted that viruses carried by insects and known to transmit disease to man are RNA rather than DNA viruses and do not reproduce via DNA copied from RNA. In order, however, to make the intent clearer, the guidelines have been rewritten for experiments of this class. New language is inserted to ensure that strict containment levels are employed when the DNA comes from known pathogens or species known to carry them. Further, to reduce the potential hazards, we have also included in the guidelines the requirement that any insect must be grown under laboratory conditions for at least 10 generations prior to its use as a DNA source.

2. As alluded to above, certain commentators expressed concern that when *E. coli* becomes the host of recombinant DNA from prokaryotes with which DNA is not usually exchanged, there is hazard of altered host characteristics resulting from translation of the DNA into functioning proteins. The committee was asked to review the guidelines and take into account this potential hazard. They agreed that the containment levels should be increased for this category of experiment, from P2+EK1 to either P2+EK2 or P3+EK1. That recommendation is included in the present guidelines.

Comments were made concerning that class of experiments in which the recombinant DNA, regardless of source, has been cloned. A clone is a population of cells derived from a single cell and therefore all the cells are presumed to be genetically identical. As outlined in the proposed guidelines, clones could be used at lower containment levels if they had been rigorously characterized and shown to be free of harmful genes. Several commentators inquired how the characterization was to be performed and the freedom from harmful genes demonstrated. Although the committee acknowledges that these terms are unavoidably vague, they do cite appropriate scientific methods to make relevant determinations. Again, this is a rapidly changing area and more clarity and precision can be expected with experience. Reduced containment requirements for this class of experiment are warranted because of the purified nature of clones. Further, the granting agency must approve the clone before containment conditions can be reduced, thus providing an additional element of review.

4. Another comment was related to the use of DNA from organelles (intracellular elements that contain special groups of genes for particular cell functions). Concern was expressed about the potential contamination of purified organelle DNA with DNA from viruses because of the similarity of their structures. The committee agrees, and the guidelines now specify a requirement, that the organelles be isolated prior to extracting DNA, as a further means of reducing the hazard of viral contamination.

5. Some commentators were troubled about the lowering of containment for that class of experiments involving recombinations with cell DNA segments purified by chemical or physical methods. They asked that procedures for determining the state of purification be more fully detailed and that the Recombinant Advisory Committee certify the purity. There are, however, appropriate techniques, such as gel electrophoresis, with which a purity of 99 percent by mass can be achieved and ascertained. There is no way for the committee to certify these results beyond repeating the experiments themselves. These techniques are well documented and described in the literature. I do not believe it is necessary or feasible for the committee to review each procedure for purification of DNA.

6. Comments were made concerning the use of DNA derived from animal viruses. It

[a] A committee member, David S. Hogness, Ph. D., Professor, Department of Biochemistry, Stanford University, California, submitted a statement in support of lower containment levels based on current scientific evidence. That evidence is based on certain differences between cold- and warm-blooded vertebrates. One of the criteria used for the evaluation of the relative risk that might be encountered with different levels of shotgun experiment is the degree of sequence homology between the DNA of the given species and that of humans. This criterion is used to estimate the likelihood that segments of DNA from the given species might be integrated into the human genome by recombination; the greater the homology, the greater the likelihood of integration. Studies of sequence homologies indicate that there is a considerable degree of homology between human DNA and DNA from other primates, much less homology between primates and other mammals, and even lower but detectable homology between birds and primates. By contrast, no significant homologies between cold-blooded vertebrates and primates have been detected.

was urged that containment levels for this class of experiment be increased. On the basis of my review, I find the containment conditions appropriate to the potential hazard posed. As defined in the guidelines, experiments are to be done at very strict levels of containment and these can be lowered only when the cloned DNA recombinants have been shown to be free of possibly harmful genes by suitable biochemical and biological tests. This also pertains to DNA that is copied from RNA viruses. In no instance are the guidelines more lenient, and in most instances they are more stringent than conditions obtaining in many laboratories where such viruses are studied in non-DNA-recombinant experiments.

VI. Classification of Experiments Using Containment Systems Other than E. Coli K–12

1. No issue with regard to these guidelines raised more comment than the use of animal viruses as vectors. Of special concern to many commentators was the use of the simian (monkey) virus 40 (hereafter "SV40"). Some suggested a complete ban on the use of this virus; others urged its retention as a vector. SV40 is not known to produce any disease in man, although it can be grown in human cells and on very rare occasions has been isolated from humans. Many humans have received SV40 virus inadvertently in vaccines prepared from virus grown in monkey kidney-cell cultures. An intensive search has been made and is continuing for evidence that SV40 might cause cancer or be otherwise pathogenic for man. At present, it is my view that the extensive knowledge we have of SV40 virus provides us with sufficient sophistication to ensure its safe handling under the conditions developed for its use in the guidelines.

I believe work with SV40 should continue under the most careful conditions, but I do recognize and appreciate the concerns expressed over its possible harmful effects in humans. In light of these concerns, I asked the Recombinant Advisory Committee to review this section of the guidelines. The committee reconsidered the containment conditions for this class of experiments and judged them appropriate to meet the potential hazards.[4]

This class of experiments will proceed under the most careful and stringent conditions. Work with SV40 virus will be done at the maximum level of physical containment (P4). The extraordinary precautions required in a P4 facility lessen the likelihood of a potential hazard from this work. Only defective SV40 virus will be used as vector; that is, the SV40 virus particles that carry the foreign DNA cannot multiply by themselves. When a number of strict conditions are met, this work will be permitted to go on at the third level of containment (P3), which in itself requires care and precision. It should be noted that SV40 virus and its DNA can be efficiently disinfected by Clorox and autoclaving. These are customary procedures for disinfecting glassware and other items used in SV40 animal-cell work.

Some commentators suggested that the containment criteria for experiments using polyoma virus as the vector be strengthened. There is no evidence that polyoma infects humans or replicates to any significant extent in human cells. It holds promise as a vector, as is more fully documented in an appendix to these guidelines.

[4] One member dissented from this position. During the discussion, additional language was recommended (and adopted) to ensure that the defective SV40-virus/helper-virus system, with its inserted non-SV40 DNA segment, does not replicate in human cells with significantly more efficiency than does SV40.

2. Several commentators found the guidelines inadequate regarding experiments with plant host-vector systems. Because NIH shared these concerns, a group of extensive experience with plants was appointed to review this section. The group met concurrently with the Recombinant Advisory Committee in April 1976 and made several modifications. The suggested revisions were acceptable to the full committee, and we have included them in the guidelines.

The modifications are responsive to the stated concerns of the commenators. A description of greenhouse facilities is given, and physical containment conditions have been modified to take into account operations with whole plants. On the whole the respective portions of the guidelines relating to plants are more fully explained and the intent is clarified.

I have also accepted the recommendation of the subcommittee to lower the biological containment level from EK2 to EK1 for experiments in which the DNA from plants is used in conjunction with the *E. coli* K–12 host-vector system, thereby setting containment in this instance at the same level required for experiments with lower-eukaryote DNA.

VII. Roles and Responsibilities

1. Most commentators had suggestions for the section on the roles and responsibilities of investigators, their local institutions, and NIH. Commentators generally urged openness, candor, and public participation in the process, emphasizing shared responsibility and accountability from the local to the national level. We reviewed that section of the guidelines in light of these comments and have asked the Recombinant Advisory Committee to review certain issues.

It is clear that much of the success of the guidelines will lie in the wisdom with which they are implemented. Because of the importance of this section, especially in terms of safety programs and plans, we have carefully weighed the comments and suggestions made in this regard. NIH has a special responsibility to take a leading role in ensuring that safety programs are part of all recombinant DNA research. Dr. Barkley and a specially convened committee were asked to provide greater detail for safety, accident, and training plans for this section of the guidelines. Based on their recommendations, the section has been extensively rewritten to clarify the respective responsibilities of the principal investigator, the institution (including the institutional biohazards committee), the NIH initial review group (study section), the NIH Recombinant DNA Molecule Program Advisory Committee, and NIH staff.

This section has a definitive administrative framework for assuring that safety is an essential and integrated component of research involving recombinant DNA molecules. The guidelines require investigators to institute, monitor, and evaluate containment and safety practices and procedures. Before research is done, the investigator must have safety and accident plans in place and training exercises for the staff well under way.

Some commentators suggested that the investigator be required to obtain informed consent of laboratory personnel prior to their participation. Rather than rely explicitly on an informed consent document, the guidelines now make the investigator responsible for advising his program and support staff as to the nature and assessment of the real and potential biohazards. He must explain and provide for any advised or requested precautionary medical policies, vaccinations, or serum collections. Further, an appendix to the guidelines includes detailed explanations for dealing with accidents, as well as instructions for the training of staff in safety and accident procedures.

In response to suggestions for epidemiological monitoring, the guidelines now require the principal investigator to report certain categories of accidents, in writing, to appropriate officials. NIH is investigating procedures for long-term surveillance of workers engaged in recombinant DNA research.

2. A number of comments on the role and responsibilities of the institutional biohazards committee were received. Comments were directed to the structure of the committee, the scope of its responsibility, and the methods for operation. Comments on structure included suggestions that the committee have a broadly based representation, especially in terms of health and safety expertise. Some others suggested NIH require certain classes of representation. In response to these suggestions, the guidelines now recommend membership from a diversity of disciplines relevant to recombinant DNA molecule technology, biological safety, and engineering.

For broader representation beyond the immediate scientific expertise, the guidelines now recommend that local committees should possess, or have available, the competence necessary to determine the acceptability of their findings in terms of applicable laws, regulations, standards of practice, community attitudes, and health and environmental considerations. The names of and relevant background information on the committee members will be reported to NIH.

In response to suggestions that decisions of the committee be made publicly available, the guidelines now recommend that minutes of the meetings should be kept and made available for public inspection.

Commentators generally approved of the responsibility given to the institutional biohazards committee to serve as a source of advice and reference to the investigator on scientific and safety questions. It was further suggested that the committee's responsibility be broadened in the development, monitoring, and evaluation of safety standards and procedures. In response to these suggestions, the guidelines now indicate that the institutional biohazards committee has the responsibility to certify, and recertify annually, to NIH that the facilities, procedures, practices, training, and expertise of involved personnel have been reviewed and approved. The Recombinant Advisory Committee suggested that examination might be unnecessary for P1 facilities, but we believe that all facilities should be reviewed to emphasize the importance of safety programs.

Some commentators suggested that the guidelines should stipulate that the local committees be required to determine the containment conditions to be imposed for a given project (which the draft guidelines specifically noted was not their responsibility). The Recombinant Advisory Committee took exception to this suggestion. They urged NIH not to include these conditions as local requirements, arguing among other things that review by the NIH study sections would provide the necessary scrutiny at the national level and assure uniformity of standards in application of the guidelines. I do not believe that NIH should require the local institution to have its biohazards committee assess what containment conditions are required for a given project. On the other hand, the guidelines should not prohibit the local institution from having its biohazards committee perform this function. Accordingly, I have deleted the prohibition that appeared in the proposed guidelines.

Another suggestion was that the local committee ensure that research is carried out in accordance with standards and procedures under the Occupational Safety and Health

Act (OSHA). This is an area of importance to the local institutions under Federal and State law, but need not be included as a requirement in the guidelines. NIH will maintain liaison with the Occupational Safety and Health Administration (Department of Labor) to ensure maximum Federal cooperation in this venture.

I would also encourage all institutions, as suggested by several commentators, to review their insurance compensation programs to determine whether their laboratory personnel, in the research area, are covered for injuries.

3. The commentators approved of having the NIH study sections responsible for making an independent evaluation of the classification of the proposed research under the guidelines, along with the customary judgment of the scientific merit of each grant application. This additional element of review will ensure careful attention to potential hazards in the research activity. The study sections will also scrutinize the proposed safeguards. Biological safety expertise shall be available to the study section for consultation and guidance in this regard.

4. Several commentators made suggestions concerning the structure, function, and scope of responsibility of the NIH Recombinant DNA Molecule Program Advisory Committee.

Comments on possible structural mechanisms for decision making included suggestions that there be a scientific and technical committee and a general advisory public policy committee. It was also suggested that the scientific committee include scientists who are not actively engaged in recombinant research, and that the public policy committee have a broad scientific and public representation.

I have carefully reviewed these comments and suggestions. In response, the following structure has been devised. The Recombinant Advisory Committee shall serve as the scientific and technical committee. Its membership shall continue to include scientists who represent disciplines actively engaged in recombinant DNA research. In my view, it is most important that this committee have the necessary expertise to assure that the guidelines are of the highest scientific quality. The committee has provided this expertise in the past, and it must continue to do so. The committee shall also include members from other scientific disciplines.

It should be noted that the present committee recommended on its own initiative that a nonscientist be appointed. Emmette S. Redford, Ph. D., LL. D., Ashbel Smith Professor of Government and Public Affairs at the Lyndon B. Johnson School of Public Affairs, University of Texas at Austin, serves in that capacity. An ethicist has also been nominated for appointment.

The Advisory Committee to the Director, NIH, shall serve to provide the broader public policy perspectives. This committee, at its meeting on February 9–10, 1976, reviewed the proposed guidelines with the participation of public witnesses, and shall continue to provide such review for future activities of the Recombinant Advisory Committee.

In response to suggestions, the responsibilities of the Recombinant Advisory Committee have been expanded. In addition to reviewing the guidelines for possible modification as scientific evidence warrants, the committee will certify EK2 and EK3 systems. In response to requests by the investigator, local committee, or study section, the committee will also provide evaluation and review in order to advise on levels of required containment, on lowering of requirements when coloned recombinants are to be used, and on questions concerning potential biohazard and adequacy of containment provisions.

Commentators also asked that the committee review ongoing research initiated prior to the implementation of the guidelines. Now that the guidelines are being released, NIH-funded investigators in this field will be asked to give assurance, within a given period, that they will comply. Any investigators who constructed clones under the Asilomar guidelines will be asked to petition NIH for special consideration of their case, if the new guidelines require higher containment than did the Asilomar guidelines. Here the advice of the Recombinant Advisory Committee will be sought.

There were also suggestions that the committee certify chemical purification of recombinant DNA, but as I indicated earlier, these procedures are too well known to require NIH monitoring.

5. In light of comments received, NIH will provide review, through appropriate NIH offices, of data from institutional biohazards committees (including accident reports) and will ensure dissemination of these findings as appropriate. Dr. William Gartland will head the newly created NIH Office of Recombinant DNA Activities for these purposes. In addition, NIH will provide for rapid dissemination of information through its Nucleic Acid Recombinant Scientific Memoranda (NARSM), distributed by the National Institute for Allergy and Infectious Diseases. NIH will also provide an appropriate mechanism for approving and certifying clones before containment conditions can be lowered.

With these extended modifications, the section of the guidelines dealing with roles and responsibilities now sets forth a more fully developed review structure involving the principal investigator, local biohazards committees, and the Recombinant Advisory Committee, as well as peer review committees. Guidelines now provide extensive opportunity for advice, from the local to the national level. Several levels of review and scrutiny are provided, ensuring the highest standards for scientific merit and conditions for safety.

The Recombinant Advisory Committee in conjunction with the Director's Advisory Committee shall continue to serve as an ongoing forum for examining progress in the technology and safety of recombinant DNA research. Their responsibility, and that of the NIH Director, is to ensure that the guidelines, through modification when called for, reflect the soundest scientific and safety evidence as it accrues in this area. Their task, in a sense, is just beginning.

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NATIONAL INSTITUTES OF HEALTH

GUIDELINES FOR RESEARCH INVOLVING RECOMBINANT DNA MOLECULES

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I. INTRODUCTION

The purpose of these guidelines is to recommend safeguards for research on recombinant DNA molecules to the National Institutes of Health and to other institutions that support such research. In this context we define recombinant DNAs as molecules that consist of different segments of DNA which have been joined together in cell-free systems, and which have the capacity to infect and replicate in some host cell, either autonomously or as an integrated part of the host's genome.

This is the first attempt to provide a detailed set of guidelines for use by study sections as well as practicing scientists for evaluating research on recombinant DNA molecules. We cannot hope to anticipate all possible lines of imaginative research that are possible with this powerful new methodology. Nevertheless, a considerable volume of written and verbal contributions from scientists in a variety of disciplines has been received. In many instances the views presented to us were contradictory. At present, the hazards may be guessed at, speculated about, or voted upon, but they cannot be

known absolutely in the absence of firm experimental data—and, unfortunately, the needed data were, more often than not, unavailable. Our problem then has been to construct guidelines that allow the promise of the methodology to be realized while advocating the considerable caution that is demanded by what we and others view as potential hazards.

In designing these guidelines we have adopted the following principles, which are consistent with the general conclusions that were formulated at the International Conference Center, Pacific Grove, California, in February 1975 (3): (i) There are certain experiments for which the assessed potential hazard is so serious that they are not to be attempted to the present time. (ii) The remainder can be undertaken at the present time provided that the experiment is justifiable on the basis that new knowledge or benefits to humankind will accrue that cannot readily be obtained by use of conventional methodology and that appropriate safeguards are incorporated into the design and execution of the experiment. In addition to an insistence on the practice of good microbiological techniques, these safeguards consist of providing both physical and biological barriers to the dissemination of the potentially hazardous agents. (iii) The level of containment provided by these barriers is to match the estimated potential hazard for each of the different classes of recombinants. For projects in a given class, this level is to be highest at initiation and modified subsequently only if there is a substantiated change in the assessed risk or in the applied methodology. (iv) The guidelines will be subjected to periodic review (at least annually) and modified to reflect improvements in our knowledge of the potential biohazards and of the available safeguards.

In constructing these guidelines it has been necessary to define boundary conditions for the different levels of physical and biological containment and for the classes of experiments to which they apply. We recognize that these definitions do not take into account existing and anticipated special procedures and information that will allow particular experiments to be carried out under different conditions than indicated here without sacrifice of safety. Indeed, we urge that individual investigators devise simple and more effective containment procedures and that study sections give consideration to such procedures which may allow change in the containment levels recommended here.

It is recommended that all publications dealing with recombinant DNA work include a description of the physical and biological containment procedures practiced, to aid and forewarn others who might consider repeating the work.

II. Containment

Effective biological safety programs have been operative in a variety of laboratories for many years. Considerable information therefore already exists for the design of physical containment facilities and the selection of laboratory procedures applicable to organisms carrying recombinant DNAs (4–17). The existing programs rely upon mechanisms that, for convenience, can be divided into two categories: (i) A set of standard practices that are generally used in microbiological laboratories, and (ii) special procedures, equipment, and laboratory installations that provide physical barriers which are applied in varying degrees according to the estimated biohazard.

Experiments on recombinant DNAs by their very nature lend themselves to a third containment mechanism—namely, the application of highly specific biological barriers. In fact, natural barriers do exist which either limit the infectivity of a vector or vehicle (plasmid, bacteriophage or virus) to specific hosts, or its dissemination and survival in the environment. The vectors that provide the means for replication of the recombinant DNAs and/or the host cells in which they replicate can be genetically designed to decrease by many orders of magnitude the probability of dissemination of recombinant DNAs outside the laboratory.

As these three means of containment are complementary, different levels of containment appropriate for experiments with different recombinants can be established by applying different combinations of the physical and biological barriers to a constant use of the standard practices. We consider these categories of containment separately here in order that such combinations can be conveniently expressed in the guidelines for research on the different kinds of recombinant DNAs (Section III).

A. *Standard practices and training.* The first principle of containment is a strict adherence to good microbiological practices (4–13). Consequently, all personnel directly or indirectly involved in experiments on recombinant DNAs must receive adequate instruction. This should include at least training in aseptic techniques and instruction in the biology of the organisms used in the experiments so that the potential biohazards can be understood and appreciated.

Any research group working with agents with a known or potential biohazard should have an emergency plan which describes the procedures to be followed if an accident contaminates personnel or environment. The principal investigator must ensure that everyone in the laboratory is familiar with both the potential hazards of the work and the emergency plan. If a research group is working with a known pathogen for which an effective vaccine is available, all workers should be immunized. Serological monitoring, where appropriate, should be provided.

B. *Physical containment levels.* A variety of combinations (levels) of special practices, equipment, and laboratory installations that provide additional physical barriers can be formed. For example, 31 combinations are listed in "Laboratory Safety at the Center for Disease Control" (4); four levels are associated with the "Classification of Etiologic Agents on the Basis of Hazard" (5), four levels were recommended in the "Summary Statement of the Asilomar Conference on Recombinant DNA Molecules" (3); and the National Cancer Institute uses three levels for research on oncogenic viruses (6). We emphasize that these are an aid to, and not a substitute for, good technique. Personnel must be competent in the effective use of all equipment needed for the required containment level as described below. We define only four levels of physical containment here, both because the accuracy with which one can presently assess the biohazards that may result from recombinant DNAs does not warrant a more detailed classification, and because additional flexibility can be obtained by combination of the physical with the biological barriers. Though different in detail, these four levels (P1<P2<P3<P4) approximate those given for human etiologic agents by the Center for Disease Control (i.e., classes 1 through 4; ref. 5), in the Asilomar summary statement (i.e., minimal, low moderate, and high; ref. 3), and by the National Cancer Institute for oncogenic viruses (i.e., low, moderate, and high; ref. 6), as is indicated by the P-number or adjective in the following headings. It should be emphasized that the descriptions and assignments of physical containment detailed below are based on existing approaches to containment of hazardous organisms.

We anticipate, and indeed already know of, procedures (14) which enhance physical containment capability in novel ways. For example, miniaturization of screening, handling, and analytical procedures provides substantial containment of a given host-vector system. Thus, such procedures should reduce the need for the standard types of physical containment, and such innovations will be considered by the Recombinant DNA Molecule Program Advisory Committee.

The special practices, equipment and facility installations indicated for each level of physical containment are required for the safety of laboratory workers, other persons, and for the protection of the environment. Optional items have been excluded; only those items deemed absolutely necessary for safety are presented. Thus, the listed requirements present basic safety criteria for each level of physical containment. Other microbiological practices and laboratory techniques which promote safety are to be encouraged. Additional information giving further guidance on physical containment is provided in a supplement to the guidelines (Appendix D).

P1 Level (Minimal). A laboratory suitable for experiments involving recombinant DNA molecules requiring physical containment at the P1 level is a laboratory that possesses no special engineering design features. It is a laboratory commonly used for microorganisms of no or minimal biohazard under ordinary conditions of handling. Work in this laboratory is generally conducted on open bench tops. Special containment equipment is neither required nor generally available in this laboratory. The laboratory is not separated from the general traffic patterns of the building. Public access is permitted.

The control of biohazards at the P1 level is provided by standard microbiological practices of which the following are examples: (i) Laboratory doors should be kept closed while experiments are in progress. (ii) Work surfaces should be decontaminated daily and following spills of recombinant DNA materials. (iii) Liquid wastes containing recombinant DNA materials should be decontaminated before disposal. (iv) Solid wastes contaminated with recombinant DNA materials should be decontaminated or packaged in a durable leak-proof container before removal from the laboratory. (v) Although pipetting by mouth is permitted, it is preferable that mechanical pipetting devices be used. When pipetting by mouth, cotton-plugged pipettes shall be employed. (vi) Eating, drinking, smoking, and storage of food in the working area should be discouraged. (vii) Facilities to wash hands should be available. (viii) An insect and rodent control program should be provided. (ix) The use of laboratory gowns, coats, or uniforms is discretionary with the laboratory supervisor.

P2 Level (Low). A laboratory suitable for experiments involving recombinant DNA molecules requiring physical containment at the P2 level is similar in construction and design to the P1 laboratory. The P2 laboratory must have access to an autoclave within the building; it may have a Biological Safety Cabinet.[1] Work which does not produce a considerable aerosol is conducted on the open bench. Although this laboratory is not separated from the general traffic patterns of the building, access to the laboratory is limited when experiments requiring P2 level physical containment are being conducted. Experiments of lesser biohazard potential can be carried out concurrently in carefully demarcated areas of the same laboratory.

The P2 laboratory is commonly used for experiments involving microorganisms of low biohazard such as those which have been classified by the Center for Disease Control as Class 2 agents (5).

See footnotes on p. 38459.

The following practices shall apply to all experiments requiring P2 level physical containment: (i) Laboratory doors shall be kept closed while experiments are in progress. (ii) Only persons who have been advised of the potential biohazard shall enter the laboratory. (iii) Children under 12 years of age shall not enter the laboratory. (iv) Work surfaces shall be decontaminated daily and immediately following spills of recombinant DNA materials. (v) Liquid wastes of recombinant DNA materials shall be decontaminated before disposal. (vi) Solid wastes contaminated with recombinant DNA materials shall be decontaminated or packaged in a durable leak-proof container before removal from the laboratory. Packaged materials shall be disposed of by incineration or sterilized before disposal by other methods. Contaminated materials that are to be processed and reused (i.e., glassware) shall be decontaminated before removal from the laboratory. (vii) Pipetting by mouth is prohibited; mechanical pipetting devices shall be used. (viii) Eating, drinking, smoking, and storage of food are not permitted in the working area. (ix) Facilities to wash hands shall be available within the laboratory. Persons handling recombinant DNA materials should be encouraged to wash their hands frequently and when they leave the laboratory. (x) An insect and rodent control program shall be provided. (xi) The use of laboratory gowns, coats, or uniforms is required. Such clothing shall not be worn to the lunch room or outside the building. (xii) Animals not related to the experiment shall not be permitted in the laboratory. (xiii) Biological Safety Cabinets [1] and/or other physical containment equipment shall be used to minimize the hazard of aerosolization of recombinant DNA materials from operations or devices that produce a considerable aerosol (e.g., blender, lyophilizer, sonicator, shaking machine, etc.). (xiv) Use of the hypodermic needle and syringe shall be avoided when alternate methods are available.

P3 Level (Moderate). A laboratory suitable for experiments involving recombinant DNA molecules requiring physical containment at the P3 level has special engineering design features and physical containment equipment. The laboratory is separated from areas which are open to the general public. Separation is generally achieved by controlled access corridors, air locks, locker rooms or other double-doored facilities which are not available for use by the general public. Access to the laboratory is controlled. Biological Safety Cabinets [1] are available within the controlled laboratory area. An autoclave shall be available within the building and preferably within the controlled laboratory area. The surfaces of walls, floors, bench tops, and ceilings are easily cleanable to facilitate housekeeping and space decontamination.

Directional air flow is provided within the controlled laboratory area. The ventilation system is balanced to provide for an inflow of supply air from the access corridor into the laboratory. The general exhaust air from the laboratory is discharged outdoors and so dispersed to the atmosphere as to prevent reentry into the building. No recirculation of the exhaust air shall be permitted without appropriate treatment.

No work in open vessels involving hosts or vectors containing recombinant DNA molecules requiring P3 physical containment is conducted on the open bench. All such procedures are confined to Biological Safety Cabinets.[1]

The following practices shall apply to all experiments requiring P3 level physical containment: (i) The universal biohazard sign is required on all laboratory access doors. Only persons whose entry into the laboratory is required on the basis of program or support needs shall be authorized to enter. Such persons shall be advised of the potential biohazards before entry and they shall comply with posted entry and exit procedures. Children under 12 years of age shall not enter the laboratory. (ii) Laboratory doors shall be kept closed while experiments are in progress. (iii) Biological Safety Cabinets [1] and other physical containment equipment shall be used for all procedures that produce aerosols of recombinant DNA materials (e.g., pipetting, plating, flaming, transfer operations, grinding, blending, drying, sonicating, shaking, etc.). (iv) The work surfaces of Biological Safety Cabinets [1] and other equipment shall be decontaminated following the completion of the experimental activity contained within them. (v) Liquid wastes containing recombinant DNA materials shall be decontaminated before disposal. Solid wastes contaminated with recombinant DNA materials shall be decontaminated or packaged in a durable leak-proof container before removal from the laboratory. Packaged material shall be sterilized before disposal. Contaminated materials that are to be processed and reused (i.e., glassware) shall be sterilized in the controlled laboratory area or placed in a durable leak-proof container before removal from the controlled laboratory area. This container shall be sterilized before the materials are processed. (vii) Pipetting by mouth is prohibited; mechanical pipetting devices shall be used. (viii) Eating, drinking, smoking, and storage of food are not permitted in the laboratory. (ix) Facilities to wash hands shall be available within the laboratory. Persons shall wash hands after experiments involving recombinant DNA materials and before leaving the laboratory. (x) An insect and rodent control program shall be provided. (xi) Laboratory clothing that protects street clothing (i.e., long sleeve solid-front or wrap-around gowns, no-button or slipover jackets, etc.) shall be worn in the laboratory. FRONT-BUTTON LABORATORY COATS ARE UNSUITABLE. Gloves shall be worn when handling recombinant DNA materials. Provision for laboratory shoes is recommended. Laboratory clothing shall not be worn outside the laboratory and shall be decontaminated before it is sent to the laundry. (xii) Raincoats, overcoats, topcoats, coats, hats, caps, and such street outerwear shall not be kept in the laboratory. (xiii) Animals and plants not related to the experiment shall not be permitted in the laboratory. (xiv) Vacuum lines shall be protected by filters and liquid traps. (xv) Use of the hypodermic needle and syringe shall be avoided when alternate methods are available. (xvi) If experiments of lesser biohazard potential are to be conducted in the same laboratory concurrently with experiments requiring P3 level physical containment they shall be conducted only in accordance with all P3 level requirements. (xvii) Experiments requiring P3 level physical containment can be conducted in laboratories where the directional air flow and general exhaust air conditions described above cannot be achieved, provided that this work is conducted in accordance with all other requirements listed and is contained in a Biological Safety Cabinet [1] with attached glove ports and gloves. All materials before removal from the Biological Safety Cabinet [1] shall be sterilized or transferred to a non-breakable, sealed container, which is then removed from the cabinet through a chemical decontamination tank, autoclave, ultraviolet air lock, or after the entire cabinet has been decontaminated.

P4 Level High. Experiments involving recombinant DNA molecules requiring physical containment at the P4 level shall be confined to work areas in a facility of the type designed to contain microorganisms that are extremely hazardous to man or may cause serious epidemic disease. The facility is either a separate building or it is a controlled area, within a building, which is completely isolated from all other areas of the building. Access to the facility is under strict control. A specific facility operations manual is available. Class III Biological Safety Cabinets [1] are available within work areas of the facility.

A P4 facility has engineering features which are designed to prevent the escape of microorganisms to the environment (14, 15, 16, 17). These features include: (i) Monolithic walls, floors, and ceilings in which all penetrations such as for air ducts, electrical conduits, and utility pipes are sealed to assure the physical isolation of the work area and to facilitate housekeeping and space decontamination; (ii) air locks through which supplies and materials can be brought safely into the facility; (iii) contiguous clothing change and shower rooms through which personnel enter into and exit from the facility; (iv) double-door autoclaves to sterilize and safely remove wastes and other materials from the facility; (v) a biowaste treatment system to sterilize liquid effluents if facility drains are installed; (vi) a separate ventilation system which maintains negative air pressures and directional air flow within the facility; and (vii) a treatment system to decontaminate exhaust air before it is dispersed to the atmosphere. A central vacuum utility system is not encouraged; if one is installed, each branch line leading to a laboratory shall be protected by a high efficiency particulate air filter.

The following practices shall apply to all experiments requiring P4 level physical containment: (i) The universal biohazard sign is required on all facility access doors and all interior doors to individual laboratory rooms where experiments are conducted. Only persons whose entry into the facility or individual laboratory rooms is required on the basis of program or support needs shall be authorized to enter. Such persons shall be advised of the potential biohazards and instructed as to the appropriate safeguards to ensure their safety before entry. Such persons shall comply with the instructions and all other posted entry and exit procedures. Under no condition shall children under 15 years of age be allowed entry. (ii) Personnel shall enter into and exit from the facility only through the clothing change and shower rooms. Personnel shall shower at each exit from the facility. The air locks shall not be used for personnel entry or exit except for emergencies. (iii) Street clothing shall be removed in the outer facility side of the clothing change area and kept there. Complete laboratory clothing including undergarments, pants and shirts or jumpsuits, shoes, head cover, and gloves shall be provided and used by all persons who enter into the facility shall be placed in an entry air be stored in lockers provided for this purpose or discarded into collection hampers before personnel enter into the shower area. (iv) Supplies and materials to be taken into the facility shall be placed in an entry air lock. After the outer door (opening to the corridor outside of facility) has been secured, personnel occupying the facility shall retrieve the supplies and materials by opening the interior air lock door. This door shall be secured after supplies and materials are brought into the facility. (v) Doors to laboratory rooms within the facility shall be kept closed while experiments are in progress. (vi) Experimental procedures requiring P4 level physical containment shall be confined to Class III Biological Safety Cabinets.[1] All materials, before removal from these cabinets, shall be sterilized or transferred to a nonbreakable sealed container, which is then removed from the system through a chemical decontaminated tank, autoclave, or after the

See footnotes on p. 38459.

entire system has been decontaminated. (vii) No materials shall be removed from the facility unless they have been sterilized or decontaminated in a manner to prevent the release of agents requiring P4 physical containment. All wastes and other materials and equipment not damaged by high temperature or steam shall be sterilized in the double-door autoclave. Biological materials to be removed from the facility shall be transferred to a non-breakable sealed container which is then removed from the facility through a chemical decontamination tank or a chamber designed for gas sterilization. Other materials which may be damaged by temperature or steam shall be sterilized by gaseous or vapor methods in an air lock or chamber designed for this purpose. (viii) Eating, drinking, smoking, and storage of food are not permitted in the facility. Foot-operated water fountains located in the facility corridors are permitted. Separate potable water piping shall be provided for these water fountains. (ix) Facilities to wash hands shall be available within the facility. Persons shall wash hands after experiments. (x) An insect and rodent control program shall be provided. (xi) Animals and plants not related to the experiment shall not be permitted in the facility. (xii) If a central vacuum system is provided, each vacuum outlet shall be protected by a filter and liquid trap in addition to the branch line HEPA filter mentioned above. (xiii) Use of the hypodermic needle and syringe shall be avoided when alternate methods are available. (xiv) If experiments of lesser biohazard potential are to be conducted in the facility concurrently with experiments requiring P4 level containment, they shall be confined in Class I or Class II Biological Safety Cabinets [1] or isolated by other physical containment equipment. Work surfaces of Biological Safety Cabinets [1] and other equipment shall be decontaminated following the completion of the experimental activity contained within them. Mechanical pipetting devices shall be used. All other practices listed above with the exception of (vi) shall apply.

C. *Shipment.* To protect product, personnel, and the environment, all recombinant DNA material will be shipped in containers that meet the requirements issued by the U.S. Public Health Service (Section 72.25 of Part 72, Title 42, Code of Federal Regulations), Department of Transportation (Section 173.387 (b) of Part 173, Title 49, Code of Federal Regulations) and the Civil Aeronautics Board (C.A.B. No. 82, Official Air Transport Restricted Articles Tariff No. 6–D) for shipment of etiologic agents. Labeling requirements specified in these Federal regulations and tariffs will apply to all viable recombinant DNA materials in which any portion of the material is derived from an etiologic agent listed in paragraph (c) of 42 CFR 72.25. Additional information on packing and shipping is given in a supplement to the guidelines (Appendix D, part X).

D. *Biological containment levels.* Biological barriers are specific to each host-vector system. Hence the criteria for this mechanism of containment cannot be generalized to the same extent as for physical containment. This is particularly true at the present time when our experience with existing host-vector systems and our predictive knowledge about projected systems are sparse. The classification of experiments with recombinant DNAs that is necessary for the construction of the experimental guidelines (Section III) can be accomplished with least confusion if we use the host-vector system as the primary element and the source of the inserted DNA as the secondary element in the classification. It is therefore convenient to specify the nature of the biological containment under host-vector headings such as those given below for *Escherichia coli* K–12.

III. Experimental Guidelines

A general rule that, though obvious, deserves statement is that the level of containment required for any experiment on DNA recombinants shall never be less than that required for the most hazardous component used to construct and clone the recombinant DNA (i.e. vector, host, and inserted DNA). In most cases the level of containment will be greater, particularly when the recombinant DNA is formed from species that ordinarily do not exchange genetic information. Handling the purified DNA will generally require less stringent precautions than will propagating the DNA. However, the DNA itself should be handled at least as carefully as one would handle the most dangerous of the DNAs used to make it.

The above rule by itself effectively precludes certain experiments—namely, those in which one of the components is in Class 5 of the "Classification of Etiologic Agents on the Basis of Hazard" (5), as these are excluded from the United States by law and USDA administrative policy. There are additional experiments which may engender such serious biohazards that they are not to be performed at this time. These are considered prior to presentation of the containment guidelines for permissible experiments.

A. *Experiments that are not to be performed.* We recognize that it can be argued that certain of the recombinants placed in this category could be adequately contained at this time. Nonetheless, our estimates of the possible dangers that may ensue if that containment fails are of such magnitude that we consider it the wisest policy to at least defer experiments on these recombinant DNAs until there is more information to accurately assess that danger and to allow the construction of more effective biological barriers. In this respect, these guidelines are more stringent than those initially recommended (1).

The following experiments are not to be initiated at the present time: (i) Cloning of recombinant DNAs derived from the pathogenic organisms in Classes 3, 4, and 5 of "Classification of Etiologic Agents on the Basis of Hazard" (5), or oncogenic viruses classified by NCI as moderate risk (6), or cells known to be infected with such agents, regardless of the host-vector system used. (ii) Deliberate formation of recombinant DNAs containing genes for the biosynthesis of potent toxins (e.g., botulinum or diphtheria toxins; venoms from insects, snakes, etc.). (iii) Deliberate creation from plant pathogens of recombinant DNAs that are likely to increase virulence and host range. (iv) Deliberate release into the environment of any organism containing a recombinant DNA molecule. (v) Transfer of a drug resistance trait to microorganisms that are not known to acquire it naturally if such acquisition could compromise the use of a drug to control disease agents in human or veterinary medicine or agriculture.

In addition, at this time large-scale experiments (e.g., more than 10 liters of culture) with recombinant DNAs known to make harmful products are not to be carried out. We differentiate between small- and large-scale experiemnts with such DNAs because the probability of escape from containment barriers normally increases with increasing scale. However, specific experiments in this category that are of direct societal benefit may be excepted from this rule if special biological containment precautions and equipment designed for large-scale operations are used, and provided that these experiments are expressly approved by the Recombinant DNA Molecule Program Advisory Committee of NIH.

B. *Containment guidelines for permissible experiments.* It is anticipated that most recombinant DNA experiments initiated before these guidelines are next reviewed (i.e., within the year) will employ *E. coli* K–12 host-vector ssytems. These are also the systems for which we have the most experience and knowledge regarding the effectiveness of the containment provided by existing hosts and vectors necessary for the construction of more effective biological barriers.

For these reasons, *E. coli* K–12 appears to be the system of choice at this time, although we have carefully considered arguments that many of the potential dangers are compounded by using an organism as intimately connected with a man as is *E. coli*. Thus, while proceeding cautiously with *E. coli*, serious efforts should be made toward developing alternate host-vector systems; this subject is discussed in considerable detail in Appendix A.

We therefore consider DNA recombinants in *E. coli* K–12 before proceeding to other host-vector systems.

1. *Biological containment criteria using E. coli K–12 host-vectors EK1 host-vectors.* These are host-vector systems that can be estimated to already provide a moderate level of containment, and include most of the presently available systems. The host is always *E. coli* K–12, and the vectors include nonconjugative plasmids [e.g., pSC101, ColE$_1$ or derivatives thereof (19–26)] and variants of bacteriophage γ (27–29).

The *E. coli* K–12 nonconjugative plasmid system is taken as an example to illustrate the approximate level of containment referred to here. The available data from experiments involving the feeding of bacteria to humans and calves (30–32) indicate that *E. coli* K–12 did not usually colonize the normal bowel, and exhibited little, if any, multiplication while passing through the alimentary tract even after feeding high doses (i.e., 10^9 to 10^{10} bacteria per human or calf). However, general extrapolation of these results may not be warranted because the implantation of bacteria into the intestinal tract depends on a number of parameters, such as the nature of the intestinal flora persent in a given individual and the physiological state of the inoculum. Moreover, since viable *E. coli* K–12 can be found in the feces after humans are fed 10^7 bacteria in broth (30) or 3×10^4 bacteria protected by suspension in milk (31), transductional and conjugational transfer of the plasmid vectors from *E. coli* K–12 to resident bacteria in the fecal matter before and after excretion must also be considered.

The nonconjugative plasmid vectors cannot promote their own transfer, but require the presence of a conjugative plasmid for mobilization and transfer to other bacteria. When present in the same cell with derepressed conjugative plasmids such as F or R1drd19, the nonconjugative ColE1, ColE1-trp and pSC101 plasmids are transferred to suitable recipient strains under ideal laboratory conditions at frequencies of about 0.5, 10^{-4} to 10^{-5}, and 10^{-6} per donor cell, respectively. These frequencies are reduced by another factor of 10^2 to 10^4 if the conjugative plasmid employed is repressed with respect to expression of donor fertility.

The experimental transfer system which most closely resembles nonconjugative plasmid transfer in nature is a triparental mating. In such matings, the bacterial cell possessing the nonconjugative plasmid must first acquire a conjugative plasmid from another cell before it can transfer the nonconjugative plasmid to a secondary recipient. With ColE1, the frequencies of transfer are 10^{-2} and 10^{-4} to 10^{-5} when using conjugative plasmid donors possessing derepressed and repressed plasmids, respectively. Mobilization of ColE1-trp and pSC101 under similar laboratory conditions is so low as to be usually undetectable (33). Since most conjugative plasmids in nature are repressed for expres-

sion of donor fertility, the frequency at which nonconjugative plasmids are mobilized and transferred by this sequence of events *in vivo* is difficult to estimate. However, in calves fed on an antibiotic-supplemented diet, it has been estimated that such triparental nonconjugative R plasmid transfer occurs at frequencies of no more than 10^{-16} to 10^{-12} per 24 hours per calf (32). In terms of considering other means for plasmid transmission in nature, it should be noted that transduction does operate *in vivo* for *Staphylococcus aureus* (34) and probably for *E. coli* as well. However, no data are available to indicate the frequencies of plasmid transfer *in vivo* by either transduction or transformation.

These observations indicate the low probabilities for possible dissemination of such plasmid vectors by accidental ingestion, which would probably involve only a few hundred or thousand bacteria provided that at least the standard practices (Section II–A above) are followed, particularly the avoidance of mouth pipetting. The possibility of colonization and hence of transfer are increased, however, if the normal flora in the bowel is disrupted by, for example, antibiotic therapy (35). For this reason, persons receiving such therapy must not work with DNA recombinants formed with any *E. coli* K–12 host-vector system during the therapy period and for seven days thereafter; similarly, persons who have achlorhydria or who have had surgical removal of part of the stomach or bowel should avoid such work, as should those who require large doses of antacids.

The observations on the fate of *E. coli* K–12 in the human alimentary tract are also relevant to the containment of recombinant DNA formed with bacteriophage λ variants. Bacteriophage can escape from the laboratory either as mature infectious phage particles or in bacterial host cells in which the phage genome is carried as a plasmid or prophage. The fate of *E. coli* K–12 host cells carrying the phage genome as a plasmid or prophage is similar to that for plasmid-containing host cells as discussed above. The survival of the λ phage genome when released as infectious particles depends on their stability in nature, their infectivity and on the probability of subsequent encounters with naturally occurring λ-sensitive *E. coli* strains. Although the probability of survival of λ and its infection of resident intestinal *E. coli* in animals and humans has not been measured, it is estimated to be small given the high sensitivity of λ to the low pH of the stomach, the insusceptibility to λ infection of smooth *E. coli* cells (the type that normally resides in the gut), the infrequency of naturally occurring λ-sensitive *E. coli* (36) and the failure to detect infective λ particles in human feces after ingestion of up to 10^{11} λ particles (37).

Moreover, λ particles are very sensitive to desiccation.

Establishment of λ as a stable lysogen is a frequent event (10^{0} to 10^{-1}) for the att^{+} int^{+} cI^{+} phage so that this mode of escape would be the preponderant laboratory hazard; however, most EK1 λ vectors currently in use lack the att and int functions (27–29) thus reducing the probability of lysogenization to about 10^{-5} to 10^{-6} (38–40). The frequency for the conversion of λ to a plasmid state for persistence and replication is also only about 10^{-6} (41). Moreover, the routine treatment of phage lysates with chloroform (42) should eliminate all surviving bacteria including lysogens and λ plasmid carriers. Lysogenization could also occur when an infectious λ containing cloned DNA infects a λ-sensitive cell in nature, and recombines with a resident lambdoid prophage. Although λ-sensitive *E. coli* strains seem to be rare, a significant fraction do carry lambdoid prophages (43–44) and thus this route of escape should be considered.

While not exact, the estimates for containment afforded by using these host-vectors are at least as accurate as those for physical containment, and are sufficient to indicate that currently employed plasmid and λ vector systems provide a moderate level of biological containment. Other nonconjugative plasmids and bacteriophages that, in association with *E. coli* K–12 can be estimated to provide the same approximate level of moderate containment are included in the EK1 class.

EK2 host-vectors. These are host-vector systems that have been genetically constructed and shown to provide a high level of biological containment as demonstrated by data from suitable tests performed in the laboratory. The genetic modifications of the *E. coli* K–12 host and/or the plasmid or phage vector should not permit survival of a genetic marker carried on the vector, preferably a marker within an inserted DNA fragment, in other than specially designed and carefully regulated laboratory environments at a frequency greater than 10^{-8}. This measure of biological containment has been selected because it is a measurable entity. Indeed, by testing the contributions of pre-existing and newly introduced genetic properties of vectors and hosts, individually or in various combinations, it should be possible to estimate with considerable precision, that the specially designed host-vector system can provide a margin of biological containment in excess of that required. For the time being, no host-vector system will be considered to be a bona fide EK2 host-vector system until it is so certified by the NIH Recombinant DNA Molecule Program Advisory Committee.

For EK2 host-vector systems in which the vector is a plasmid, no more than one in 10^{8} host cells should be able to perpetuate the vector and/or a cloned DNA fragment under non-permissive conditions designed to represent the natural environment either by survival of the original host or as a consequence of transmission of the vector and/or a cloned DNA fragment by transformation, transduction or conjugation to a host with properties common to those in the natural environment.

In terms of potential EK2 plasmid-host systems, the following types of genetic modifications should reduce survival of cloned DNA. The examples given are for illustrative purposes and should not be contrued to encompass all possibilities. The presence of the non-conjugative plasmids ColE1-trp and pS101 in an *E. coli*. K–12 strain possessing a mutation eliminating host-controlled restriction and modification (hsdS) results in about 10^{2}-fold reduction in mobilization to restriction-proficient recipients. The combination of the dapD8, ΔbioH-asd, Δgal-chl^{r} and rfb mutations in *E. coli* K–12 results in no detectable survivors in feces of rats following feeding by stomach tube of 10^{10} cells in milk and similarly leads to complete lysis of cells suspended in broth medium lacking diaminopimelic acid. *E. coli* K–12 strains with ΔthyA and deoC(dra) mutations undergo thymineless death in growth medium lacking thymine and give a 10^{5}-fold reduced survival during passage through the rat intestine compared to wild-type thy^{+} *E. coli* K–12. (However, the ΔthyA mutation alone or in combination with a deoB(drm) mutation only reduces *in vivo* survival by a factor of 10^{2}.) Other host mutations, as yet untested, that might further reduce survival of the plasmid-host system or reduce plasmid transmission are: the combination polA(TS) recA(TS) ΔthyA which might interfere with ColE1 replication and lead to DNA degradation at body temperatures; Con mutations that reduce the ability of conjugative plasmids to enter the plasmid-host complex and thus should reduce mobilization of the cloned DNA to other strains; and mutations that confer resistance to known transducing phages Mutations can also be introduced into the plasmid to cause it to be dependent on a specific host, to make its replication thermosensitive and/or to endow it with a killer capability such that all cells (other than its host) into which it might be transferred will not survive.

In the construction of EK2 plasmid-host systems it is important to use the most stable mutations available, preferably deletions. Obviously, the presence of all mutations contributing to higher degrees of biological containment must be verified periodically by appropriate tests. In testing the level of biological containment afforded by a proposed EK2 plasmid-host system, it is important to design relevant tests to evaluate the survival of the vector and/or a cloned DNA fragment under conditions that are possible in nature and that are also most advantageous for its perpetuation. For example, one might conduct a triparental mating with a primary donor possessing a redepressed F-type or I-type conjugative plasmid, the safer host with ΔbioH-asd, dapD8, Δgal-chl^{r}, rfb, ΔthyA, deoC, trp and hsdS mutations and a plasmid vector carrying an easily detectable marker such as for ampicillin resistance or an inserted gene such as trp^{+}, and a secondary recipient that is Su^{+} hsdS trp (i.e., permissive for the recombinant plasmid). Such matings would be conducted in a medium lacking diamino pimelic acid and thymine and survival of the Ap^{r} or trp marker in any of the three strains followed as a function of time. Survival of the vector and/or a cloned marker by transduction could also be evaluated by introducing a known generalized transducing phage into the system. Similar experiments should also be done using a secondary recipient that is restrictive for the plasmid vector as well as with primary donors possessing repressed conjugative plasmids with incompatibility group properties like those commonly found in enteric microorganisms. Since a common route of escape of plasmid-host systems in the laboratory might be by accidental ingestion, it is suggested that the same types of experiments be conducted in suitable animal-model systems. In addition to these tests on survival of the vector and/or a cloned DNA fragment, it would be useful to determine the survival of the host strain under nongrowth conditions such as in water and as a function of drying time after a culture has been spilled on a lab bench.

For EK2 host-vector systems in which the vector is a phage, no more than one in 10^{8} phage particles should be able to perpetuate itself and/or a cloned DNA fragment under non-permissive conditions designed to represent the natural environment either (a) as a prophage or plasmid in the laboratory host used for phage propagation or (b) by surviving in natural environments and transferring itself and/or a cloned DNA fragment to a host (or its resident lambdoid prophage) with properties common to those in the natural environment.

In terms of potential EK2 λ-host systems, the following types of genetic modification should reduce survival of cloned DNA. The examples given are for illustrative purposes and should not be construed to encompass all possibilities. The probability of establishing λ lysogeny in the normal laboratory host should be reduced by removal of the phage att site, the Int function, the repressor gene(s) and adding virulence-enhancing mutations. The frequency of plasmid formation, although normally already less than 10^{-6}, could be further reduced by defects in

the P_R–Q region, including mutations such as *vir*-s, *cro*(TS), *cI7*, *ri*^{s}, *O*(TS), *P*(TS), and *nin*. Moreover, chloroform treatment used routinely following cell lysis would reduce the number of surviving cells, including possible lysogens or plasmid carriers, by more than 10^8. The host may also be modified by deletion of the host *λatt* site and inclusion of one or more of the mutations described above for plasmid-host systems to further reduce the chance of formation and survival of any lysogen or plasmid carrier cell.

The survival of escaping phage and the chance of encountering a sensitive host in nature are very low, as discussed for EK1 systems. The infectivity of the phage particles could be further reduced by introducing mutations (e.g., suppressed ambers) which would make the phage particles extremely unstable except under special laboratory conditions (e.g., high concentrations of salts or putrescine). Another means would be to make the phage itself a two-component system, by eliminating the tail genes and reproducing the phage as heads packed with DNA; when necessary and under specially controlled conditions, these heads could be made infective by adding tail preparations. An additional safety factor in this regimen is the extreme instability of the heads, unless they are stored in 10mM putrescine, a condition easy to obtain in the laboratory but not in nature. The propagation of the escaping phage in nature could further be blocked by adding various conditional mutations which would permit growth only under special laboratory conditions or in a special permissive laboratory host with suppressor or *gro*-type (*mop*, *dnaB*, *rpoB*) mutations. An additional safety feature would be the use of an r$^-$ m$^-$ (*hsdS*) laboratory host, which produces phage with unmodified DNA which should be restricted in r$^+$ m$^+$ bacteria that are probably prevalent in nature. The likelihood of recombination between the λ vector and lambdoid prophages which are present in some *E. coli* strains might be reduced by elimination of the Red function and the presence of the recombination-reducing Gam function together with mutations contributing to the high lethality of the λ phage. However, these second-order precautions might not be relevant if the stability and infectivity of the escaping λ particles are reduced by special mutations or by propagating the highly unstable heads.

Despite multiple mutations in the phage vectors and laboratory hosts, the yield of phage particles under suitable laboratory conditions should be high (10^{10} —10^{11} particles/ml). This permits phage propagation in relatively small volumes and constitutes an additional safety feature.

The phenotypes and genetic stabilities of the mutations and chromosome alterations included in these λ-host systems indicate that containment well in excess of the required 10^{-8} or lower survival frequency for the λ vector with or without a cloned DNA fragment should be attained. Obviously the presence of all mutations contributing to this high degree of biological containment must be verified periodically by appropriate tests. Laboratory tests should be performed with the bacterial host to measure all possible routes of escape such as the frequency of lysogen formation, the frequency of plasmid formation and the survival of the lysogen or carrier bacterium. Similarly, the potential for perpetuation of a cloned DNA fragment carried by infectious phage particles can be tested by challenging typical wild-type *E. coli* strains or a λ-sensitive nonpermissive laboratory K–12 strain, especially one lysogenic for a lambdoid phage.

In view of the fact that accurate assessment of the probabilities for escape of infectious λ grown on r$^-$ m$^-$ Su$^+$ hosts is dependent upon the frequencies of r$^-$, Su$^+$, and λ-sensitive strains in nature, investigators need to screen *E. coli* strains for these properties. These data will also be useful in predicting frequencies of successful escape of plasmid cloning vectors harbored in r$^-$ m$^-$ Su$^+$ strains.

When any investigator has obtained data on the level of containment provided by a proposed EK2 system, these should be reported as rapidly as possible to permit general awareness and evaluation of the safety features of the new system. Investigators are also encouraged to make such new safer cloning systems generally available to other scientists. NIH will take appropriate steps to aid in the distribution of these safer vectors and hosts.

EK3 host-vectors. These are EK2 systems for which the specified containment shown by laboratory tests has been independently confirmed by appropriate tests in animals, including humans or primates, and in other relevant environments in order to provide additional data to validate the levels of containment afforded by the EK2 host-vector systems. Evaluation of the effects of individual or combinations of mutations contributing to the biological containment should be performed as a means to confirm the degree of safety provided and to further advance the technology of developing even safer vectors and hosts. For the time being, no host-vector system will be considered to be a bona fide EK3 host-vector system, until it is so certified by the NIH Recombinant DNA Molecule Program Advisory Committee.

2. *Classification of experiments using the E. coli K–2 containment systems.* In the following classification of containment criteria for different kinds of recombinant DNAs, the stated levels of physical and biological containment are minimums. Higher levels of biological containment (EK3>EK2>EK1) are to be used if they are available and are equally appropriate for the purposes of the experiment.

<*a*>*Shotgun experiments.* These experiments involve the production of recombinant DNAs between the vector and the total DNA or (preferably) any partially purified fraction thereof from the specified cellular source.

(i) *Eukaryotic DNA recombinants—Primates.* P3 physical containment+an EK3 host-vector, or P4 physical containment+an EK2 host-vector, except for DNA from uncontaminated embryonic tissue or primary tissue cultures therefrom, and germ-line cells for which P3 physical containment+an EK2 host-vector can be used. The basis for the lower estimated hazard in the case of DNA from the latter tissues (if freed of adult tissue) is their relative freedom from horizontally acquired adventitious viruses.

Other mammals. P3 physical containment +an EK2 host-vector.

Birds. P3 physical containment+an EK2 host-vector.

Cold-blooded vertebrates. P2 physical containment+an EK2 host-vector except for embryonic or germ-line DNA which require P2 physical containment+an EK1 host-vector. If the eukaryote is known to produce a potent toxin, the containment shall be increased to P3+EK2.

Other cold-blooded animals and lower eukaryotes. This large class of eukaryotes is divided into the following two groups:

(*1*) Species that are known to produce a potent toxin or are known pathogens (i.e., an agent listed in Class 2 of ref. 5 or a plant pathogen) or are known to carry such pathogenic agents must use P3 physical containment+an EK2 host-vector. Any species that has a demonstrated capacity for carrying particular pathogenic agents is included in this group unless it has been shown that those organisms used as the source of DNA do not contain these agents; in this case they may be placed in the second group.

(*2*) The remainder of the species in this class can use P2÷EK1. However, any insect in this group should have been grown under laboratory conditions for at least 10 generations prior to its use as a source of DNA.

Plants. P2 physical containment÷an EK1 host-vector. If the plant carries a known pathogenic agent or makes a product known to be dangerous to any species, the containment must be raised to P3 physical containment÷an EK2 host-vector.

(ii) *Prokaryotes DNA recombinants—Prokaryotes that exchange genetic informatio with E. coli*[2].

The level of physical containment is directly determined by the rule of the most dangerous component (see introduction to Section III). Thus P1 conditions can be used for DNAs from those bacteria in Class 1 of ref. 5. ("Agents of no or minimal hazard * * *") which naturally exchange genes with *E. coli*; and P2 conditions should be used for such bacteria if they fall in Class 2 of ref. 5 ("Agents of ordinary potential hazard * * *"), or plant pathogens or symbionts. EK1 host-vectors can be used for all experiments requiring only P1 physical containment; in fact, experiments in this category can be performed with *E. coli* K–12 vectors exhibiting a lesser containment (e.g., conjugative plasmids) than EK1 vectors. Experiments with DNA from species requiring P2 physical containment which are of low pathogenicity (for example, enteropathogenic *Escherichia coli*, *Salmonella typhimurium*, and *Klebsiella pneumoniae*) can use EK1 host-vectors, but those of moderate pathogenicity (for example, *Salmonella typhi*, *Shigella dysenteriae* type I, and *Vibrio cholerae*) must use EK2 host-vectors.[3] A specific example of an experiment with a plant pathogen requiring P2 physical containment÷an EK2 host-vector would be cloning the tumor gene of *Agrobacterium tumefaciens*.

Prokaryotes that do not exchange genetic information with E. coli. The minimum containment conditions for this class consist of P2 physical containment÷an EK2 host-vector or P3 physical containment÷an EK1 host-vector, and apply when the risk that the recombinant DNAs will increase the pathogenicity or ecological potential of the host is judged to be minimal. Experiments with DNAs from pathogenic species (Class 2 ref. 5 plus plant pathogens) must use P3÷EK2.

(iii) *Characterized clones of DNA recombinants derived from shotgun experiments.* When a cloned DNA recombinant has been rigorously characterized[4] and there is sufficient evidence that it is free of harmful genes,[4] then experiments involving this recombinant DNA can be carried out under P1+EK1 conditions if the inserted DNA is from a species that exchanges genes with *E. coli*, and under P2+EK1 conditions if not.

<*b*> *Purified cellular DNAs other than plasmids, bacteriophages, and other viruses.* The formation of DNA recombinants from cellular DNAs that have been enriched[5] by physical and chemical techniques (i.e., not by cloning) and which are free of harmful genes can be carried out under lower containment conditions than used for the corresponding shotgun experiment. In general, the containment can be decreased one step in physical containment (P4→P3→P2→P1) while maintaining the biological containment specified for the shotgun experiment, or one step in biological containment (EK3→EK2→EK1) while maintaining the specified physical containment—provided that the

See footnotes on p. 38459.

new condition is not less than that specified above for characterized clones from shotgun experiments (Section <a> —iii).

<c> *Plasmids, bacteriophages, and other viruses.* Recombinants formed between EK-type vectors and other plasmid or virus DNAs have in common the potential for acting as double vectors because of the replication functions in these DNAs. The containment conditions given below apply only to propagation of the DNA recombinants in *E. coli* K-12 hosts. They do not apply to other hosts where they may be able to replicate as a result of functions provided by the DNA inserted into the EK vectors. These are considered under other host-vector systems.

(i) *Animal viruses.* P4+EK2 or P3+EK3 shall be used to isolate DNA recombinants that include all or part of the genome of an animal virus. This recommendation applies not only to experiments of the "shotgun" type but also to those involving partially characterized subgenomic segments of viral DNAs (for example, the genome of defective viruses, DNA fragments isolated after treatment of viral genomes with restriction enzymes, etc). When cloned recombinants have been shown by suitable biochemical and biological tests to be free of harmful regions, they can be handled in P3+EK2 conditions. In the case of DNA viruses, harmless regions include the late region of the genome; in the case of DNA copies of RNA viruses, they might include the genes coding for capsid proteins or envelope proteins.

(ii) *Plant viruses.* P3+EK1 or P2+EK2 conditions shall be used to form DNA recombinants that include all or part of the genome of a plant virus.

(iii) *Eukaryotic organelle DNAs.* The containment conditions given below apply only when the organelle DNA has been purified [6] from isolated organelles. Mitochondrial DNA from primates: P3+EK1 or P2+EK2. Mitochondrial or chloroplast DNA from other eukaryotes: P2+EK1. Otherwise, the conditions given under shotgun experiments apply.

(iv) *Prokaryotic plasmid and phage DNAs. Plasmids and phage from hosts that exchange genetic—information with E. coli.* Experiments with DNA recombinants formed from plasmids or phage genomes that have not been characterized with regard to presence of harmful genes or are known to contribute significantly to the pathogenicity of their normal hosts must use the containment conditions specified for shotgun experiments with DNAs from the respective host. If the DNA recombinants are formed from plasmids or phage that are known not to contain harmful genes, or from purified [6] and characterized plasmid or phage DNA segments known not to contain harmful genes, the experiments can be performed with P1 physical containment+an EK1 host-vector.

Plasmids and phage from hosts that do not exchange genetic information with E. coli. The rules for shotgun experiments with DNA from the host apply to their plasmids or phages. The minimum containment conditions for this category (P2+EK2, or P3+EK1) can be used for plasmid and phage, or for purified [6] and characterized segments of plasmid and phage DNAs, when the risk that the recombinant DNAs will increase the pathogenicity or ecological potential of the host is judged to be minimal.

NOTE: Where applicable, cDNAs (i.e., complementary DNAs) synthesized in vitro from cellular or viral RNAs are included within each of the above classifications. For example, cDNAs formed from cellular RNAs that are not purified and characterized are included under <a>, shotgun experiments; cDNAs formed from purified and characterized RNAs are included under <b>; cDNAs formed from viral RNAs are included under <c>; etc.

3. *Experiments with other prokaryotic host-vectors.* Other prokaryotic host-vector systems are at the speculative, planning, or developmental stage, and consequently do not warrant detailed treatment here at this time. However, the containment criteria for different types of DNA recombinants formed with *E. coli* K-12 host-vectors can, with the aid of some general principles given here, serve as a guide for containment conditions with other host-vectors when appropriate adjustment is made for their different habitats and characteristics. The newly developed host-vector systems should offer some distinct advantage over the *E. coli* K-12 host-vectors—for instance, thermophilic organism or other host-vectors whose major habitats do not include humans and/or economically important animals and plants. In general, the strain of any prokaryotic species used as the host is to conform to the definition of Class 1 etiologic agents given in ref. 5 (i.e., "Agents for no or minimal hazard * * *"), and the plasmid or phage vector should not make the host more hazardous. Appendix A gives a detailed discussion of the *B. subtilis* system, the most promising alternative to date.

At the initial stage, the host-vector must exhibit at least a moderate level of biological containment comparable to EK1 systems, and should be capable of modification to obtain high levels of containment comparable to EK2 and EK3. The type of confirmation test(s) required to move a host-vector from an EK2-type classification to an EK3-type will clearly depend upon the preponderant habitat of the host-vector. For example, if the unmodified host-vector propagates mostly in, on, or around higher plants, but not appreciably in warm-blooded animals, modification should be designed to reduce the probability that the host-vector can escape to and propagate in, on, or around such plants, or transmit recombinant DNA to other bacterial hosts that are able to occupy these ecological niches, and it is these lower probabilities which must be confirmed. The following principles are to be followed in using the containment criteria given for experiments with *E. coli* K-12 host-vectors as a guide for other prokaryotic systems. Experiments with DNA from prokaryotes (and their plasmids or viruses) are classified according to whether the prokaryote in question exchanges genetic information with the host-vector or not, and the containment conditions given for these two classes with *E. coli* K-12 host-vectors applied. Experiments with recombinants between plasmid or phage vectors and DNA that extends the range of resistance of the recipient species to therapeutically useful drugs must use P3 physical containment + a host-vector comparable to EK1 or P2 physical containment + a host-vector comparable to EK2. Transfer of recombinant DNA to plant pathogens can be made safer by using nonreverting, doubly auxotrophic, non-pathogenic variants. Experiments using a plant pathogen that affects an element of the local flora will require more stringent containment than if carried out in areas where the host plant is not common.

Experiments with DNAs from eukaryotes (and their plasmids or viruses) can also follow the criteria for the corresponding experiments with *E. coli* K-12 vectors if the major habitats of the given host-vector overlap those of *E. coli*. If the host-vector has a major habitat that does not overlap those of *E. coli* (e.g., root nodules in plants), then the containment conditions for some eukaryotic recombinant DNAs ned to be increased (for instance, higher plants and their viruses in the preceding example) while others can be reduced.

4. *Experiments with eukaryotic host-vectors*—<a> *Animal host-vector systems.* Because host cell lines generally have little if any capacity for propagation outside the laboratory, the primary focus for containment is the vector, although cells should also be derived from cultures expected to be of minimal hazard. Given good microbiological practices, the most likely mode of escape of recombinant DNAs from a physically contained laboratory is carriage by humans; thus vectors should be chosen that have little or no ability to replicate in human cells. To be used as a vector in a eukaryotic host, a DNA molecule needs to display all of the following properties:

(1) It shall not consist of the whole genome of any agent that is infectious for humans or that replicates to a significant extent in human cells in tissue culture.

(2) Its functional anatomy should be known—that is, there should be a clear idea of the location within the molecule of:

(a) The sites at which DNA synthesis originates and terminates,

(b) The sites that are cleaved by restriction endonucleases,

(c) The template regions for the major gene products.

(3) It should be well studied genetically. It is desirable that mutants be available in adequate number and variety, and that quantitative studies of recombination have been performed.

(4) The recombinant must be defective, that is, its propagation as a virus is dependent upon the presence of a complementing helper genome. This helper should either (a) be integrated into the genome of a stable line of host cells (a situation that would effectively limit the growth of the vector to that particular cell line) or (b) consist of a defective genome or an appropriate conditional lethal mutant virus (in which case the experiments would be done under non-permissive conditions), making vector and helper dependent upon each other for propagation. However, if none of these is available, the use of a non-defective genome as helper would be acceptable.

Currently only two viral DNAs can be considered as meeting these requirements: These are the genomes of polyoma virus and SV40.

Of these, polyoma virus is highly to be preferred. SV40 is known to propagate in human cells, both *in vivo* and *in vitro*, and to infect laboratory personnel, as evidenced by the frequency of their conversion to producing SV40 antibodies. Also, SV40 and related viruses have been found in association with certain human neurological and malignant diseases. SV40 shares many properties, and gives complementation, with the common human papova viruses. By contrast, there is no evidence that polyoma infects humans, nor does it replicate to any significant extent in human cells *in vitro*. However, this system still needs to be studied more extensively. Appendix B gives further details and documentation.

Taking account of all these factors:

1. Polyoma virus. a Recombinant DNA molecules consisting of defective polyoma virus genomes plus DNA sequences of any nonpathogenic organism, including Class 1 viruses (5), can be propagated in or used to transform cultured cells. P3 conditions are required. Appropriate helper virus can be used if needed. Whenever there is a choice, it is urged that mouse cells, derived preferably from embryos, be used as the source of eukaryotic DNA. Polyma virus is a mouse virus and recombinant DNA molecules containing both viral and cellular sequences are already known to be present in virus stocks grown at a high multiplicity. Thus, recombinants formed *in vitro* between polyoma virus DNA

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and mouse DNA are presumably not novel from an evolutionary point of view.

b. Such experiments are to be done under P4 conditions if the recombinant DNA contains segments of the genomes of Class 2 animal viruses (5). Once it has been shown by suitable biochemical and biological tests that the cloned recombinant contains only harmless regions of the viral genome (see Section IIIB-2-c-1) and that the host range of the polyoma virus vector has not been altered, experiments can be continued under P3 conditions.

2. SV40 Virus. a. Defective SV40 genomes, with appropriate helper, can be used as a vector for recombinant DNA molecules containing sequences of any non-pathogenic organism or Class I virsus (5), (i.e., a shotgun type experiment). P4 conditions are required. Established lines of cultured cells should be used.

b. Such experiments are to be carried out in P3 (or P4) conditions if the non-SV40 DNA segment is (a) a purified [6] segment of prokaryotic DNA lacking toxigenic genes, or (b) a segment of eukaryotic DNA whose function has been established, which does not code for a toxic product, and which has been previously cloned in a prokaryotic host-vector system. It shall be confirmed that the defective virus—helper virus system does not replicate significantly more efficiently in human cells in tissue culture than does SV40, following infection at a multiplicity of infection of one or more helper SV40 viruses per cell.

c. A recombinant DNA molecule consisting of defective SV40 DNA lacking substantial segments of the late region, plus DNA from non-pathogenic organisms or Class I viruses (5), can be propagated as an autonomous cellular element in established lines of cells under P3 conditions provided that there is no exogenous or endogenous helper, and that it is demonstrated that *no* infectious virus particles are being produced. Until this has been demonstrated, the appropriate containment conditions specified in *2. a.* and *2. b.* shall be used.

d. Recombinant DNA molecules consisting of defective SV40 DNA and sequences from non-pathogenic prokaryotic or eukaryotic organisms or Class I viruses (5) can be used to transform established lines of non-permissive cells under P3 conditions. It must be demonstrated that no infectious virus particles are being produced; rescue of SV40 from such transformed cells by co-cultivation or transfection techniques must be carried out in P4 conditions.

3. Efforts are to be made to ensure that all cell lines are free of virus particles and mycoplasma.

Since SV40 and polyoma are limited in their scope to act as vectors, chiefly because the amount of foreign DNA that the normal virions can carry probably cannot exceed 2×10^6 daltons, the development of systems in which recombinants can be cloned and propagated purely in the form of DNA, rather than in the coats of infectious agents is necessary. Plasmid forms of viral genomes or organelle DNA need to be explored as possible cloning vehicles in eukaryotic cells.

<b> Plant host-vector systems. For cells in tissue cultures, seedlings, or plant parts (e.g., tubers, stems, fruits, and detached leaves) or whole mature plants of small species (e.g., *Arabidopsis*) the P1–P4 containment conditions that we have specified previously are relevant concepts. However, work with most plants poses additional problems. The greenhouse facilities accompanying P2 laboratory physical containment conditions can be provided by: (i) Insect-proof greenhouses, (ii) appropriate sterilization of contaminated plants, pots, soil, and runoff water, and (iii) adoption of the other standard practices for microbiological work. P3 physical containment can be sufficiently approximated by confining the operations with whole plants to growth chambers like those used for work with radioactive isotopes: *Provided,* That (i) such chambers are modified to produce a negative pressure environment with the exhaust air appropriately filtered, (ii) that other operations with infectious materials are carried out under the specified P3 conditions, and (iii) to guard against inadvertent insect transmission of recombinant DNA, growth chambers are to be routinely fumigated and only used in insect proof rooms. The P2 and P3 conditions specified earlier are therefore extended to include these cases for work on higher plants.

The host cells for experiments on recombinant DNAs may be cells in culture, in seedling or plant parts. Whole plants or plant parts that cannot be adequately contained shall not be used as hosts for shotgun experiments at this time, and attempts to infect whole plants with recombinant DNA shall not be initiated until the effects on host cells in culture, seedlings or plant parts have been thoroughly studied.

Organelle or plasmid DNAs and DNAs of viruses of restricted host range may be used as vectors. In general, similar criteria for selecting host-vectors to those given in the preceding section on animal systems are to apply to plant systems.

DNA recombinants formed between the initial moderately contained vectors and DNA from cells of species in which the vector DNA can replicate, require P2 physical containment. However, if the source of the NA is itself pathogenic or known to carry pathogenic agents, or to produce products dangerous to plants, or if the vector is an unmodified virus of unrestricted host range, the experiments shall be carried out under P3 conditions.

Experiments on recombinant DNAs formed between the above vectors and DNAs from other species can also be carried out under P2 if that DNA has been purified [6] and determined not to contain harmful genes. Otherwise, the experiments shall be carried out under P3 conditions if the source of the inserted DNA is not itself a pathogen, or known to carry such pathogenic agents, or to produce harmful products—and under P4 conditions if these conditions are not met.

The development and use of host-vector systems that exhibit a high level of biological containment permit a decrease of one step in the physician containment specified above (P4→P3→P2→P1).

<c> Fungal or similar lower euharyotic host-vector systems. The containment criteria for experiments on recombinant DNAs using these host-vectors most closely resemble those for prokaryotes, rather than those for the preceding eukaryotes, in that the host cells usually exhibit a capacity for dissemination outside the laboratory that is similar to that for bacteria. We therefore consider that the containment guidelines given for experiments with *E. coli* K–12 and other prokaryotic host-vectors (Sections IIIB–1 and –2, respectively) provide adequate direction for experiments with these lower eukaryotic host-vectors. This is particularly true at this time since the development of these host-vectors is presently in the speculative stage.

IV. Roles and Responsibilities

Safety in research involving recombinant DNA molecules depends upon how the research team applies these guidelines. Motivation and critical judgment are necessary, in addition to specific safety knowledge, to ensure protection of personnel, the public, and the environment.

The guidelines given here are to help the principal investigator determine the nature of the safeguards that should be implemented. These guidelines will be incomplete in some respects because all conceivable experiments with recombinant DNAs cannot now be anticipated. Therefore, they cannot substitute for the investigator's own knowledgeable and discriminating evaluation. Whenever this evaluation calls for an increase in containment over that indicated in the guidelines, the investigator has a responsibility to institute such an increase. In contrast, the containment conditions called for in the guidelines should not be decreased without review and approval at the institutional and NIH levels.

The following roles and responsibilities define an administrative framework in which safety is an essential and integrated function of research involving recombinant DNA molecules.

A. *Principal investigator.* The principal investigator has the primary responsibility for: (i) Determining the real and potential biohazards of the proposed research, (ii) determining the appropriate level of biological and physical containment, (iii) selecting the microbiological practices and laboratory techniques for handling recombinant DNA materials, (iv) preparing procedures for dealing with accidental spills and overt personnel contamination, (v) determining the applicability of various precautionary medical practises, serological monitoring, and immunization, when available, (vi) securing approval of the proposed research prior to initiation of work, (vii) submitting information on purported EK2 and EK3 systems to the NIH Recombinant DNA Molecule Program Advisory Committee and making the strains available to others, (viii) reporting to the institutional biohazards committee and the NIH Office of Recombinant DNA Activities new information bearing on the guidelines, such as technical information relating to hazards and new safety procedures or innovations, (ix) applying for approval from the NIH Recombinant DNA Molecule Program Advisory Committee for large scale experiments with recombinant DNAs known to make harmful products (i.e., more than 10 liters of culture), and (x) applying to NIH for approval to lower containment levels when a cloned DNA recombinant derived from a shotgun experiment has been rigorously characterized and there is sufficient evidence that it is free of harmful genes.

Before work is begun, the principal investigator is responsible for: (i) Making available to program and support staff copies of those portions of the approved grant application that describe the biohazards and the precautions to be taken, (ii) advising the program and support staff of the nature and assessment of the real and potential biohazards, (iii) instructing and training this staff in the practices and techniques required to ensure safety, and in the procedures for dealing with accidentally created biohazards, and (iv) informing the staff of the reasons and provisions for any advised or requested precautionary medical practises, vaccinations, or serum collection.

During the conduct of the research, the principal investigator is responsible for: (i)

See footnotes on p. 38459.

Supervising the safety performance of the staff to ensure that the required safety practices and techniques are employed, (ii) investigating and reporting in writing to the NIH Office of Recombinant DNA Activities and the institutional biohazards committee any serious or extended illness of a worker or any accident that results in (a) inoculation of recombinant DNA materials through cutaneous penetration, (b) ingestion of recombinant DNA materials, (c) probable inhalation of recombinant DNA materials following gross aerosolization, or (d) any incident causing serious exposure to personnel or danger of environmental contamination, (iii) invesigating and reporting in writing to the NIH Office of Recombinant DNA Activities and the institutional biohazards committee any problems pertaining to operation and implementation of biological and physical containment safety practices and procedures, or equipment or facility failure, (iv) correcting work errors and conditions that may result in the release of recombinant DNA materials, and (v) ensuring the integrity of the physical containment (e.g., biological safety cabinets) and the biological containment (e.g., genotypic and phenotypic characteristics, purity, etc.).

B. *Institution.* Since in almost all cases, NIH grants are made to institutions rather than to individuals, all the responsibilities of the principal investigator listed above are the responsibilities of the institution under the grant, fulfilled on its behalf by the principal investigator. In addition, the institution is responsible for establishing an institutional biohazards committee[7] to: (i) Advise the institution on policies, (ii) create and maintain a central reference file and library of catalogs, books, articles, newsletters, and other communications as a source of advice and reference regarding, for example, the availability and quality of the safety equipment, the availability and level of biological containment for various host-vector systems, suitable training of personnel and data on the potential biohazards associated with certain recombinant DNAs, (iii) develop a safety and operations manual for any P4 facility maintained by the institution and used in support of recombinant DNA research, (iv) certify to the NIH on applications for research support and annually thereafter, that facilities, procedures, and practices and the training and expertise of the personnel involved have been reviewed and approved by the institutional biohazards committee.

The biohazards committee must be sufficiently qualified through the experience and expertise of its membership and the diversity of its membership to ensure respect for its advice and counsel. Its membership should include individuals from the institution or consultants, selected so as to provide a diversity of disciplines relevant to recombinant DNA technology, biological safety, and engineering. In addition to possessing the professional competence necessary to assess and review specific activities and facilities, the committee should possess or have available to it, the competence to determine the acceptability of its findings in terms of applicable laws, regulations, standards of practices, community attitudes, and health and environmental considerations. Minutes of the meetings should be kept and made available for public inspection. The institution is responsible for reporting names of and relevant background information on the members of its biohazards committee to the NIH.

C. *NIH Initial Review Groups (Study Sections).* The NIH Study Sections, in addition to reviewing the scientific merit of each grant application involving recombinant DNA molecules, are responsible for: (i) Making an independent evaluation of the real and potential biohazards of the proposed research on the basis of these guidelines, (ii) determining whether the proposed physical containment safeguards certified by the institutional biohazards committee are appropriate for control of these biohazards, (iii) determining whether the proposed biological containment safeguards are appropriate, (iv) referring to the NIH Recombinant DNA Molecule Program Advisory Committee or the NIH Office of Recombinant DNA Activities those problems pertaining to assessment of biohazards or safeguard determination that cannot be resolved by the Study Sections.

The membership of the Study Sections will be selected in the usual manner. Biological safety expertise, however, will be available to the Study Sections for consultation and guidance.

D. *NIH Recombinant DNA Molecule Program Advisory Committee.* The Recombinant DNA Molecule Program Advisory Committee advises the Secretary, Department of Health, Education, and Welfare, the Assistant Secretary for Health, Department of Health, Education, and Welfare, and the Director, National Institutes of Health, on a program for the evaluation of potential biological and ecological hazards of recombinant DNAs (molecules resulting from different segments of DNA that have been joined together in cell-free systems, and which have the capacity to infect and replicate in some host cell, either autonomously or as an integrated part of their host's genome), on the development of procedures which are designed to prevent the spread of such molecules within human and other populations, and on guidelines to be followed by investigators working with potentially hazardous recombinants.

The NIH Recombinant DNA Molecule Program Advisory Committee has responsibility for: (i) Revising and updating guidelines to be followed by investigators working with DNA recombinants, (ii) for the time being, receiving information on purported EK2 and EK3 systems and evaluating and certifying that host-vector systems meet EK2 or EK3 criteria, (iii) resolving questions concerning potential biohazard and adequacy of containment capability if NIH staff or NIH Initial Review Group so request, and (iv) reviewing and approving large scale experiments with recombinant DNAs known to make harmful products (e.g., more than 10 liters of culture).

E. *NIH Staff.* NIH Staff has responsibility for: (i) assuring that no NIH grants or contracts are awarded for DNA recombinant research unless they (a) conform to these guidelines, (b) have been properly reviewed and recommended for approval, and (c) include a properly executed Memorandum of Understanding and Agreement, (ii) reviewing and responding to questions or problems or reports submitted by institutional biohazards committees or principal investigators, and disseminating findings, as appropriate, (iii) receiving and reviewing applications for approval to lower containment levels when a cloned DNA recombinant derived from a shotgun experiment has been rigorously characterized and there is sufficient evidence that it is free of harmful genes, (iv) referring items covered under (ii) and (iii) above to the NIH Recombinant DNA Molecule Program Advisory Committee, as deemed necessary, and (v) performing site inspections of all P4 physical containment facilities, engaged in DNA recombinant research, and of other facilities as deemed necessary.

APPENDIX D

V. FOOTOTES

[1] Biological Safety Cabinets referred to in this section are classified as *Class I, Class II* or *Class III* cabinets. A *Class I* cabinet is a ventilated cabinet for personnel protection having an inward flow of air away from the operator. The exhaust air from this cabinet is filtered through a high efficiency or high efficiency particulate air (HEPA) filter before discharged to the outside atmosphere. This cabinet is used in three operational modes; (1) with an 8 inch high full width open front, (2) with an installed front closure panel (having four eight inch diameter openings) without gloves, and (3) with an installed front closure panel equipped with arm lerigth rubber gloves. The face velocity of the inward flow of air through the full width open front is 75 feet per minute or greater. A *Class II* cabinet is a ventilated cabinet for personnel and product protection having an open front with inward air flow for personnel protection, and HEPA filtered mass recirculated air flow for product protection. The cabinet exhaust air is filtered through a HEPA filter. The face velocity of the inward flow of air through the full width open front is 75 feet per minute or greater. Design and performance specifications for *Class II* cabinets have been adopted by the National Sanitation Foundation, Ann Arbor, Michigan. A *Class III* cabinet is a closed front ventilated cabinet of gas tight construction which provides the highest level of personnel protection of all Biohazard Safety Cabinets. The interior of the cabinet is protected from contaminants exterior to the cabinet. The cabinet is fitted with arm length rubber gloves and is operated under a negative pressure of at least 0.5 inches water gauge. All supply air is filtered through HEPA filters. Exhaust air is filtered through HEPA filters or incinerated before being discharged to the outside environment.

[2] Defined as observable under optimal laboratory conditions by transformation, transduction, phage infection and/or conjugation with transfer of phage, plasmid and/or chromosomal genetic information.

[3] The bacteria which constitute Class 2 of ref. 5 ("Agents of ordinary potential hazard . . .") represent a broad spectrum of etiologic agents which possess different levels of virulence and degrees of communicability. We think it appropriate for our specific purpose to further subdivide the agents of Class 2 into those which we believe to be of relatively low pathogenicity and those which are moderately pathogenic. The several specific examples given may suffice to illustrate the principle.

[4] The terms "characterized" and "free of harmful genes" are unavoidably vague. But in this instance, before containment conditions lower than the ones used to clone the DNA can be adopted, the investigator must obtain approval from the National Institutes of Health. Such approval would be contingent upon data concerning: (a) The absence of potentially harmful genes (e.g., sequences contained in indigenous tumor viruses or which code for toxic substances), (b) the relation between the recovered and desired segment (e.g., hybridization and restriction endonuclease fragmentation analysis where applicable), and (c) maintenance of the biological properties of the vector.

[5] A DNA preparation is defined as enriched if the desired DNA represents at least 99% (w/w) of the total DNA in the preparation. The reason for lowering the containment level when this degree of enrichment has been obtained is based on the fact that the total number of clones that must be examined to obtain the desired clone is

markedly reduced. Thus, the probability of cloning a harmful gene could, for example, be reduced by more that 10^8-fold when a non-repetitive gene from mammals was being sought. Furthermore, the level of purity specified here makes it easier to establish that the desired DNA does not contain harmful genes.

* The DNA preparation is defined as purified if the desired DNA represents at least 99 percent (w/w) of the total DNA in the preparation, provided that it was verified by more than one procedure.

† In special circumstances, in consultation with the NIH Office of Recombinant DNA Activities, an area biohazards committee may be formed, composed of members from the institution and/or other organizations beyond its own staff, as an alternative when additional expertise outside the institution is needed for the indicated reviews.

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APPENDIX A TO APPENDIX D

STATEMENT ON THE USE OF BACILLUS SUBTILIS IN RECOMBINANT MOLECULE TECHNOLOGY

Unquestionably, *Escherichia coli* is the most well characterized unicellular organism. Years of basic research have enabled investigators to develop a well characterized genetic map, to obtain detailed knowledge of virulent and temperate bacteriophages, and to explore the physiology, genetics, and regulation of plasmids. More recently, the development of DNA-mediated transformation has permitted exogenous fragments or molecules of DNA to be incorporated into the genome or to reside as self-replicating units. The discovery of transformation of *Bacillus subtilis* by Spizizen (1) stimulated the development of an alternative model system. The purpose of this report is to summarize the current status of this genetic system and to describe the actual and potential vectors and vehicles available for recombinant molecule technology.

A. *Current knowledge of the chromosomal architecture and mechanisms of genetic exchange in B. subtilis.* Two mechanisms of genetic exchange have been utilized to establish the linkage map of *B. subtilis*, DNA-mediated transformation (capable of transferring approximately 1 percent of the genome) and transduction with bacteriophage PBSI (capable of transferring 5–8 percent of the chromosome). Recent detailed genetic studies with PBSI by Lepesant-Kejzlorova *et al.* (2) have resulted in the development of a circular genetic map for this organism. The current edition of the map (3) contains 196 loci. Biophysical analyses have established that the chromosome is circular (4) and replicates bidirectionally (5).

Transformation with purified fragments of DNA is a highly efficient process in *B. subtilis* with frequencies of 1 to 4 percent usually attained for any auxotrophic or antibiotic resistance markers. Frequencies of approximately 10 percent transformation can be achieved with DNA prepared from gently lysed L-forms or protoplasts (6). These large fragments of DNA are readily incorporated by the recipient cell. Generalized transduction occurs with bacteriophages SP10 (7), PBS1 (8), and SPP1 (9), while a low frequency of specialized transduction has been reported with bacteriophage ϕ105 (10).

Although transformation is most efficient in homologous crosses (*B. subtilis* into *B. subtilis*), it has also been possible to exchange DNA among closely related species (11). The most extensively studied members of the *B. subtilis* genospecies include *B. licheniformis*, *B. pumilus*, *B. amyloliquefaciens*, and *B. globigii* (refer to reference 12 for a review and references 13–15 for examples of this heterologous exchange). This exchange occurs even though there is a surprisingly wide discrepancy between DNA–DNA hybridization among these organisms (16). Even though the frequency of transformation is low in the heterologous cross [e.g., *B. amyloliquefaciens* (donor)/*B subtilis* (recipient)], the newly acquired DNA from *B. amyloliquefaciens* in the *B. subtilis* background can be readily transferred at high efficiencies to other recipient strains of *B. subtilis* (14). Therefore, the extremely high frequency of transformation permits the recognition and selection of rare events.

B. *Current and potential vectors for recombinant molecule experiments.* Lovett and coworkers have recently described crypti plasmids in *B. pumilus* (17) and *B. subtilis* (18). Of these organisms, *B. subtilis* ATCC 7003 appears to be the most useful since it carries one to two copies of a plasmid with a molecular weight of 46 $\times$ 10^6. This strain is also closely related to *B. subtilis* 168. Another strain of *B. subtilis* (ATCC 15841) contains 16 copies of a plasmid with a molecular weight of 4.6 $\times$ 10^6. Currently it is not known whether genetic markers can be readily introduced into these plasmids. To date it has not been possible to readily stabilize plasmids derived from *B. pumilus* in *B. subtilis* even with heavy selective pressure (P. Lovett, personal communication).

Two temperate bacteriophages are under development as vectors in *B. subtilis*, Φ3T and SPO2. Lysogeny of thymine auxotrophs (strains carrying *thyA thyB*) by bacteriophage Φ3T results in "conversion" to a Thy$^+$ phenotype. The attachment site for this bacteriophage and the bacteriophage gene for thymidylate synthetase (*thyP*) map between the bacterial *thyA* and *thyB* loci in the terminal region of the chromosome of *B. subtilis* (19). The viral genome is readily cleaved by the site-specific endonuclease, Bam 1 (20), to produce 5 fragments (one of which carries the *thyP* gene). The *thyP* carrying gene can be integrated into the bacterial genome in the absence of the intact viral genome. Because deletions are available that include the *thyP* region, it is theoretically possible to introduce *thyP* at many sites on the chromosome. The *thyP* gene can be readily purified for insertion into plasmids or utilized as a scaffold to integrate other heterologous DNA into the chromosome of *B. subtilis*. Alternatively, it is possible to purify fragments of the chromosome by gel electrophoresis (21, 22), for insertion into bacteriophage Φ3T or SPO2. At present, unfortunately, only the former carries a selective marker, i.e., the gene for thymidylate synthetase, *thyP*.

C. *Development of vehicles. B. subtilis* is a Gram-positive sporulating rod that usually inhabits soil. Although it can exist on cutaneous surfaces of man (23) and experimental animals, it rarely produces disease. To develop a suitable vehicle it is imperative to have a host that is asporogenic. The most appropriate deletion mutation is deletion 29 (cit D). In addition to a deficiency in sporulation this mutant rapidly lyses when it has reached the end of its growth cycle. Presumably this is due to the failure to inactivate one of the autolytic enzymes (24). Through the introduction of a D-alanine requirement (34 ug/ml) it is possible to block transport of compounds that are transported by active transport (25,26). The further introduction of thymine auxotrophy (defects in the *thyA thyB* loci) will enable the strain to survive only with a plasmid vector carrying the purified *thyP* gene from bacteriophage Φ3T or a defective bacteriophage Φ3T carrying the *thyP* gene but attached to the chromosome at an alternative site (due to the presence of deletion 29 in the host). We have recently isolated temperature-sensitive *thyP* mutants. If we can isolate a temperature-dependent lysogen that will grow only at 48°C it should be possible to make an unusual vehicle.

D. *Site-specific endonucleases.* Recently two restriction modification systems have been observed between *B. subtilis* 168 and other bacilli. Trautner *et al.* have isolated an effective system that inhibits infection of the R strain of *B. subtilis* by bacteriophage SPPI propagated on *B. subtilis* 168 (27). The site-specific nuclease recognizes the sequence GGCC.
CCGG
Young, Radnay, and Wilson observed a restriction modificaiton system between *B. amyloliquefaciens* and *B. subtilis* 168 (28). The endonuclease from *B. amyloliquefaciens* (20) recognizes the sequence GGTAC (29).
CCTAGG
More recently, two additional enzymes have been isolated from *B. globigii* (30). The recognition sequence is not known.

E. *Advantages and liabilities of the B. subtilis system*—a. *Advantages.* 1. *B. subtilis* is nonpathogenic. Asporogenic deletion mutants are available to preclude the problem of persistence through sporulation.

2. The circular chromosomal map is well defined. At least 196 loci have been positioned.

3. The organism is commercially important in the fermentation industry.

4. Large numbers of organisms can be disposed of readily with minimal environmental impact.

5. Unlike *E. coli*, it lacks endotoxin in the cell wall. Therefore the cells can be used as a single cell protein source.

6. The frequency of transformation is very high, facilitating the detection of rare events.

7. A unique bacteriophage, ϕ3T, exists that carries a gene that can be readily purified for "scaffolding" experiments.

b. *Disadvantages.* 1. The knowledge of genetics and physiology of plasmids and viruses is primitive compared with *E. coli*.

2. High-frequency, specialized transduction is not available as a means of gene enrichment.

Based on its promise, it seems appropriate, and not chauvinistic, to urge development of this system.

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Appendix B to Appendix D

Polyoma and SV40 Virus

Polyoma virus is a virus of mice, and infection of wild mouse populations is a common events, for the virus has often been isolated from a high proportion of healthy adult animals, both wild and laboratory bred, of many colonies (Gross, L., Proc. Soc. Exp. Biol. *88*, 362–368, 1955; Rowe, W. P., Bact. Rev. *25*, 18–31, 1961). As far as is known the virus almost never causes a disease in these animals. However, when large quantities of the virus are inoculated into newborn or suckling mice or hamsters, a variety of solid tumors is induced (Gross, L., Oncogenic Viruses, Second Edition, Pergamon Press, NY).

Polyoma virus grows lytically in mouse cells in tissue culture. Thus mouse cells in culture are probably transformed only by virus particles that contain certain kinds of defective geonmes. Cells of other rodent species, however, can be transformed by polyoma virus particles that contain complete genomes (Folk, W., J. Virol., *11*, 424–431, 1973). The virus does not replicate to a significant extent in human cells in tissue culture (Eddy, B.E., Virol. Monogr., *7*, 1–114, 1969; Pollack, R. E., Salas, J., Wang R. Kusano T., and Green, H., J. Cell Physiol. *77*, 117–120, 1971). The resistance of the cells seems to be a consequence of the failure of the virus to absorb or uncoat. However even when naked viral DNA is introduced into the cells only an abortive cycle of replication ensues; early viral proteins are made, there is induction of cellular DNA synthesis, but no expression of late viral proteins is detectable (Gruen, R., Grassmann, M. and Grassmann, A. Virology, *58*, 290–293, 1974).

There is no evidence that polyoma virus can infect humans (Hartley, J., Huebner, R., Parker, J. and Rowe, W. P., unpublished data). Thus no antibodies to the virus have been detected in people living in buildings that are infested with virus-infected mice, nor in laboratory workers who have been exposed to the virus for a number of years.

At most, a small segment of polyoma virus DNA shows weak homology with a portion of the late region of SV40 DNA (Ferguson, J. and Davis, R. W., J. Mol. Biol., *94*, 135–150, 1975). However, there appears to be no genetic interaction between the two viruses and there is no immunological cross-reaction between the gene products of the two viruses.

SV40 causes persitent but apparently harmless infections of the kidneys of virtually all adult rhesus monkeys (Hsiung, G. D., Bact. Revs. *32*, 185–205, 1968), it causes tumors when injected into newborn hamsters (Girardi, A. J., Sweet, B. H., Slotnick, V. B. and Hillemann, M. R., Proc. Soc. Exp. Biol. Med., *105*, 420–427, 1964) and transforms cells of several mammalian species (including human). SV40 is able to infect humans since antibodies to the virus are found in a small proportion of the human population (Shah, K. V., Goverdhan, M. K. and Ozer, H. L., Am. J. Epid. *93*, 291–298, 1970) and serum conversions have been noted in many laboratory personnel who have been exposed to the virus (Horvath, L. B., Acta Microbiol. Acta Sci. Hung. *12*, 201–206, 1965).

Isolations of SV40 have been reported from humans, twice from patients suffering from the rare demyelinating disease, progressive multifocal leukoencephalopathy (Weiner, L., Herndon, R., Narayon, O., Johnson, R. T., Shah, K., Rubinstein L. G. Prezozisi T. J. and Conley, F. K., New England J. Med *286*, 385–390, 1972) and apparently from a tumor of a person with metastatic melanoma (Soriano, F., Shelburne, C. E. and Gokcen, M., Nature, *249*, 421–424, 1974). In other studies a nonstructural antigen characteristic of papovaviruses, T antigen, has been detected in the nuclei of cells cultured from 2 meningiomas, while another SV40-specific antigen, U antigen, has been found in the cells of a third tumor of the same type (Weiss, A. F., Portman, R., Fisher, H., Simon, J. and Zang, K. D., Proc. Nat. Acad. Sci. USA *72*, 609–613, 1975). Furthermore new papovaviruses have been isolated from the brains of patients with PML (JC virus-Padgett, B. L., Walker, D. L., zuRhein, G. M., Eckroade, R. I. and Dessel, B. H., Lancet *1*, 1257–1260, 1971), from the urine of a patient carrying a renal allograft (BK virus-Gardner, S. D., Field, A. M., Coleman, D. V. and Hulme, B. Lancet *1*, 1253–1257, 1971) and from a reticulum cell sarcoma and the urine of patients with the sex-linked recessive disorder, Wiskott-Aldrich syndrome (Takemoto, K. K., Rabson, A. S., Mullarkey, M. F., Blaese, R. M. Garon, C. F. and Nelson, D. J., Nat. Cancer Inst., *53*, 1205–1207, 1974). All of these viruses which are distributed widely throughout human populations share antigenic and biological properties with SV 40; the virus particles are identical in size and architecture (Madeley, C. R., In Virus Morphology, Churchill-Livingstone, London, 134–135, 1972); the non-structural intracellular T antigen, which appears to be coded by the A gene of SV40 cross reacts extensively with antigens found in cells infected or transformed by BK or JC viruses; both JC and BK viruses induce tumors in newborn hamsters (Walter, D. L., Padgett, B. L., zuRhein, B. M., Albert, A. E. and Marsh, R. F., Science *181*. 674–676, 1973: Shah, K. V., Daniel, R. W. and Strandberg, J., J. Nat. Cancer Inst. *54*, 945–950, 1975); BK virus causes transformation of hamster cells in culture (Major, E. D., and DiMayorca, G., Proc. Nat. Acad. Sci. US *70*, 3210–3212, 1973; Portolani, M., Barbanti, A., Brodano, G, and LaPlaca, M.J., Virol, *15*, 420–422, 1975) and is able to complement the growth of certain temperature-sensitive mutants of SV40 (Mason, D. H. and Takemoto, K. K., submitted for publication).

Further Work

At present, a potential eukaryotic vector of choice is polyoma virus. And while available information indicates that it fulfills all the necessary criteria, we recommend that the following subjects be further investigated:

1. The molecular mechanism of resistance of human cells to the virus.

2. The extent of homology between polyoma virus DNA and the DNAs of human papovaviruses.

3. The ability of human papovaviruses to complement defective polyoma virus genomes.

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APPENDIX C TO APPENDIX D

SUMMARY OF THE WORKSHOP ON THE DESIGN AND TESTING OF SAFER PROKARYOTIC VEHICLES AND BACTERIAL HOSTS FOR RESEARCH ON RECOMBINANT DNA MOLECULES

Torrey Pines Inn, La Jolla, California

The development of techniques for the cloning of DNA from both prokaryotic and eukaryotic organisms in bacteria has had great impact on research in biology and medicine and promises extraordinary social benefits. The biohazards involved in the use of this technology in many instances are very difficult to assess. For this reason codes of practice are being formulated in the United States and other countries for the conduct of those experiments that present a potential biohazard. One of the requirements for conducting certain cloning experiments is the use of safer vector (bacteriophage or plasmid) -host systems, i.e., vector-bacterium systems that have restricted capacity to survive outside of controlled conditions in the laboratory. Approximately sixty scientists from the United States and several foreign countries participated in a workshop on the Design and Testing of Safer Prokaryotic Vehicles and Bacterial Hosts for Research on Recombinant DNA Molecules at La Jolla, California, on December 1 to 3, 1975. The workshop was sponsored by the Research Resources Branch of the National Institute of Allergy and Infectious Diseases. The purposes of the meeting were the exchange of recent data on the development of safer prokaryotic host-vector systems, devising methods of testing the level of containment provided by these systems and exploring the various directions that future research should take in the construction of safer bacterial systems for the cloning of foreign DNA.

The first session of the workshop, chaired by W. Szybalski (University of Wisconsin), was devoted to bacteriophage vectors. Szybalski outlined the main safety features of the two-component, phage-bacterial system, in which the host bacteria offer the safety feature of not carrying the cloned DNA, and the phage vectors cannot be propagated in the absence of an appropriate host. There are two primary escape routes for the clones of foreign DNA carried by the phage vector: (1) Establishment of a stable prophage or plasmid in the laboratory host used for phage propagation, and subsequent escape of this self replicating lysogen or carrier system, and (2) escape of the phage vector which carries the cloned DNA and its subsequent productive encounter with a suitable host in the natural environment. The general consensus was that to ensure safety, both routes should be blocked by appropriate genetic modifications. For phage λ, route (1) can be blocked by phage mutations that interfere with lysogenization (*att*-, *int*-, cI-, cIII-, *vir*) and plasmid formation (*N*$^+$, *nin*R, *v*S, *ri*^{c}, c17, Ots, *cro*ts), and by mutations on the *Escherichia coli* host that affect these processes (*att*B-, *dnc*Ats) and host survival. Route (2), (which is of low probability since λ phages do not survive well in natural environments (no λcI phage was recovered after ingestion of 10^8–10^{11} particles), are killed by desiccation, and have a low chance to encounter a naturally sensitive host) can be blocked further by the following phage modifications: (a) Mutations which result in extreme instability of the infectious phage particles under all conditions other than those specially designed for phage propagation in the laboratory (e.g., high concentrations of putrescine or some other compound), or (b) employing phage vectors in which the tail genes are deleted and which permit propagation of only the DNA-packed heads; only under laboratory conditions could such heads be made transiently infectious by rejoining them with separately prepared tails. The high instability of the phage would minimize the possibility of transfer of the cloned genes into receptive bacteria found in nature. Moreover, the propagation of the phage can be blocked by many conditional mutations, which would be designed to block any secondary route of escape, mainly depending on transfer of the cloned DNA into another phage or bacterial host. It was recommended further that the vector be designed in such a manner as to permit easy insertion and monitoring of the foreign DNA and rapid assay of the safety features and give a high yield of cloned DNA (not less than 10^{11} molecules per ml). There also was general agreement that host-phage systems other than *E. coli* should be considered, especially those restricted to very rare and unusual environments. Also, plasmids derived from phage vectors and which give very high DNA yields while exhibiting safety features, e.g., λdv*cro*ts, should be considered as vehicles for cloned DNA.

Szybalski and S. Brenner (Cambridge University) stressed that research on recombinant DNA molecules may lend itself to very simple and inexpensive mechanical containment, e.g., a small sealed glove box, since all the vectors that carry such recombinant molecules possibly can be both created and destroyed in such a box, while development of special methods might permit study of many properties of the recombinant DNA, without ever removing it from the box.

These safety features were reflected in the subsequent presentations. F. Blattner and W. Williams (Universiy of Wisconsin) described four specially constructed λ-φ80 phages which incorporate many of these safety features, and which they named Charon phages, for the mythical boatman of the river Styx. Some of these highly contained phages give yields of over 10^{11} particles/ml. R. Davis, J. Cameron and K. Struhl (Stanford University) found that λ phages that carry foreign DNA never grow as well as the parental vector, which would select against their survival in nature. They also reported that some eukaryotic genes could be expressed in *E. coli*, partially compensating for deficiencies in the histidine pathway or in *polA* or *lig* functions. These investigators surveyed over 1000 strains of *E. coli* isolated in the natural environment and did not find a single strain that could support propagation of the λ*vir* vector.

V. Bode (Kansas State University) discussed the possibility of growing tail-free λ heads. Such heads, which are packed with DNA, are very fragile, unless stored in 0.1 M putrescine buffer. Head yields close to 10^{11}/ml could easily be attained and, when required, heads could be quantitatively rejoined with separately supplied tails under special laboratory conditions. W. Arber, D. Scandella and J. Elliott (University of Basel) described bacterial host mutants that permit efficient infection only by phages with a full complement of DNA. This permits selecting for vectors that carry long fragments of foreign DNA.

K. Matsubara, T. Mukai and Y. Takagi (University of Osaka and Kyushu University), and G. Hobom and P. Phillippsen (University of Freiburg and Stanford University) described various defective λ plasmids (λdv) that could be used as efficient vectors. Matsubara has shown that temperature-sensitive *cro* mutations permit obtaining between 1000 and 3000 cloned molecules per cell and at the same time result in killing of the carrier cells at body temperature. The mutations Ots and *P*ts were also evaluated as safety features. Phillippsen described many new λdv plasmids created by cutting λ DNA with *Hind*III and *Bam*I restriction endonucleases followed by ligation. The final talk by F. Young, G. Wilson and M. Williams (University of Rochester) summarized the progress on the development of safer *Bacillus subtilis* host mutants and phages, especially φ3, as vectors. New restriction nucleases, Bgl–1 and Bgl–2, were also described.

The morning session on bacteriophage vectors was followed by a session on plasmid vectors that was chaired by D. Helinski (University of California, San Diego). Helinski presented the following properties as highly desirable characteristics of a safer plasmid vehicle: (a) Non-conjugative; (b) non-mobilizable or poorly mobilizable by a conjugative plasmid; (c) possesses little or no extraneous genetic information; (d) poorly recombines or does not recombine with the chromosome of the host cell; (e) provides no selective advantage to the host cell or the selective property is conditional; and (f) possesses mutations that restrict its maintenance to a specific host, prevent replication at mammalian body temperature and/or provide with the capability of killing any cell to which it might be transmitted other than the host cell. V. Hershfield (University of California, San Diego) described the properties of a variety of derivatives of the ColE1 derivatives, ColE1-*trp*, constructed in collaboration with C. Yanofsky and N. Franklin (Stanford University) provides the means to use the tryptophan genes of *E. coli* as a selective marker in transformation with recombinant DNA in situations where it is desirable to avoid antibiotic resistance genes. In addition, Hershfield described collaborative work with H. Boyer that resulted in the development of a mini-ColE1 plasmid and derivatives of this plasmid (mini-ColE1-*kan* and mini-ColE1-*trp*) as cloning vehicles. Finally, she described the temperature-sensitivity properties of *trp* and *kan* derivatives of a temperature-sensitive replication mutant of ColE1 isolated by J. Collins (Molecular Biology Institute, Stockheim) and hybrid ColE1 plasmids carrying the *Eco*RI generated Cts fragment of bacteriophage λ-trp61.

J. Carbon (University of California, Santa Barbara) described a replica plating method that greatly facilitates the detection of *E. coli* clones bearing ColE1 plasmids. The procedure, which utilizes the F' plasmid to promote the transfer of a hybrid ColE1 plasmid to a suitable auxotrophic recipient, was successful in identifying clones bearing hybrid plasmids carrying a number of different regions of the *E. coli* chromosome. The contributions of A. J. Clark and collaborators (University of California, Berkeley) were relevant to the problem of the mobilization and subsequent transfer of non-conjugative plasmids carrying foreign DNA of a potentially hazardous nature. Clark described the variations in transmission frequencies between the nonconjugative plasmids pSC101, pML31, pSC138 and a number of pSC101 hybrids containing various *Eco*RI fragments of F when the conjugal transfer of these plasmids was promoted by several different conjugative plasmids.

I. C. Gunsalus and collaborators (University of Illinois) and A. Chakrabarty (General Electric Research and Development Center)

described the properties of a variety of plasmids isolated from *Pseudomonas putida*. These contributions were followed by a discussion on the merits of developing plasmid-host systems involving *Pseudomonas* strains that naturally exhibit unusual growth requirements. Similar studies with plasmids isolated from *Bacillus megaterium* by B. Carlton (University of Georgia) from *B. subtilis* by P. Lovett (University of Maryland) and other naturally occurring *Bacillus* species by W. Goebel and K. Bernhard (Microbiology Institute, Wurzburg) were discussed and their further development as plasmid-host cloning systems was explored. It was clear from these presentations that considerable progress has meen made recently in the identification and characterization of a variety of plasmid elements that occur naturally in *Pseudomonas* and *Bacillus* species. Several of the plasmids described show considerable promise as plasmid cloning systems involving a host other than *E. coli*.

A third session on the ecology and epidemiology of vector-host systems was chaired by S. Falkow (University of Washington). This workshop emerged, in part, from expressed fears that microorganisms containing cloned fragments of foreign DNA may potentially pose a threat to health or disrupt the normal ecological chain in some manner. Consequently, this session was devoted to a review of currently available information on the ecology and epidemiology of *E. coli* and related bacterial species since it was recognized that *E. coli* K–12 would be the prokaryotic host most commonly employed in the cloning of DNA molecules in the immediate future. F. Ørskov (Escherichia Reference Center, Copenhagen) reviewed the state of *E. coli* serotyping and what has been learned about the distribution of *E. coli* types in health and disease. Only certain *E. coli* types are generally recognized as good colonizers of the human gut and such strains come from a handful of the 160 well defined O (lipopolysaccharide) antigen types and invariably possess K (acidic polysaccharide capsule) antigens. Some serotypes apparently have become disseminated worldwide and possibly represent the proliferation of a bacterial clone because of, as yet unknown, selective pressures. In contrast, *E. coli* K–12 has no detectable O or K antigens and is considered to be rough. This may account, at least in part, for its demonstrate poor ability to colonize the human or animal gut. However, R. Freter (University of Michigan) pointed out that we still remain largely ignorant of the factors which control intestinal *E. coli* populations. Freter also noted that while adherence to the mucosal surface of the small intestine is important in the pathogenesis of *E. coli* diarrheal disease, the 'normal' long-lasting symbiotic relationship between a mammalian host and bacterium is established in the cecum and colon. It is in these locations that factors come into play to determine whether an *E. coli* strain passing through the intestine will become successfully implanted or whether it will be quickly eliminated in the feces. The factors controlling implantation include competition for substrates, inhibitors and the physiological state of the organism when it reaches the large bowel. For example, ingested *E. coli* previously grown under usual laboratory conditions fare poorly while cells of the same strain 'pre-adapted' in Eh, pH, etc., often colonize well. Freter has developed a continuous flow culture model which may be useful in studying the mechanisms of implantation. Falkow reviewed the pathogenicity of *E. coli*. *E. coli* causes diarrheal disease either by direct invasion of the bowel epithelium or by elaboration of enterotoxin(s). While invasive *E. coli* appear to owe their pathogenicity to a constellation of at least five unlinked chromosomal gene clusters, toxigenic *E. coli* species generally owe their pathogenicity to the possession of two species, Ent and K. The introduction of Ent and K plasmids may be sufficient to convert a normal wild-type *E. coli* into a strain now capable of causing overt clinical disease. However, the introduction of these plasmids into *E. coli* K–12 sublines had no discernible effect on their ability to cause disease, although the K–12 strains could now better colonize calves. Despite the observation that *E. coli* K–12 did not appear to offer a significant hazard as a potential enteric pathogen even when it possessed well-defined determinants of pathogenicity it was emphasized by Ørskov, Freter and Falkow that *E. coli* K–12 strains carrying recombinant DNA molecules could still act as effective genetic donors *in vivo* and still posed a significant problem requiring control. E. Geldreich (U.S. Environmental Protection Agency, Cincinnati, Ohio) discussed the possible outcomes of the release of *E. coli* containing recombinant DNA molecules into the aquatic environment and concluded that total reliance cannot be placed on sewage treatment and the natural self-purification capacity of receiving waters to limit potential hazards. While these are realistic barriers to the dissemination of *E. coli* and associated fecal organisms via the water route, they are not infallible because of technological limitations, improper operational practices and system overloading. Finally, M. Starr (University of California, Davis) described the numerous genera of gram-negative bacteria found naturally occurring in the soil and on plants. He stated that most of these organisms do not appear to be a reasonable alternative to *E. coli* K–12 as a host for recombinant DNA molecules. Indeed, Starr pointed out that since such genera as *Erwinia*, *Rhizobium* and *Agrobacterium* are known to conjugate with *E. coli*, the potential dissemination of recombinant DNA molecule includes a greater spectrum of microorganisms than just enteric species.

The fourth session of the workshop, chaired by R. Curtiss III (University of Alabama), was concerned with the construction of safer bacterial hosts for DNA cloning. The goals in constructing safer host strains enumerated at the beginning of the session included introduction of mutations that would: (a) Preclude colonization in normal ecological niches; (b) preclude cell wall biosynthesis except in specially defined media; (c) cause degradation of genetic information in normal ecological niches; (d) cause vectors to be host-dependent; (e) minimize transmission of recombinant DNA to other strains in normal ecological niches; (f) increase usefulness for recombinant DNA molecule research; and (g) permit monitoring.

Most of the progress in developing safer hosts has been achieved with *E. coli* K–12, although F. Young described a *B. subtilis* strain with a deletion for sporulation genes which readily undergoes autolysis. The strain also has defects in genes for purine and TTP biosynthesis and a mutation conferring a D-alanine requirement can be introduced to cause cell wall biosynthesis to be defective. This strain may be defective in transformation, however, and therefore might be useful only with a phage vector which has yet to be developed and/or discovered.

A. I. Bukhari (Cold Spring Harbor Laboratory) described the use of the *dapD8* mutation in *E. coli* K–12 to block cell wall biosynthesis and another non-reverting mutation which causes sensitivity to bile salts and detergents. The *dapD8* allele is the most stable *dap* point mutation known, although it does revert at frequencies of 10^{-8} to 10^{-9}. The mutation conferring bile salts sensivity was obtained after Mu-1 infection of an Hfr strain and, although exhibiting the theoretically useful properties of ease of DNA isolation and inability to survive in the intestinal tract, might be due to Mu insertion which would compromise its use for safe strain construction.

Curtiss reported on the work performed by him and his coworkers in constructing and testing numerous strains with different mutations. Survival of strains *in vivo* was tested by feeding rats 10^{10} cells in milk by stomach tube. *Δpur* mutations did not reduce strain titers in feces whereas *ΔthyA; ΔthyA drm;* and *ΔthyA dra* mutations gave 10^{3}-fold, 10^{5}-fold and 10^{6}-fold reductions, respectively, in strain titers in feces. Strains with *ΔthyA* mutations also exhibited thymineless death in *in vitro* tests. Since strains with *dapD8* allele can revert to Dap^{+}, strains were constructed with both *dapD8* and *ΔbioH-asd* mutations. These strains have not been observed to revert to Dap^{+} but can survive passage through the rat intestine and in growth media lacking diaminopimelic acid but containing NaCl and 0.5% usable carbon sources. This survival was due to the production of the mucopolysaccharide, colanic acid, which permits many of the cells to grow and survive as spheroplasts. A *Δgal-chl*^{r} mutation (also deletes *λatt, bio* and *uvrB* genes) was introduced which blocks colanic acid biosynthesis and leads to no detectable survivors in media lacking diaminopimelic acid or following passage through the rat intestine. The *dapD8 ΔbioH-asd Δgal-chl* strains are more readily lysed, transform at higher frequencies and are conjugation-defective in matings with donors possessing conjugative plasmids in the P, W and O incompatability groups but Con^{+} as recipients for F, I and T group plasmids when compared to the *dap*$^{+}$ *gal*$^{+}$ parent strain. Strains with *endA* mutations were also observed to exhibit increased transformation frequencies. Attempts to introduce temperature-sensitive *polA* alleles into strains to block replication of ColE1 cloning vectors at elevated temperatures and to cause DNA degradation at elevated temperatures in the presence of *recA* and *ΔthyA* alleles often do not have the same properties in the constructed strains as in the strains in which the allele was originally induced. Many mutations causing a Con^{-} phenotype have been investigated, but many of these revert and/or do not exhibit a Con^{-} phenotype in matings with donors possessing conjugative plasmids of the incompatibility groups commonly found in enteric microorganisms. Some Con^{-} mutants exhibit increased sensitivity to bile salts; thus, the mutant described by Bukhari may also exhibit a Con^{-} phenotype. All of the strains constructed by the Curtiss group are SuI^{+} and most have mutations abolishing restriction alone or both restriction and modification. Thus, sufficient information is now known to construct a usable safer *E. coli* K-12 host. Curtiss and collaborators are now introducing *ΔthyA* and *dna* mutations into their *dapD8 ΔbioH-asd Δgal-chl*^{r}*-uvrB hsr nalA*^{r} (for ease in monitoring) Su^{+} λ^{r} $\Phi 80^{r}$ strain to accomplish this objective.

The final session involved a general discussion of some of the major points raised previously in the workshop. There was general agreement at this session that both plasmid-host and phage-host systems have been developed that should meet the criteria of an EK2 system specified by the National Institutes of Health guidelines for research on recombinant DNA molecules. Additional testing is required to confirm the EK2 properties of these available systems, but it is anticipated that these vector-host systems will meet these tests.

Dr. Donald R. Helinski, University of California, San Diego.
Dr. Stanley Falkow, University of Washington.
Dr. Roy Curtiss III, University of Alabama.
Dr. Waclaw Szybalski, University of Wisconsin.

Appendix D to Appendix D

Supplementary Information on Physical Containment

Contents

I. Biological safety cabinets.
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I. Biological Safety Cabinets

Biological Safety Cabinets suitable for confining operations involving recombinant DNA molecules are described below:

1. *Class I.* A ventilated cabinet for personnel protection only, with an unrecirculated inward flow of air away from the operator. The exhaust air from this cabinet may be filtered through a high-efficiency or high-efficiency particulate air (HEPA) filter before being discharged to the outside atmosphere. This cabinet is suitable for research work with the Center for Disease Control (CDC) classes of etiologic agents 1, 2 and 3 where no product protection is required. This cabinet may be used in three operational modes: (i) With an eight-inch high, full-width open front; (ii) with an installed front closure panel (having four, eight-inch diameter openings) without gloves; and (iii) with an installed front closure panel equipped with arm length rubber gloves. See Table I for ventilation requirements, agent use limitations, and minimum performance requirements.

2. *Class II.* A ventilated cabinet for personnel and product protection having an open front with inward air flow for personnel protection, and HEPA-filtered recirculated mass air flow for product protection. The cabinet exhaust air is filtered through a HEPA filter. Two models of this cabinet are available, Type 1 and Type 2.

(i) *Type 1.* The Type 1 recirculates approximately 70 percent of the air. The exhaust air from this cabinet may discharge into the laboratory or be diverted out of the laboratory. This cabinet is suitable for CDC classes of etiologic agents 1, 2, and 3. Vapors or gases which are hazardous from a toxic, radioactive, or flammability standpoint should not be used in this cabinet because of the high quantity of recirculated air.

(ii) *Type 2.* The Type 2 cabinet recirculates approximately 30 percent of the air. The exhaust air from this cabinet is normally ducted out of the laboratory through a HEPA filter and, occasionally, an activated charcoal filter depending on the operation. The cabinet may be used with gases or vapors that are hazardous from a toxic, radioactive, or flammability standpoint. However, any consideration of use of such materials should be evaluated carefully from the standpoint of build-up to dangerous levels and problems of decontamination of the cabinet. See Table I for ventilation requirements, agent use limitations, and minimum performance requirements.

3. *Class III.* A closed front ventilated cabinet of gastight construction providing total protection for personnel and product from contaminants exterior to the cabinet. The cabinet is operated under a negative pressure of at least 0.5 inches water gauge. All supply air is HEPA-filtered. Exhaust air is HEPA-filtered or incinerated to protect the environment. This cabinet, fitted with arm length rubber gloves, provides the highest containment of these three classes of cabinets and is utilized for all activities involving high risk agents (i.e., CDC etiologic agents, class 4). See Table I for ventilation requirements, agent use limitations, and minimum performance requirements.

The integrity of any cabinet depends on initial and periodic evaluation to meet established performance tests. Table I outlines the minimum performance required to assure that the cabinets will provide protection of personnel and the environment.

TABLE I

BIOLOGICAL SAFETY CABINETS

SAFETY PERFORMANCE REQUIREMENTS AND SPECIFICATIONS
JUNE 1976

CABINET	USE CLASSIFICATION		PERFORMANCE REQUIREMENTS				
	DNA[a]	CDC[b]	FACE VELOCITY (linear feet per minute)	EXHAUST AIR (CFM)[c] 4'hood	6'hood	LEAK TIGHTNESS	EXHAUST FILTER EFFICIENCY
Class I	P1-P3	1-3	75	200	300	Not applicable	99.97%
Class II, Type 1	P1-P3	1-3	75	260	400	Gas tight; Leak rate < $1x10^{-5}$ cc/sec at 2"wg pressure	99.97%
Class II, Type 2	P1-P3	1-3	100	250	360	Pressure tight; No air/soap bubble at 2"wg pressure	99.97%
Class III	P4	4	Not applicable	d	d	Gas tight; Leak rate < $1x10^{-6}$ cc/sec at 3"wg pressure	99.97%

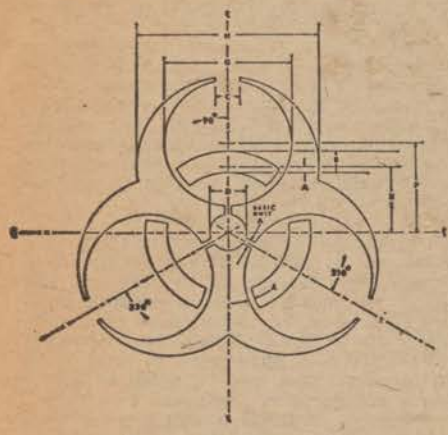
a - For work with recombinant DNA molecules.
b - Center for Disease Control (US Public Health Service).
c - CFM-cubic feet per minute.
d - Based on one volume of air change each 3 minutes, in the absence of unusual heat or moisture that would require more air changes.

APPENDIX D, Page D-4

II. UNIVERSAL BIOHAZARD WARNING SYMBOL (1)

The biological hazard warning symbol (biohazard symbol) specified herein shall be used to signify the actual or potential presence of a biohazard and to identify equipment, containers, rooms, materials, experimental animals or combinations thereof which contain or are contaminated with viable hazardous agents.

The biohazard symbol shall be designed and proportioned as illustrated here:



DIMENSION	A	B	C	D	E	F	G	H
UNITS	7	3½	4	11	12	31	30	

The symbol shall be as prominent as practical, and of a size consistent with the size of the equipment or material to which it is affixed, provided the proportions shown above are maintained, and, in any case, that the symbol can be easily seen from as many directions as possible.

Except when circumstances do not permit, the symbol shall be oriented with one of the three open circles pointed up and the other two forming a base.

The symbol color shall be a fluorescent orange or orange-red color.* Background color is optional as long as there is sufficient contrast for the symbol to be clearly defined.



Revised 9-9-66

*Day-Glo® Fire Orange of the Switzer Brothers, Inc. is cited as an example, not an endorsement.

The biohazard symbol shall be used or displayed only to signify the actual or potential presence of biological hazard.

Appropriate wording may be used in association with the symbol to indicate the nature or identity of the hazard, name of individual responsible for its control, precautionary information, etc., but never should this information be superimposed on the symbol. (See next page)



ADMITTANCE TO AUTHORIZED PERSONNEL ONLY

Hazard identity: _____

Responsible Investigator: _____

In case of emergency call:

Daytime phone _____ Home phone _____

Authorization for entrance must be obtained from the Responsible Investigator named above.

III. LABORATORY TECHNIQUES FOR BIOHAZARD CONTROL

A. *Pipetting.* 1. No infectious or toxic materials should be pipetted by mouth (2, 3, 4).

2. No infectious mixtures should be prepared by bubbling expiratory air through a liquid with a pipette (2, 3, 4).

3. No infectious material should be blown out of pipettes (2, 3, 4).

4. Pipettes used for the pipetting of infectious or toxic materials should be plugged with cotton (2, 3, 4).

5. Contaminated pipettes should be placed horizontally in a pan containing enough suitable disinfectant to allow complete immersion (2, 3, 4). They should not be placed vertically in a cyclinder.

6. The pan and pipettes should be autoclaved as a unit and replaced by a clean pan with fresh disinfectant (2, 3, 4).

7. Infectious material should not be mixed by alternate suction and expulsion through a pipette (2, 3, 4).

8. Mark-to-mark pipettes are preferable to other types, as they do not require expulsion of the last drop (5).

9. Discharge should be as close as possible to the fluid or agar level, or the contents should be allowed to run down the wall of the tube or bottle whenever possible—not dropped from a height (5).

10. A disinfectant-wetted towel over the immediate work surface is useful in some cases to minimize the splash from accidental droppage (9).

B. *Syringes and Needles* (9). 1. To lessen the chance of accidental injection, aerosol production or spills, avoid unnecessary use of the syringe and needle. For instance:

(i) Use the needle for parenteral injections but use a blunt needle or a cannula on the syringe for oral or intranasal inoculations.

(ii) Do not use a syringe and needle as a substitute for a pipette in making dilutions of dangerous fluids.

2. Use the syringe and needle in a Biological Safety Cabinet only and avoid quick and unnecessary movements of the hand holding the syringe.

3. Examine glass syringes for chips and cracks, and needles for barbs and plugs.

NOTE: This should be done *prior* to sterilization before use.

4. Use needle-locking (Luer-Lok® type) syringes only, and be sure that the needle is locked securely into the barrel. A disposable syringe-needle unit (where the needle is an integral part of the unit) is preferred.

5. Wear surgical or other type rubber gloves for all manipulations with needles and syringes.

6. Fill the syringe carefully to minimize air bubbles and frothing of the inoculum.

7. Expel excess air, liquid and bubbles from a syringe vertically into a cotton pledget moistened with the proper disinfectant, or into a small bottle of sterile cotton.

8. Do not use the syringe to expel forcefully a stream of infectious fluid into an open vial or tube for the purpose of mixing. Mixing with a syringe is condoned only if the tip of the needle is held below the surface of the fluid in the tube.

9. If syringes are filled from test tubes, take care not to contaminate the hub of the needle, as this may result in transfer of infectious material to the fingers.

10. When removing a syringe and needle from a rubber-stoppered bottle, wrap the needle and stopper in a cotton pledget moistened with the proper disinfectant. If there is danger of the disinfectant contaminating sensitive experiments, a sterile dry pledget may be used and discarded immediately into disinfectant solution.

11. Inoculate animals with the hand "behind" the needle to avoid punctures.

12. Be sure the animal is properly restrained prior to the inoculation, and be on the alert for any unexpected movements of the animal.

13. Before and after injection of an animal, swab the site of injection with a disinfectant.

14. Discard syringes into a pan of disinfectant without removing the needle. The syringe first may be filled with disinfectant by immersing the needle and slowly withdrawing the plunger, and finally removing the plunger and placing it separately into the disinfectant. The filling action clears the needle and dilutes the contents of the syringe. Autoclave syringes and needles in the pan of disinfectant.

15. Use separate pans of disinfectant for disposable and nondisposable syringes and needles to eliminate a sorting problem in the service area.

16. Do not discard syringes and needles into pans containing pipettes or other glassware that must be sorted out from the syringes and needles.

C. *Opening Culture Plates, Tubes, Bottles, and Ampoules.* 1. Plates, tubes and bottles of fungi may release spores in large nur bers when opened. Such cultures should be manipulated in a Biological Safety Cabinet (6,15).

2. In the absence of definite accidents or obvious spillage, it is not certain that opening of plates, tubes and bottles of other microorganisms has caused laboratory infection. However, it is probable that among the highly infective agents, some infections have occurred by this means and are represented in the 80% for which no known act or accident is ascribable (3).

3. Water of syneresis in petri dish cultures is usually infected and forms a film between the rim and lid of the inverted

plate. Aerosols are dispersed when this film is broken by opening the plate. Vented plastic petri dishes where the lid touches the rim at only three points are less likely to offer this hazard (8,19).

4. The risk may also be minimized by using properly dried plates, but even these (when incubated anaerobically) are likely to be wet after removal from an anaerboci jar. Filter papers fitted into the lids reduce, but do not prevent, dispersal. If plates are obviously wet they should be opened in the Biological Safety Cabinet (8).

5. Less obvious is the release of aerosols when screw-capped bottles or plugged tubes are opened. This happens when a film of infected liquid which may collect between the rim and the liner is broken during removal of the closure (8).

6. Dried, infected culture material may also collect at or near the rim or neck of culture tubes and may be disposed into the air when disturbed (18). Containers of dry powdered hazardous materials, (e.g., Class 3 fungal agents in the spore phase of growth) should be opened only in a Biological Safety Cabinet (6, 14).

7. When the neck of an ampoule containing liquid is broken after nicking with a file, the snapping action creates aerosols. The following methods have been recommended:

(i) After nicking the ampoule with a file, wrap the ampoule in disinfectant-wetted cotton before breaking. Wear gloves (2).

(ii) The bottom of the ampoule should be held in several layers of tissue paper to protect the hands, and a file mark made at the neck. A hot glass rod should be carefully applied to the mark. The glass will crack, allowing air to enter the ampoule and equalize the pressures. After a few seconds the ampoule should be wrapped in a few layers of tissue and broken along the crack. The tissues and ampoule neck can then be discarded into disinfectant, and the contents of the ampoule removed with a syringe. If the ampoule contains dried cultures, about 0.5 cm^3 of broth should be added slowly to avoid blowing dried material out. The contents may then be mixed without bubbling and withdrawn into a culture tube (8).

(iii) The researcher uses an intense, but tiny, gas-oxygen flame and heats the tip of the hard glass ampoule until the expanding internal air pressure blows a bubble. After allowing this to cool, he breaks the bubble while holding it in a large low temperature flame; this immediately incinerates any infectious dust which may come from the ampoule when the glass is broken (16). Preliminary practice with a simulant ampoule of the same type actually in use is necessary to develop a technique that will not cause explosion of the ampoule.

(iv) A simple device has been recommended consisting of a sleeve of rubber tubing into which the ampoule is inserted before it is broken (17,18).

D. *Centrifuging.* 1. A safety centrifuge cabinet or safety centrifuge cup (3,7,8,14,22) may be used to house or safeguard all centrifuging of infectious substances. When bench type centrifuges are used in a Biological Safety Cabinet, the glove panel should be in place with the glove ports covered. The centrifuge operation creates air currents that may cause escape of agent from an open cabinet (2,3,4,13).

2. In some situations, in the absence of O-ring cap sealed trunnion cups, specimens can be enclosed in sealed plastic bags before centrifugation (12).

3. Before centrifuging, inspect tubes for cracks, inspect the inside of the trunnion cup for rough walls caused by erosion or adhering matter, and carefully remove bits of glass from the rubber cushion (4,10).

4. A germicidal solution should be added between the tube and trunnion cup to disinfect the materials in case of accidental breakage. This practice also provides an excellent cushion against shocks that might otherwise break the tube (4,10).

5. Avoid decanting centrifuge tubes. If you must do so, afterwards wipe off the outer rim with a disinfectant; otherwise the infectious fluid will spin off as an aerosol (4, 10).

6. Avoid filling the tube to the point that the rim, cap or cotton plug ever becomes wet with culture (4, 10).

7. Screw caps, or caps which fit over the rim outside the centrifuge tube are safer than plug-in closures. Some fluid usually collects betwen a plug-in closure and the rim of the tube. Even screw-capped bottles are not without risk, however; if the rim is soiled some fluid will escape down the outside of the tube. Screw-capped bottles may jam in the bucket, and removing them is hazardous. Propping such bottles higher in the bucket with additional rubber buffers is mechanically unsound (8).

8. Kitchen foil is often used to cap centrifuge tubes. This creates more risk then the screw cap. Foil caps often become detached in handling and centrifuging (8).

9. The balancing of buckets is often mismanaged. Care must be taken to ensure that matched sets of trunnios, buckets and plastic inserts do not become mixed. If the components are not inscribed with their weights by the manufacturer, colored stains can be applied to avoid confusion. When the tubes are balanced, the buckets, trunnions and inserts should be included in the procedure; and care must be taken to ensure that the centers of gravity of the tubes are equidistant from the axis of rotation. To illustrate the importance of this, two identical tubes containing 20g of mercury and 20g of water respectively will balance perfectly on the scales; but their performance in motion is totally different, leading to violent vibration with all its attendant hazards (5).

10. Fill and open centrifuge tubes or trunnion cups in a Biological Safety Cabinet (10).

E. *High-Speed Centrifuges* (22). 1. In high-speed centrifuges the bowl is connected to a vacuum pump. If there is a breakage or accidental dispersion of infected particles the pump and the oil in it will become contaminated. A high efficiency filter should be placed between the centrifuge and the pump (8).

2. High speed rotor heads are prone to metal fatigue, and where there is a chance that they may be used on more than one machine each rotor should be accompanied by its own log book indicating the number of hours run at top or de-rated speeds. Failure to observe this precaution can result in dangerous and expensive disintegration. Frequent inspection, cleaning and drying are important to ensure absence of corrosion or other traumata which may lead to creeping cracks. Rubber O-rings and tube closures must be examined for deterioration and be kept lubricated with the material recommended by the makers. Where tubes of different materials are provided (e.g., celluloid, polypropylene, stainless steel), care must be taken that the tube closures designed specifically for the type of tube in use are employed. These caps are often similar in appearance, but are prone to leakage if applied to tubes of the wrong material. When properly designed tubes and rotors are well maintained and handled, leaking should never occur (5).

3. Cleaning and disinfection of tubes, rotors and other components requires considerable care. It is unfortunate that no single process is suitable for all items, and the various manufacturers' recommendations must be followed meticulously if fatigue, distortion and corrosion are to be avoided. This is not the place to catalogue recommended methods, but one less well appreciated fact is worthy of mention. Celluloid (cellulose nitrate) centrifuge tubes are not only highly inflammable and prone to shrinkage with age and distortion on boiling, but can behave as high explosive in an autoclave (5). Large-scale zonal centrifugation requires special attention (11).

F. *Blenders, ultrasonic disintegrators, colloid mills, ball mills, jet mills, grinders, motar and pestle.* All these devices release considerable aerosols during their operation. For maximum protection to the operator during the blending of infectious materials, the following practices should be observed:

1. Operate blending and cell-disruption and grinding equipment in a Biological Safety Cabinet (9).

2. Use safety blenders designed to prevent leakage from the rotor bearing at the bottom of the bowl (9).

3. In the absence of a leak-proof rotor, inspect the rotor bearing at the bottom of the blender bowl for leakage prior to operation. Test it in a preliminary run with sterile saline or methylene blue solution prior to use with infected material (9).

4. Sterilize the device and residual infectious contents promptly after use. Use a towel moistened with disinfectant over the top of the blender (9).

5. Glass blender bowls are undesirable for use with infectious material because of potential breakage. If used, they should be covered with a polypropylene jar to prevent dispersal of glass (8).

6. A new machine, the Colworth Stomacker (England), in which material is homogenized in a plastic bag in a closed container, would appear to be safer than some of the other blenders (8).

7. A heat-sealed flexible plastic film enclosure for a grinder or blender can be used, but it must be opened in a Biological Safety Cabinet (7).

8. Blender bowls sometimes require supplemental cooling to prevent destruction of the bearings and to minimize thermal efforts on the product (7).

9. Before opening the safety blender bowl, permit the blender to rest for at least one minute to allow settling of the aerosol cloud.

10. Clinical or other laboratories handling human blood should be aware of the aerosols produced by the microhaematocrit centrifuge, the autoanalyzer stirrer, and the micotonometer, inasmuch as it seems that airborne transmission of infectious hepatitis may occur in the laboratory (20).

G. *Miscellaneous precautions and recommendations.* 1. Water baths and Warburg baths used to inactivate, incubate, or test infectious substances should contain a disinfectant. For cold water baths, 70 percent propylene glycol is recomemnded (4, 10).

2. Deepfreeze, liquid nitrogen, and dry ice chests and refrigerators should be checked and cleaned out periodically to remove any broken ampoules, tubes, etc., containing infectious material, and decontaminated. Use rubber gloves and respiratory protection during this cleaning. All infectious or toxic material stored in refrigerators or deep-freezes should be properly labelled. Security measures should be commensurate with the hazards (4,10,21).

3. Freeze-dried culture ampoules should always be opened in a Biological Safety Cabinet. The ampoule should be wrapped in a disinfectant-soaked swab before breaking it open to minimize the risk of cutting the hands, and to a lesser extent of releasing

aerosol of dried material. Whenever possible, ampoules should be filled with dry nitrogen after freeze-drying, thus avoiding implosion that may occur during the sealing as well as opening of evacuated ampoules. The whole process of freeze-drying itself should be performed in a Biological Safety Cabinet. Filtration of the effluent air from the vacuum pump is desirable either up (preferably), or down stream of the pump (5).

4. Ensure that all virulent fluid cultures or viable powdered infectious materials in glass vessels are transported, incubated, and stored in easily handled, nonbreakable leak-proof containers that are large enough to contain all the fluid or powder in case of leakage or breakage of the glass vessel (4,10).

5. All inoculated petri plates or other inoculated solid media should be transported and incubated in leak-proof pans or leak-proof containers (4,10).

6. Care must be exercised in the use of membrane filters to obtain sterile filtrates of infectious materials. Because of the fragility of the membrane and other factors, such filtrates cannot be handled as noninfectious until culture or other tests have proved their sterility (4,10).

7. Shaking machines should be examined carefully for potential breakage of flasks or other containers being shaken. Screw capped durable plastic or heavy walled glass flasks should be used. These should be securely fastened to the shaker platform. An additional precaution would be to enclose the flask in a plastic bag with or without an absorbent material.

8. No person should work alone on an extremely hazardous operation (4,10).

IV. PERSONAL HYGIENE, HABITS, AND PRACTICES

Personal hygienic practices in the laboratory are directed, in most part, toward the prevention of occupationally acquired physical injury or disease. To a less obvious extent, they can raise the quality of the laboratory work by reducing the possibilities for contamination of experimental materials. The reasons for many of the recommended precautions and practices are obvious, but, in some instances, amplification will permit a better review of the applicability to any one specific laboratory.

Consequently, what might be forbidden in one laboratory might be only discouraged in another, and be permissible in a third. Nevertheless, adherence to safe practices that become habitual, even when seemingly not essential, provides a margin of safety in situations where the hazard is unrecognized. The history of occupational injury is replete with examples of hazards unrecognized until too late. The following guidelines, recommendations, and comments are presented with this in mind:

1. Food, candy, gum, and beverages for human consumption will be stored and consumed only outside the laboratory (5, 10).

2. Foot-operated drinking fountains should be the sole source of water for drinking by human occupants of the laboratory (27).

3. Smoking is not permitted in the laboratory or animal quarters. Cigarettes, pipes, and tobacco will be kept only in clean areas (5, 10, 26).

4. Shaving and brushing of teeth are not permitted in the laboratory. Razors, toothbrushes, toiletry supplies, and cosmetics are permissible only in clean change rooms or other clean areas, and should never be used until after showering or thorough washing of the face and hands (27).

5. A beard may be undesirable in the laboratory in the presence of actual or potential airborne contamination, because it retains particulate contamination more persistently than clean-shaven skin. A clean-shaven face is essential to the adequate facial fit of a face mask or respirator when the work requires respiratory protection (10,27,31).

6. Develop the habit of keeping hands away from mouth, nose, eyes, face, and hair. This may prevent self-inoculation (10,27).

7. For product protection, persons with long hair should wear a suitable hair net or head cover that can be decontaminated. This has long been a requirement in hospital operating rooms and in the manufacture of biological pharmaceutical products. A head cover also will protect the hair from fluid splashes, from swinging into Bunsen flames and petri dishes, and will reduce facial contamination caused by habitual repetitive manual adjustment of the hair (5).

8. Long-flowing hair and loose-flapping clothing are dangerous in the presence of open flame or moving machinery. Rings and wrist watches also are a mechanical hazard during operation of some types of machines (5, 10).

9. Contact lenses do not provide eye protection. The capillary space between the contact lenses and the cornea may trap any material present on the surface of the eye. Caustic chemicals trapped in this space cannot be washed off the surface of the cornea. If the material in the eye is painful or the contact lens is displaced, muscle spasms will make it very difficult, if not impossible, to remove the lens. For this reason, contact lenses must not be worn by persons exposed to caustic chemicals unless safety glasses with side shields, goggles, or plastic face masks are also worn to provide full protection. It is the responsibility of supervisors to identify employees who wear contact lenses (25, 26).

10. Personal items, such as coats, hats, storm rubbers or overshoes, umbrellas, purses, etc., do not belong in the laboratory. These articles should be kept elsewhere (25).

11. Plants, cut flowers, an aquarium, and pets of any kind are undesirable sources of yeast, molds, and other potential microbial contaminants of biological experimental materials (25).

12. Books and journals returnable to the institutional library should be used only in the clean areas as much as possible (10,27).

13. When change rooms with showers are provided, the employer should furnish skin lotion (27).

14. When employees are subject to potential occupational infection, the shower and/or face/hand-washing facilities should be provided with germicidal soap (8,27).

15. Personal cloth handkerchiefs should not be used in the laboratory. Cleansing tissue should be available instead.

16. Hand washing for personal protection:

(i) This should be done promptly after removing protective gloves. Tests show it is not unusual for microbial or chemical contamination to be present despite use of gloves, due to unrecognized small holes, abrasions, tears, or entry at the wrist.

(ii) Throughout the day, at intervals dictated by the nature of the work, the hands should be washed. Presence of a wrist watch discourages adequate washing of the wrist (10,25).

(iii) Hands should be washed after removing soiled protective clothing, before leaving the laboratory area, before eating, and before smoking. The provision of hand cream by the employer encourages these practices (5,8,10).

(iv) A disinfectant wash or dip may be desirable in some cases, but its use must not be carried to the point of causing roughening, desiccation or sensitization of the skin.

17. Anyone with a fresh or healing cut, abrasion, or skin lesion should not work with infective material unless the injured area is completely protected (8,25).

18. Persons vaccinated for smallpox may be shedders of vaccinia virus during the phase of cutaneous reaction. Therefore, vaccination requires permission of the appropriate supervisor, because two weeks' absence may be necessary before returning to work with normal cell cultures or with susceptible animals, especially the normal mouse colony (25).

19. The surgeon's mask of gauze or filter paper is of little value for personal respiratory protection (29). It is designed to prevent escape of droplets from the nose or mouth (23G). If biohazards demand respiratory protection, then nothing but a full face respirator or ventilated hood will suffice. A half-mask respirator does not protect the eyes, which are an unevaluated avenue of infection through the conjuctiva and the nasolacrimal duct (5,8).

20. Nonspecific contamination by environmental organisms from humans, animals, equipment, containers for specimens or supplies, and outside air is a complication that may affect or invalidate the results of an experiment. The human sources of this contamination are evaluated as follows:

(i) Sneezing, coughing and talking (23A, 24A). Sneezing, variously reported to generate as many as 32,000 or 1,000,000 droplets below 100 microns in diameter; coughing, which produces fewer and larger droplets; and talking, which has been reported to average only 250 droplets when speaking 100 words, show great differences between persons in regard to the number of microorganisms aerosolized. As a general rule, it may be said that these actions by normal healthy persons may play a less important role in transmission of airborne infection to humans or experimental materials than does liberation of microorganisms from human skin.

(ii) Dispersal of bacteria from human skin. There is a tremendous variation in the number of bacteria shed from the skin by a clothed subject. For instance, in one study, the number varied from 6,000 to 60,000 per minute (23C). These bacteria were released on skin scales which were of a size that could penetrate the coarse fabric used for the laboratory and surgical clothing in the test (23D). Dispersal of skin bacteria was several times greater from below the waist than from upper parts of the body (24D). Effective reduction is accomplished by use of closely-woven or impervious clothing fitted tightly at the neck, wrists, and ankles to prevent the clothing from acting as a bellows that disperses air carrying skin scales laden with bacteria (23B). Such clothing sometimes is too warm to work in. It was found that a significant reduction in dispersal of bacteria occurred with the wearing of close-fitting and closely-woven underpants beneath the usual laboratory clothing (23D). The purpose of this summary is to alert laboratory personnel to the existence of this source of contamination (9).

(iii) Prolific dispersal of bacteria occurs from infected abrasions, small pustules, boils, and skin disease (23F, 24B). Washing the lesions with germicidal soap will greatly decrease the number of organisms on the skin and dispersal into the air. Healthy nasal carriers who generate aerosolized staphylococci usually can be identified by the presence of heavy contamination of their fingers, face, and hair (23E). This point may be useful in investigating the source of staphylococcal contamination of cell lines.

(iv) Footwear. In moderate and high risk situations, shoes reserved for only laboratory use have been recommended as a precaution against transporting spilled infectious agents outside the laboratory. However, in experiments during which reduction of potential contamination of experimental materials is important, laboratory-only shoes can reduce the microbial load brought into the

laboratory each day by street shoes. Shoes are efficient transporters. In one study, there were 4 to 850 times as many bacteria per square centimeter on the laboratory footwear as on the floor itself (30).

V. CARE AND USE OF LABORATORY ANIMALS (10,32-37)

A. *Care and handling.* 1. Special attention must be given to the humane treatment of all laboratory animals in accordance with the Animal Welfare Act of 1970. The implementing rules and regulations appear in the Code of Federal Regulations (CFR) Title 9, Chapter I, Subchapter A, Parts 1, 2, 3. Recommended provisions and practices that meet the requirements of the Act have been published by the U.S. Public Health Service (32).

2. There are specific minimum requirements (33) concerning the caging, feeding, watering, and sanitation for dogs, cats, guinea pigs, hamsters, rabbits, and nonhuman primates. To meet these requirements, the animal room supervisor must have a copy of 9 CFR Chapter I, Subchapter A, Parts 1, 2, 3.

3. Each laboratory should establish procedures to ensure the use of animals that are free of diseases prejudicial to the proposed experiments and free from carriers of disease or vectors, such as ectoparasites, which endanger other experimental animals or personnel (10).

B. *Cages housing infected animals* (10). 1. Careful handling procedures should be employed to minimize the dissemination of dust from cage refuse and animals.

2. Cages should be sterilized by autoclaving. Refuse, bowls and watering devices should remain in the cage during sterilization.

3. All watering devices should be of the "non-drip" type.

4. Cages should be examined each morning and at each feeding time so that dead animals can be removed.

5. Heavy gloves should be worn when feeding, watering, handling, or removing infected animals. Bare hands should NEVER be placed in the cage to move any object therein.

6. When animals are to be injected with biohazardous material, the animal caretaker should wear protective gloves and the laboratory workers should wear surgeons gloves. Animals should be properly restrained to avoid accidents that might result in disseminating biohazardous material, as well as to prevent injury to the animal and to personnel.

7. Animals exposed to biohazardous aerosols should be housed in ventilated cages, in gastight cabinet systems, or in rooms designed for protection of personnel by use of ventilated suits.

8. Animals inoculated by means other than by aerosols should be housed in equipment suitable for the level of risk involved.

9. Infected animals to be transferred between buildings should be placed in ventilated cages or other aerosol-proof containers.

10. The oversize canine teeth of large monkeys present a particular biting hazard; these are important in the potential transmission of naturally-occurring, and very dangerous, monkey virus infections. Such teeth should be blunted or surgically removed by a veterinarian.

11. Presently available epidemiological evidence indicates that infectious hepatitis may be transmitted from non-human primates (typically chimpanzees) to man. Newly imported animals may be naturally infected with this disease, and persons in close contact with such animals may become infected. After six months residence in this country, chimpanzees apparently no longer transmit the disease. A record should be maintained for each newly imported animal. A sign should be posted at rooms housing these animals to warn that the animals are potentially infectious.

C. *General Guidelines that Apply to Animal Room Maintenance* (10). 1. Doors to animal rooms should be kept closed at all times except for necessary entrance and exit.

2. Unauthorized persons should not be permitted to enter animal rooms.

3. A container of disinfectant should be kept in each animal room for disinfecting gloves and hands, and for general decontamination, even though no infectious animals are present. Hands, floors, walls, and cage racks should be washed with an approved disinfectant at the recommended strength as frequently as the supervisor directs.

4. Floor drains in animal rooms, as well as floor drains throughout the building should be flooded with water or disinfectant periodically to prevent backup of sewer gases.

5. Shavings or other refuse on floors should *not* be washed down the floor drain because such refuse clogs the sewer lines.

6. An insect and rodent control program should be maintained in all animal rooms and in animal food storage areas.

7. Special care should be taken to prevent live animals, especially mice, from finding their way into disposable trash.

D. *Necropsy rules for infected animals* (10). 1. Necropsy of infected animals should be carried out by trained personnel in Biological Safety Cabinets with the hinged glass panel down. The glove port panel with or without attached gloves, and a respirator should be used at the discretion of the supervisor.

2. Surgeons gowns should be worn over laboratory clothing during necropsies.

3. Rubber gloves should be worn when performing necropsies.

4. The fur of the animal should be wetted with a suitable disinfectant.

5. Small animals should be pinned down or fastened on wood or metal in a metal tray.

6. Upon completion of necropsy, all potentially biohazardous material should be placed in suitable containers and sterilized immediately.

7. Contaminated instruments should be placed in a horizontal bath containing a suitable disinfectant.

8. The inside of the Biological Safety Cabinets and other potentially contaminated surfaces should be disinfected with a suitable germicide.

9. Grossly contaminated rubber gloves should be cleaned in disinfectant before removal from the hands, preparatory to sterilization.

10. Dead animals should be placed in proper leak-proof containers, autoclaved and properly tagged before being placed outside for removal and incineration.

VI. DECONTAMINATION AND DISPOSAL (7, 10, 38-42)

A. *Introduction.* Available data on the efficacy of various decontaminants for etiologic agents indicate that no major surprises will be forthcoming regarding the susceptibility of organisms containing recombinant DNA molecules. In the absence of adequate information, tests to determine the efficacy of candidate decontaminants should be conducted with the specific agent of interest. The goal of decontamination is not only the protection of personnel and the environment from exposure to infectious agents, but also the prevention of contamination of experimental materials by a variable, persistent, and unwanted background of microorganisms. This additional factor should be considered in selecting decontamination materials and methods.

B. *Decontamination Methods.* Physical and chemical means of decontamination fall into four main categories: Heat; Liquid Decontaminants; Vapors and Gases; and UV Radiation.

1. *Heat.* The application of heat, either moist or dry, is recommended as the most effective method of sterilization. Steam at 121 C under pressure in the autoclave is the most convenient method of rapidly achieving sterility. Dry heat at 160 to 170 C for periods of 2 to 4 hours is suitable for destruction of viable agents on impermeable nonorganic material such as glass, but is not reliable in even shallow layers of organic or inorganic material that can act as insulation. Incineration is another use of heat in the decontamination of microorganisms and also serves as an efficient means for disposal.

2. *Liquid Decontaminants.* In general, the liquid decontaminants find their most practical use in surface decontamination and, at sufficient concentration, as decontaminants of liquid wastes for final disposal in sanitary sewer systems. There are many misconceptions concerning the use of liquid decontaminants. This is due largely to a characteristic capacity of such liquids to perform dramatically in the test tube and to fail miserably in a practical situation. Such failures often occur because proper consideration was not given to such factors as temperature, time of contact, pH, concentration, and the presence and state of dispersion, penetrability and reactivity of organic material at the site of application. Small variations in the above factors may make large differences in effectiveness of decontmination. For this reason, even when used under highly favorable conditions, complete reliance should not be placed on liquid decontaminants when the end result must be sterility.

There are many liquid decontaminants available under a wide variety of trade names. In general, these can be categorized as halogens, acids or alkalies, heavy metal salts, quaternary ammonium compounds, phenolic compounds, aldehydes, ketones, alcohols and amines. Unfortunately, the more active the decontaminant the more likely it is that the decontaminant will possess undesirable characteristics, such as the possession of corrosive properties. None is equally useful or effective under all conditions.

3. *Vapors and Gases.* A variety of vapors and gases possess decontamination properties. The most useful of these are formaldehyde and ethylene oxide. When these can be employed in closed systems and under controlled conditions of temperature and humidity, excellent decontamination can result. Vapor and gas decontaminants are primarily useful in decontaminating: (i) Biological Safety Cabinets and associated effluent air-handling systems and air filters; (ii) bulky or stationary equipment that resists pentration by liquid surface decontaminants; (iii) instruments and optics that might be damaged by other decontamination methods; and (iv) rooms and buildings and associated air-handling systems.

4. *Radiation.* The usefulness of ultraviolet (UV) irradiation as a decontaminant is limited by its low penetrating power. No information is available regarding the effectiveness of UV irradiation for decontaminating microorganisms containing recombinant DNA molecules. Dependence on UV must be based on the results of experiments imitating particular anticipated environmental conditions and applications. Ultraviolet light is generally of limited application and is primarily useful in air locks and animal holding areas for controlling low levels of airborne contaminants.

No one procedure or material will solve all decontamination problems. The only method of assuring the efficacy of selected methodologies is to critically examine the results

obtained in practical tests with the microorganism(s) of interest.

C. *Laboratory spills.* A troublesome problem that may occur in the laboratory is the decontamination of an overt biological spill. The occurrence of a spill poses less of a problem if it occurs in a Biological Safety Cabinet provided splattering to the outside of the cabinet does not occur. Direct application of concentrated liquid decontaminant and a thorough wipe down of the internal surfaces of such cabinetry will usually be effective for decontaminating the work zone but gaseous decontaminants would be required to rid the interior sections of the cabinet of contaminants. Each researcher must realize that in the event of an overt accident, research materials such as tissue cultures, media, and animals within such cabinets may well be lost to the experiment.

The greater problem arises if the incident occurs in the open laboratory. All laboratory protocols should be designed to prevent such occurrences. The first action in the event of an overt laboratory spill is evacuation of the affected area to minimize the exposure of personnel involved. Next, the spill area must be isolated to prevent exposure of personnel and experimental materials beyond those involved in the immediate area of the spill. The procedures adopted must be rapidly effective and must not create additional aerosol or foster mechanical transfer of materials to unaffected areas. Personnel carrying out the procedures must be provided with protective clothing and equipment, including respiratory protection. Consideration must be given to the safe disposal of all materials and liquids resulting from cleanup procedures. Reentry of personnel to the area should be avoided until it can be reasonably established that the area has been effectively decontaminated. Further specific details are provided in Section VIII.

D. *Disposal.* Decontamination and disposal in infectious disease laboratories are closely interrelated acts in which decontamination constitutes the introductory phase of disposal. All materials and equipment used in research on recombinant DNA molecules will ultimately be disposed of; however, in the sense of daily use, only a portion of these will require actual removal from the laboratory complex or on-site destruction. The remainder will be recycled for use either within the same laboratory or in other laboratories that may or may not engage in DNA recombinant research. Examples of the latter that immediately come to mind are: Reusable laboratory glassware, instruments used in necropsy of infected animals, and laboratory clothing. Disposal should therefore be interpreted in the broadest sense of the word, rather than in the restrictive sense of dealing solely with a destructive process.

The principal questions to be answered prior to disposal of any objects or materials from laboratories dealing with potentially infectious microorganisms or animal tissues are:

1. Have the objects or materials been effectively decontaminated by an approved procedure?

2. If not, have the objects or materials been packaged in an approved manner for immediate on-site incineration or transfer to another laboratory?

3. Does disposal of the decontaminated objects or materials involve any additional potential hazards, biological or otherwise, to personnel either: (i) Those carrying out the immediate disposal procedures or (ii) Those who might come into contact with the objects or materials outside the laboratory complex?

Laboratory materials requiring disposal will normally occur as liquid, solid, and animal room wastes. The volume of these can become a major problem when there is the requirement that all wastes be decontaminated prior to disposal. It is most evident that a significant portion of this problem can be eliminated if the kinds of materials initially entering the laboratory are reduced. In any case, and wherever possible, materials not essential to the research should be retained in the nonresearch areas for disposal by conventional methods. Examples are the packaging materials in which goods are delivered, disposable carton-cages for transport of animals, and large carboys or tanks of fluids which can be left outside and drawn from as required. Reduction of this bulk will free autoclaves and other decontamination and disposal processes within the laboratory for the more rapid and efficient handling of materials known to be contaminated.

Inevitably, disposal of materials raises the question, "How can we be sure that the materials have been treated adequately to assure that their disposal does not constitute a hazard?" In the small laboratory, the problem is often solved by requiring that each investigator decontaminate all contaminated materials not of immediate use at the end of each day and place them in suitable containers for routine disposal. In larger laboratories where the mass of materials for disposal becomes much greater and sterilization and decontamination bottlenecks occur, materials handling and disposal will likely be the chore of personnel not engaged in the actual research. In either situation, a case can be made for establishing a positive method of designating the state of materials to be disposed of. This may consist of a tagging system stating that the materials are either sterile or contaminated.

Disposal of materials from the laboratory and animal holding areas will be required for research projects ranging in size from an individual researcher to those involving large numbers of researchers of many disciplines. Procedures and facilities to accomplish this will range from the simplest to the most elaborate. The primary consideration in any of these is to dispel the notion that laboratory wastes can be disposed of in the same manner and with as little thought as household wastes. Selection and enforcement of safe procedures for disposal of laboratory materials are of no less importance than the consideration given to any other methodology for the accomplishment of research objectives.

Materials of dissimilar nature will be common in laboratories studying recombinant DNA molecules. Examples are combinations of common flammable solvents, chemical carcinogens, radioactive isotopes, and concentrated viruses or nucleic acids. These may require input from a number of disciplines in arriving at the most practical approach for their decontamination.

E. *Characteristics of chemical decontaminants in common use in laboratory operations.* Every person actively working with viable miroorganisms, no matter how remote the field of specialization, will, from time to time, find it necessary to decontaminate by chemical methods work areas and materials, equipment, and specialized instruments. Chemical decontamination is necessary because the use of pressurized steam, the most rapid and reliable method of sterilization, is not normally feasible for decontaminating large spaces, surfaces, and stationary equipment. Moreover, high temperatures and moisture often damage delicate instruments, particularly those having complex optical and electronic components.

Chemicals with decontaminant properties are, for the most part, available as powders, crystals, and liquid concentrates. These may be added to tap water for application as surface decontaminants, and some, when added in sufficient quantity, find use as decontaminants of bulk liquid wastes. Chemical decontaminants that are gaseous at room temperatures are useful as space-penetrating decontaminants. Others become gases at reasonably elevated temperatures and can act as either aqueous surface or gaseous space-penetrating decontaminants.

Inactivation of microorganisms by chemical decontaminants may occur in one or more of the following ways: (1) Coagulation and denaturation of protein, (2) Lysis, (3) Binding to enzymes, or inactivation of an essential enzyme by either oxidation, binding, or destruction of enzyme substrate.

The relative resistance to the action of chemical decontaminants can be substantially altered by such factors as: Concentration of active ingredient, duration of contact, pH, temperature, humidity and presence of extrinsic organic matter. Depending upon how these factors are manipulated, the degree of success achieved with chemical decontaminants may range from minimal inactivation of target microorganisms to an indicated sterility within the limits of sensitivity of the assay systems employed.

There are dozens of contaminants available under a wide variety of trade names. In general, these decontaminants can be classified as halogens, acids or alkalies, heavy metal salts, quaternary ammonium compounds, phenolic compounds, aldehydes, ketones, alcohols, and amines. Unfortuately, the more active the decontaminant the more likely it will possess undesirable characteristics. For example, peracetic acid is a fast-acting, universal decontaminant. However, in the concentrated state it is a hazardous compound that can readily decompose with explosive violence. When diluted for use, it has a short half-life, produces strong, pungent, irritating odors, and is extremely corrosive to metals. Nevertheless, it is such an outstanding decontaminant that it is commonly used in germ-free animal studies despite these undesirable characteristics.

The halogens are probably the second most active group of decontaminants. Chlorine, iodine, bromine, and fluorine will rapidly kill bacterial spores, viruses, rickettsiae, and fungi. These decontaminants are effective over a wide range of temperatures. In fact, chlorine has been shown to be effective at —40 F. (On the other hand, phenols and formaldehyde have high temperature coefficients). The halogens have several undesirable features. They readily combine with protein, so that an excess of the halogen must be used if proteins are present. Also, the halogens are relatively unstable so that fresh solutions must be prepared at frequent intervals. Finally, the halogens corrode metals. A number of manufacturers of decontaminants have treated the halogens to remove some of the undesirable features. For example, sodium hypochlorite reacts with p-toluenesulfonamide to form Chloramine T, and iodine reacts with certain surface-active agents to form the popular iodophors. These "tamed" halogens are stable, non-toxic, odorless, and relatively noncorrosive to metals. However, the halogens are highly reactive elements, and, because they are reactive they are good germicides. When a haolgen acts as a decontaminant, free halogen is the effective agent. Raising the pH or combining the halogen with other compounds to decrease the corrosive effect will also decrease the germicidal power. A trade-off situation occurs.

Ineffectiveness of a decontaminant is due primarily to the failure of the decontaminant to contact the microorganisms rather than failure of the decontaminant to act. If one places an item in

a liquid decontaminant, one can see that the item is covered with tiny bubbles. Of course, the area under the bubbles is dry, and microorganisms in these dry areas will not be affected by the decontaminant. Also, if there are spots of grease, rust or dirt on the object, microorganisms under these protective coatings will not be contacted by the decontaminant. Scrubbing an item when immersed in a decontaminant is helpful, and a decontaminant should have, and most do have, incorporated surface-active agents.

F. *Properties of some common decontaminants*—1. *Alcohol.* Ethyl or isopropyl alcohol in a concentration of 70–80 percent by weight is often used. Alcohols denature proteins and are somewhat slow in their germicidal action. However, they are effective decontaminants against lipid-containing viruses.

2. *Ether and Chloroform.* These compounds are not ordinarily used as decontaminants, but they do demonstrate the fact that lipid-containing viruses are inactivated by these organic solvents, whereas non-lipid-containing viruses are quite resistant.

3. *Formaldehyde.* Formaldehyde for use as a decontaminant is usually marketed as a solution of about 37 percent concentration referred to as formalin or as a solid polymerized compound called paraformaldehyde. Formaldehyde in a concentration of 5 percent active ingredient is an effective liquid decontaminant. It loses considerable activity at refrigeration temperatures and the pungent, irritating odors make formaldehyde solutions difficult to use in the laboratory. Formaldehyde vapor generated from formaldehyde solution is an effective space decontaminant for decontaminating rooms or buildings, but in the vapor state with water it tends to polymerize out on surfaces to form paraformaldehyde, which is persistent and unpleasant. Formaldehyde gas can be liberated by heating paraformaldehyde to depolymerize it. In the absence of high moisture content in the air, formaldehyde released in the gaseous state forms less polymerized residues on surfaces and less time is required to clear treated areas of fumes than formaldehyde released in the vapor state.

4. *Phenol.* Phenol itself is not often used as a decontaminant. The odor is somewhat unpleasant and a sticky, gummy residue remains on treated surfaces. This is especially true during steam sterilization. Although phenol itself may not be in widespread use, phenol homologs and phenolic compounds are basic to a number of popular decontaminants. The phenolic compounds are effective decontaminants against some viruses, rickettsiae, fungi and vegetative bacteria. The phenolics are not effective in ordinary usage against bacterial spores.

5. *Quaternary Ammonium Compounds or Quats.* After 30 years of testing and use, there is still a considerable controversy about the efficacy of the Quats as decontaminants. These cationic detergents are strongly surface-active and are effective against lipid-containing viruses. The Quats will attach to protein so that dilute solutions of Quats will quickly lose effectiveness in the presence of proteins. The Quats tend to clump microorganisms and are neutralized by anionic detergents, such as soap. The Quats have the advantages of being nontoxic, odorless, nonstaining, noncorrosive to metals, stable, and inexpensive.

6. *Chlorine.* This halogen is a universal decontaminant active against all microorganisms, including bacterial spores. Chlorine combines with protein and rapidly decreases in concentration in its presence. Free, available chlorine is an active element. It is a strong oxidizing agent, corrosive to metals. Chlorine solutions will gradually lose strength so that fresh solutions must be prepared frequently. Sodium hypochloride is usually used as a base for chlorine decontaminants. An excellent decontaminant can be prepared from household or laundry bleach. These bleaches usually contain 5.25 percent available chlorine or 52,500 ppm. If one dilutes them 1 to 100, the solution will contain 525 ppm of available chlorine, and, if a nonionic detergent such as Naccanol is added in a concentration of about 0.7 percent, a very good decontaminant is created.

7. *Iodine.* The characteristics of chlorine and iodine are similar. One of the most popular groups of decontaminants used in the laboratory is the iodophors, and Wescodyne is perhaps the most popular. The range of dilution of Wescodyne recommended by the manufacturer is 1 oz. in 5 gal. of water giving 25 ppm of available iodine to 3 oz. in 5 gal. giving 75 ppm. At 75 ppm, the concentration of free iodine is .0075 percent. This small amount can be rapidly taken up by any extraneous protein present. Clean surfaces or clear water can be effectively treated by 75 ppm available iodine, but difficulties may be experienced if any appreciable amount of protein is present. For bacterial spores, a dilution of 1 to 40 giving 750 ppm is recommended by the manufacturer. For washing the hands, it is recommended that Wescodyne be diluted 1 to 10 or 10 percent in 50 percent ethyl alcohol (a reasonably good decontaminant itself) which will give 1,600 ppm of available iodine, at which concentration relatively rapid inactivation of any and all microorganisms will occur.

G. *Vapors and gases.* The use of formaldehyde as a vapor or gas has already been discussed. Other chemical decontaminants which have been used this way included ethylene oxide, peracetic acid, beta-propiolactone (BPL), methyl bromide, and ethylene amine. When these can be used in closed systems and under controlled conditions of temperature and humidity, excellent decontamination can be otbained. Residues from ethylene oxide must be removed by aeration; but otherwise it is convenient to use, versatile, and noncorrosive. Paracetic acid is corrosive for metals and rubber. BPL in the vapor form acts rapidly against bacteria, rickettsiae, and viruses. It has a half-life of 3.5 hours when mixed with water, is easily neutralized with water, and lends itself to removal by aeration. The National Institutes of Health does not recommend BPL as a decontaminant because it has been identified as a suspect carcinogen.

H. *Residual action of decontaminants.* As noted in the preceding discussion of decontaminant properties, many of the chemical decontaminants often have residual properties that may be considered a desirable feature in terms of aiding in the control of background contamination. One is cautioned, however, to consider residual properties carefully. Ethylene oxide used to sterilize laboratory shoes can leave residues which cause skin irritation. Animal cell cultures, as well as viruses of interest, are also inhibited or inactivated by decontaminants persisting after routine cleaning procedures. Therefore, reusable items that are routinely held in liquid decontaminant prior to autoclaving and cleaning should receive particular attention in rinse cycles. Similarly, during general area decontamination with gases or vapors, it may be necessary to protect new and used clean items by removing them from the area or by enclosing them in gastight bags or by insuring adequate aeration following decontamination.

I. *Selecting chemical decontaminants for research on recombinant DNA molecules.* No single chemical decontaminant or method will be effective or practical for all situations in which decontamination is required. Selection of chemical decontaminants and procedures must be preceded by practical consideration of the purposes for the decontamination and the interacting factors that will ultimately determine how that purpose is to be achieved. Selection of any given procedure will be influenced by the information derived from answers to the following questions:

1. What is the target microorganism(s)?
2. What decontaminants in what form are known to, or can be expected to, inactivate the target microorganism(s)?
3. What degree of inactivation is required?
4. In what menstruum is the microorganism suspended; i.e., simple or complex, on solid or porous surfaces, and/or airborne?
5. What is the highest concentration of cells anticipated to be encountered?
6. Can the decontaminant either as an aqueous solution, a vapor, or a gas reasonably be expected to contact the microorganisms, and can effective duration of contact be maintained?
7. What restrictions apply with respect to compatibility of materials?
8. Does the anticipated use situation require immediate availability of an effective concentration of the decontaminant or will sufficient time be available for preparation of the working concentration shortly before its anticipated use?

The primary target of decontamination in the infectious disease laboratory is the microorganism under active investigation. Laboratory preparations or infectious agents usually have titers grossly in excess of those normally observed in nature. The decontamination of these high-titer materials presents certain problems. Maintenance systems for bacteria or viruses are specifically selected to preserve viability of the agent. Agar, proteinaceous nutrients, and cellular materials can be extremely effective in physically retarding or chemically binding active moieties of chemical decontaminants. Such interferences with the desired action of decontaminants may require the use of decontaminant concentrations and contact times in excess of those shown to be effective in the test tube. Similarly, a major portion of decontaminant contact time required to achieve a given level of agent inactivation may be expended in inactivating a relatively small number of the more resistant members of the population. The current state of the art provides little information on which to predict the probable virulence of these survivors. These problems are, however, common to all potentially pathogenic agents and must always be considered in selecting decontaminants and procedures for their use.

Microorganisms exhibit a range of resistance to chemical decontaminants. In terms of practical decontamination, most vegetative bacteria, fungi and lipid-containing viruses, are relatively susceptible to chemical decontamination. The non-lipid-containing viruses and bacteria with a waxy coating such as tubercle bacillus occupy a mid-range of resistance. Spore forms are the most resistant.

A decontaminant selected on the basis of its effectiveness against microorganisms on any range of the resistance scale will be ef-

fective against microorganisms lower on the scale. Therefore, if decontaminants that effectively control spore forms are selected for routine laboratory decontamination, it can be assumed that any other microorganisms generated by laboratory operations, even in high concentrations, would also be inactivated.

An additional area that must be considered and for which there is little definitive information available is the "inactivation" of nucleic acids. Nucleic acids often have better survival characteristics under adverse conditions than do the intact virions and cells from which they were derived. Strong oxidizers, strong acids and bases, and either gaseous or aqueous formaldehyde should react readily with nucleic acids. Their ability to destroy the nucleic acid being studied, however, should be confirmed in the experimenter's laboratory. Because of innate differences in the chemistry of RNA and DNA the effectiveness of a decontaminant for one cannot be extrapolated to the other. For example, RNA molecules are susceptible to mild alkaline hydrolysis by virtue of the free hydroxyl group in the 2′ position, whereas DNA molecules are not susceptible to mild alkaline hydrolysis.

Table II summarizes pertinent characteristics and potential applications for several categories of chemical decontaminants most likely to be used in the biological laboratory. Practical concentrations and contact times that may differ markedly from the recommendations of manufacturers of proprietary products are suggested. It has been assumed that micoorganisms will be afforded a high degree of potential protection by organic menstruums. It has not been assumed that a sterile state will result from application of the indicated concentrations and contact times. It should be emphasized that these data are only indicative of efficacy under artificial test conditions. The efficacy of any of the decontaminants should be conclusively determined by individual investigators. It is readily evident that each of the decontaminants has a range of advantages and disadvantages as well as a range of potential for inactivation of a diverse microflor. Equally evident is the need for compromise as an alternative to maintaining a veritable "drug store" of decontaminants.

APPENDIX B

TABLE II

SUMMARY OF PRACTICAL DECONTAMINANTS FOR USE IN THE LABORATORY

Decontaminants: Type	Category	Practical requirements: Concentration active ingredient	Contact time (minutes): Lipo virus only	Contact time (minutes): Broad spectrum	Temp. °C	Rel. humid. %	Inactivates: Veg. bact.	Lipo virus	Hydrophilic virus	Bact. spores
Liquid	Quat. Ammon. Cpds	2%	10	N.E.			•	•		
	Phenolic Cpds	3%	10	N.E.			•	•	1	
	Chlorine Cpds	3%	10	30			•	•	•	•
	Iodophor	2%	10	30			•	•	•	•
	Alcohol, Ethyl	85%	10	N.E.			•	•	1	
	Alcohol, Isopropyl	85% +	10	N.E.			•	•	1	
	Formaldehyde	8%	10	30			•	•	•	•
	Glutaraldehyde	2%	10	30			•	•	•	•
Gas	Ethylene Oxide	.4g/l	60	60	37	30	•	•	•	•
	Paraformaldehyde	.3g/ft³	60	60	> 23	> 60	•	•	•	•

Category	Important characteristics: Effective shelf life > 1 week [4]	Corrosive	Flammable	Explosion potential	Residue	Inactivated by organic matter	Lens compatible [7]	Electronics compatible	Skin irritant	Eye irritant	Respiratory irritant	Toxic [5]
Quat. Ammon. Cpds	•					•	•		•	•		•
Phenolic Cpds	•	•			•				•	•		•
Chlorine Cpds		•			•	•			•	•	•	•
Iodophor	•	•			•	•			•	•		•
Alcohol, Ethyl	•		•							•		•
Alcohol, Isopropyl	•		•							•		•
Formaldehyde	•				•				•	•		•
Glutaraldehyde	•				•		•		•	•		•
Ethylene Oxide	N.A.		• [2]	• [2]			•	•	•	•	•	•
Paraformaldehyde	N.A.		• [3]	• [3]			•	•	•	•	•	•

Category	Potential application: Work surfaces	Dirty glassware	Large area decon.	Air handling systems	Portable equip. surface decon.	Portable equip. penetrating decon.	Stationary equip. surface decon.	Stationary equip. penetrating decon.	Lenses & electronic instruments	Liquids for discard	Books, papers	Proprietary decontaminants examples [6]
Quat. Ammon. Cpds	✓	✓			✓		✓					A-33, CDQ, END-BAC, HI-TOR, MIKRO-QUAT
Phenolic Cpds	✓	✓			✓		✓					HIL-PHENE, MATAR, MIKRO-BAC, O-SYL
Chlorine Cpds	✓	✓			✓		✓			✓		CHLORAMINE T, CLOROX, PUREX
Iodophor	✓	✓			✓		✓					HI-SINE, IOPREP, MIKROKLENE, WESCODYNE
Alcohol, Ethyl	✓	✓			✓		✓					
Alcohol, Isopropyl	✓	✓			✓		✓					
Formaldehyde	✓	✓			✓		✓					STERAC
Glutaraldehyde	✓	✓			✓		✓					CIDEX
Ethylene Oxide						✓			✓		✓	CARBOXIDE, CRYOXCIDE, STEROXCIDE
Paraformaldehyde			✓	✓		✓		✓	✓			

N.A. = Not applicable — N.E. = Not effective
1. Variable results dependent on virus.
2. Neither flammable or explosive in 90% CO_2 or fluorinate hydrocarbon mix form.
3. At concentrations of 7 to 73% by volume in air, solid-exposure to open flame.
4. Protected from light and air.
5. By skin or mouth or both — refer to manufacturer's literature and/or Merck Index.
6. Space limitations preclude listing all products available. Individual listings (or omissions) do not imply endorsement or rejection of any product by the NIH.
7. Refers to microscope and camera lenses.

VII. HOUSEKEEPING

A. *Introduction*. Well-defined housekeeping procedures and schedules are essential in reducing the risks of working with etiologic agents and in protecting the integrity of the research program. This is particularly true in the biological laboratory operating under less than total containment concepts and in all areas used for the housing of animals, whether or not they have been intentionally infected. A well-conceived and well-executed housekeeping program limits physical clutter that could distract the attention and interfere with the activities of laboratory personnel at a critical moment in a potentially hazardous procedure, provides a work area that will not in itself be a source of physical injury or contamination, and provides an area that promotes the efficient use of decontaminants in the event of the inadvertent release of a harmful agent. Less immediately evident are the benefits of establishing, among personnel of widely varying levels of education, an appreciation of the nature and sources of biological contamination.

Housekeeping is an omnibus term that can be interpreted as broadly or as narrowly as one chooses. It can be seen that many of the procedures found under special headings, such as decontamination, disposal, and animal care, are, in reality, specific instructions for safely accomplishing otherwise routine housekeeping chores. In these safety suggestions for research on recombinant DNA molecules, it has been elected to address specifically only tasks of a janitorial nature under the subject of housekeeping.

The objectives of housekeeping in the biological laboratory are to:

1. Provide an orderly work area conducive to the accomplishment of the research program.
2. Provide work areas devoid of physical hazards.
3. Provide a clean work area with background contamination ideally held to a zero level but more realistically to a level such that extraordinary measures in sterile techniques are not required to maintain integrity of the biological systems being researched.
4. Prevent the accumulation of materials from current and past experiments that constitute a hazard to laboratory personnel.
5. Prevent the creation of aerosols of hazardous materials as a result of the housekeeping procedures used.

Procedures developed in the area of housekeeping should be based on the highest level of risk to which the personnel and integrity of the experiments will be subject. Such an approach avoids the confusion of multiple practices and retraining of personnel. The primary function, then, of routine housekeeping procedures is to prevent the accumulation of organic debris that (i) may harbor microorganisms that are a potential threat to the integrity of the biological systems under investigation, (ii) may enhance the survival of microorganisms inadvertently released in experimental procedures, (iii) may retard penetration of decontaminants, (iv) may be transferable from one area to another on clothing and shoes, (v) may, with sufficient buildup, become a biohazard as a consequence of secondary aerosolization by personnel and air movement, and (vi) may cause allergenic sensitization of personnel, e.g., to animal danders.

Housekeeping in animal care units has the same primary function as that stated for the laboratory and should, in addition, be as meticulously carried out in quarantine and conditioning areas as in areas used to house experimentally infected animals. No other areas in the laboratory have the constant potential for creation of significant quantities of contaminated organic debris than do animal care facilities.

In all laboratories, efforts to achieve total decontamination and to conduct a major cleanup of the biological complex are normally undertaken at relatively long time intervals. Routine housekeeping must be relied on to provide a work area free of significant sources of background contamination. The provision of such a work area is not simply a matter of indicating in a general way what has to be done, who will do it, and how often. The supervisor must view each task critically in terms of the potential biohazard involved, decide on a detailed procedure for its accomplishment, and provide instructions to laboratory personnel in a manner that minimizes the opportunity for misunderstanding.

The following checklist outlines a portion of the items requiring critical review by the laboratory supervisor. It is not intended to be complete but is presented as an example of the detailed manner in which housekeeping in the biological laboratory complex must be viewed.

Administration Areas
Aisles
Animal Food Storage
Animal Bedding Storage
Biological Safety Cabinets
Bench Tops and Other Work Surfaces
Ceilings
Change Rooms
Cleaning Solution Disposal
Cages and Cage Racks
Dry Ice Chests
Deep Freeze Chests
Entry and Exit Ways
Equipment Storage
Floors
Glassware
General Laboratory Equipment Cleanup
Hallways
Incubators
Instruments
Insect and Rodent Control
Light Fixtures
Mechanical Equipment Areas
Mops
Pipes—Wall and Ceiling Hung
Refrigerators
Showers
Supply Storage
UV Lamps
Vacuum Cleaners
Waste Accumulations
Waste Water Disposal
Others

Housekeeping in the laboratory is one of the avenues that leads to accomplishing the research program safely. It is important that housekeeping tasks be assigned to personnel who are knowledgeable of the research program and special hazards of the research environment. The recommended approach to housekeeping is the assignment of housekeeping tasks to the research teams on an individual basis for their immediate work areas and on a cooperative basis for areas of common usage. Similarly, animal caretaker personnel should be responsible for housekeeping in animal care areas. The laboratory supervisor must determine the frequency with which the individual and cooperative housekeeping chores need be accomplished. He should provide schedules and perform frequent inspection to assure compliance. This approach assures that research work flow patterns will not be interrupted by an alien cleanup crew, delicate laboratory equipment will be handled only by those most knowledgeable of its particular requirements, and the location of concentrated biological preparations and contaminated equipment used in their preparation and application will be known.

B. *Floor care.* Avoidance of dry sweeping and dusting will reduce the formation of nonspecific environmental aerosols. Wet mopping or vacuum cleaning with a high-efficiency particulate air (HEPA) filter on the exhaust is recommended.

Careful consideration must be given to design and quality in the selection of cleaning equipment and materials and in their use to prevent the substitution of one hazard for another.

In the absence of overt hazardous spills, the cleaning process commonly will consist of an initial vacuuming to remove all gross particulate matter and a follow-up wet mopping with a solution of chemical decontaminant containing a detergent. Depending on the nature of the surfaces to be cleaned and availability of floor drains, removal of residual cleaning solutions can be accomplished by a number of methods. Among these are: Pickup with a partially dry mop, pickup with a wet vacuum that has an adequately filtered exhaust, or removal to a convenient floor drain by use of a floor squeegee.

After cleaning up a spill of infected material, the residual solution should not be discharged to a sanitary sewer until it has been autoclaved or given further chemical treatment, such as by the addition of sodium hypochlorite sufficient to provide a final concentration of 500 ppm chlorine. Most household bleaches are marketed with a chlorine content of 5.25%. These in a final dilution of 1:100, yield 525 ppm of available chlorine. After allowing a contact time of 15 minutes, these solutions may be flushed down any available drain. Chlorine solutions in these high concentrations may be too corrosive for general application to floors and equipment. In any event, if solutions are used in this way, after the contact time the area should be rinsed with water.

C. *Dry sweeping.*—While it is recommended that dry sweeping be minimized, this may be the only method available or practicable under certain circumstances. In such cases, sweeping compounds used with push brooms and dry-dust mop heads treated to suppress aerosolization of dust should be used.

Sweeping compounds available from the usual janitorial supply firms fall in three categories:

Wax-based compounds used on vinyl floors and waxed floor coverings.

Oil-based compounds for concrete floors.

Oil-based compounds with abrasives (such as sand) to achieve a dry scouring action where much soil is present.

Dry-dust mop heads can be purchased as treated disposable units or as reusable, washable heads that must be treated with appropriate sprays or by other means to improve their dust-capturing property.

D. *Vacuum cleaning.* In the absence of a HEPA filter on the exhaust, the usual wet and dry industrial-type vacuum cleaner is a potent aerosol generator. The HEPA-filtered exhaust used in conjunction with a well-sealed vacuum unit, however, can negate this factor because of its ability to pass large volumes of exhaust air while retaining particles with a minimum efficiency of 99.97 percent. Wet and dry units incorporating a HEPA filter on the exhaust are available from a number of manufacturers.

There are no particular requirements with respect to the manner in which the dry vacuuming is accomplished other than to emphasize that the objective is to remove all debris and particulate matter. The manufacturer's directions adequately detail the frequency of bag changes, filter changes, and mechanical adjustments.

Dry material vacuum-collected during these floor-cleaning activities is potentially contaminated, but the nature of the risk is probably greater to the experiment than to the experimenter. It is wise to effect bag and filter changes and to clean out collection tanks in a manner that will avoid or minimize aerosolizing the contents of the vacuum cleaner.

A vacuum machine that collects debris in a disposable bag is preferable to machines that collect the major debris in a tank and on an exposed primary filter. Even though it may serve as a primary filter, the disposable bag must be removed with caution. A bellows effect may pump dust out of the bag if its intake opening is not sealed before moving it to a plastic bag for transfer out of the area. In any event, the outer surface of the disposable bag will probably bear some dust contamination, which also may occur on inner surfaces of the machine.

To avoid contaminating experimental materials, the emptying of vacuum collection tanks and changing of bags and filters are best done away from the immediate laboratory area, for example, in a small area that can be easily cleaned afterwards. The use of heavy rubber gloves is recommended when removing wastes from tanks in case broken glass is present. After making the filter changes, all external surfaces of the immediate work area and the equipment should be wiped with a cloth moistened in decontaminant. The operator might plan for a change of laboratory clothing afterwards so as to minimize carrying contamination into other areas of the laboratory.

Avoid use of dry vacuum cleaning equipment in work with high risk agents in the open laboratory. Should it be necessary to use it, it is recommended that gaseous sterilization may be used to minimize aerosolization of microorganisms before waste is emptied from the vacuum container. Because complete penetration of sterilizing gases into the collected dry dust may be a problem, all wastes should be placed in a plastic bag, which then is tightly closed and incinerated or disposed of in an approved manner.

When dry vacuum cleaning equipment has been used within a gastight safety cabinet system, it can be treated in an attached double-door carboxyclave (an autoclave equipped with an ethylene oxide gas sterilization system) to allow for removal and emptying of the collection tank.

If a wet vacuum is to be used for pickup of the detergent-germicide solution from the floor, the manufacturer's recommendations on filter life should be followed. In addition, the operation of the vacuum should be closely observed for evidence of operating changes indicating restricted airflow or, conversely, increased flow indicating filter failure. Liquids collected in the vacuum cleaner after floor mopping will contain decontaminant materials. These liquids may be poured down a convenient floor drain, except in the case of cleanup wastes from an overt spill. The collected liquid should then be autoclaved or treated with chlorine solution before disposal.

Provisions should be made for regular decontamination of the entire vacuum cleaner with formaldehyde gas or vapor, or ethylene oxide. This should be done after use if the vacuum is used in any manner for cleanup of overt spills of infectious material.

E. *Selection of a cleaning solution.* The selection of a detergent-decontaminant combination for routine cleaning of the laboratory complex should be based on the requirements of the area of greatest potential for contamination by the widest spectrum of microorganisms. With rare exception, this will be identified as the animal holding area and the expected microorganisms may well include fungi, viruses, and the vegetative and spore forms of bacteria. A decontaminating solution for such a range of microorganisms would, however, be expensive and excessively corrosive for routine use. Except in those rare instances where it can be assumed that pathogenic spores are being shed by laboratory animals, the risks from the spores are more likely to affect the experiments than the personnel. The spores tend to be associated with organic debris from bedding and food, thus offering potential for removal or at least a large initial reduction in their numbers by vacuum cleaning. A wide range of cleaning solutions that are mildly sporicidal, reasonably residual, and are not destructive to the physical plant are available. Phenol derivatives in combination with a detergent have these characteristics and have been selected for routine use in a number of research facilities. There are numerous detergent-phenolic combinations available on the market. The phenols are one type of a broad spectrum of biocidal substances that include the mercurials, quaternary ammonium compounds, chlorine compounds, iodophores, alcohols, formaldehyde, glutaraldehyde, and combinations of alcohol with either iodine or formaldehyde. These have been discussed in Section VI.

The laboratory supervisor should make a selection from those types most readily avail-

able which meet the general criteria of effectiveness, residual properties, and low corrosiveness.

F. *Wet mopping—two-bucket method.* Wet mopping of floors in laboratory and animal care areas is, from a safety standpoint, most conveniently and efficiently accomplished using a two-bucket system. The principal feature of such a system is that fresh detergent-decontaminant solution is always applied to the floor from one bucket, while all spent cleaning solution wrung from the mop is collected in the second bucket. Compact dolly-mounted double-bucket units with foot-operated wringers are available from most janitorial supply houses. A freshly laundered mop head of the cotton string type should be used daily. This requires that a mop with removable head be provided as opposed to a fixed-head type. In practice, the mop is saturated with fresh solution, very lightly wrung into the second bucket and applied to the floor using a figure eight motion of the mop head. After every four or five strokes, the mop head is turned over and the process continued until an area of approximately 100 ft^2 has been covered. After allowing a contact time of five minutes, the solution is removed with either a wet vacuum cleaner with HEPA-filtered exhaust or with the wrung-out mop. The mopping is continued in 100 ft^2 increments until the total floor area has been covered. Floor-cleaning procedures are most effectively completed after the majority of the work force has departed and should progress from areas of least potential contamination to those of greatest potential. Before a mop head is sent to a laundry, it should be autoclaved. Spent cleaning fluids are disposed of by flushing down the drain.

If the cleanup follows an overt spill of infectious material, the spent cleaning solution, after removal from the floor, should be autoclaved or treated with chlorine solution. Chlorine (as household bleach) should be added to give 500 ppm and held for a contact time of 15 minutes before dumping in the sanitary sewer.

G. *Alternative floor cleaning method for animal care areas and areas with monolithic floors.* The absence of permanently placed laboratory benches and fixed equipment, coupled with the mobility of modern cage racks, makes possible alternate floor-cleaning procedures in animal care facilities. As in all considerations of methodologies in biomedical laboratory facilities, it is necessary to assess the compatibility of procedures and facilities from the hazard point of view. The alternative floor-cleaning procedure to be discussed requires that floors are completely sealed or of monolithic construction so that liquid leakage to adjacent areas does not occur and that floor drains or wet vacuum cleaners are available.

Subsequent to the removal of all debris by dry vacuum, move the cage racks to one side of the room. Cover the floor of the remaining cleared portion of the room with detergent-decontaminant solution applied at a rate of approximately one gallon per 144 ft^2 from a one-gallon tank sprayer, using a setting on the nozzle which will cause the solution to flow on and not create a spray. The nozzle is placed close to the floor. Allow a fifteen-minute contact period; then push the cleaning solution to the floor drain with a large floor squeegee or pick it up with a wet vacuum. Allow the floor to air dry; move the cage racks into the cleaned area, and repeat the process for the remaining floor area. Floor drains in these areas should be *rim-flush*, at least six inches in diameter, and fitted with a screen or porous trap bucket to catch large debris that escapes the initial dry cleaning. Such screens and baskets should be emptied after treatment with a decontaminant. If space utilization does not require frequent floor washdown, pour a half-gallon of detergent-decontaminant solution into the drain each week to keep the trap in the waste line filled against backup of sewer gases.

VIII. CLEAN-UP OF BIOHAZARDOUS SPILLS (8, 9, 10)

A. *Biohazardous spill in a biological safety cabinet.* Chemical decontamination procedures should be initiated at once *while the cabinet continues to operate* to prevent escape of contaminants from the cabinet.

1. Spray or wipe walls, work surfaces, and equipment with a 2 percent solution of an iodophor-decontaminant (Wescodyne or equivalent). A decontaminant detergent has the advantage of detergent activity, which is important because extraneous organic substances frequently interfere with the reaction between the microorganisms and the active agent of the decontaminant. Operator should wear gloves during this procedure.

2. Flood the top work surface tray, and, if a Class II cabinet, the drain pans and catch basins below the work surface, with a decontaminant and allow to stand 10–15 minutes.

3. Remove excess decontaminant from the tray by wiping with a sponge or cloth soaked in a decontaminant. For Class II cabinets, drain the tray into the cabinet base, lift out tray and removable exhaust grille work, and wipe off top and bottom (underside) surfaces with a sponge or cloth soaked in a decontaminant. Then replace in position and drain recontaminant from cabinet base into appropriate container and autoclave according to standard procedures. Gloves, cloth or sponge should be discarded in an autoclave pan and autoclaved.

B. *Biohazard spill outside a biological safety cabinet.* 1. Hold your breath, leave the room immediately, and close the door.

2. Warn others not to enter the contaminated area.

3. Remove and put into a container contaminated garments for autoclaving and thoroughly wash hands and face.

4. Wait 30 minutes to allow dissipation of aerosols created by the spill.

5. Put on a long-sleeve gown, mask, and rubber gloves before reentering the room. (For a high risk agent, a jumpsuit with tight-fitting wrists and use of a respirator should be considered).

6. Pour a decontaminant solution (5% iodophor or 5% hypochlorite are recommended) around the spill and allow to flow into the spill. Paper towels soaked with the decontaminant may be used to cover the area. To minimize aerosolization, avoid pouring the decontaminant solution directly onto the spill.

7. Let stand 20 minutes to allow an adequate contact time.

8. Using an autoclavable dust pan and squeegee, transfer all contaminated materials (paper towels, glass, liquid, gloves, etc.) into a deep autoclave pan. Cover the pan with aluminum foil or other suitable cover and autoclave according to standard directions.

9. The dust pan and squeegee should be placed in an autoclavable bag and autoclaved according to standard directions. Contact of reusable items with non autoclavable plastic bags should be avoided—separation of the plastic after autoclaving can be very difficult.

C. *Radioactive biohazard spill outside a biological safety cabinet.* In the event that a biohazardous spill also involves a radiation hazard, the clean-up procedure may have to be modified, depending on an evaluation of the risk assessment of relative biological and radiological hazard.

Laboratories handling radioactive substances must have the services of a designated radiation protection officer available for consultation.

The following procedure indicates suggested variations from the biohazard spill procedure (above) that should be considered when a radioactive biohazard spill occurs outside a Biological Safety Cabinet.[1]

1. Holding your breath, leave the room immediately and close the door.

2. Warn others not to enter the contaminated area.

3. Remove and put in a container contaminated garments for autoclaving and thoroughly wash hands and face.

4. Wait thirty minutes to allow dissipation of aerosols created by the spill.

**Before clean-up procedures begin, a radiation protection officer should survey the spill for external radiation hazard to determine the relative degree of risk.*

5. Put on a long-sleeve gown, mask, and rubber gloves before reentering the room. (For a high risk agent, a jumpsuit with tight-fitting sleeves and a respirator should be considered).

6. Pour a decontaminant solution (5% iodophor or 5% hypochlorite are recommended) around the spill and allow to flow into the spill. Paper towels soaked with the decontaminant may be used to cover the area. To minimize aerosolization, avoid pouring the decontaminant solution directly onto the spill.

7. Let stand 20 minutes to allow adequate disinfectant contact time.

8. **In most cases, the spill will involve ^{14}C or ^{3}H, which present no external hazard. However, if more energetic beta or gamma emitters are involved, care must be taken to prevent hand and body radiation exposure. The radiation protection officer must make this determination before the clean-up operation is begun.*

If the radiation protection officer approves, the bio-hazard-handling procedure may begin: Using an autoclavable dust pan and *squeegee*, transfer all contaminated materials (paper towels, glass, liquid, gloves, etc.) into a deep autoclave pan. Cover the pan with aluminum foil or other suitable cover and autoclave according to standard directions.

**If the radiation protection officer determines that radioactive vapors may be released and thereby contaminate the autoclave, the material must not be autoclaved. In that case, sufficient decontaminant solution to immerse the contents should be added to the wastes container. The cover should be sealed with waterproof tape, and the container stored and handled for disposal as radioactive waste. Radioactive and biohazard warning symbols should be affixed to the waste container. As a general rule, autoclaving should be avoided.*

9. If autoclaving has been approved, the dust pan and squeegee should be placed in an autoclavable bag and autoclaved according to standard directions. Contact of reusable items with plastic bags should be avoided—separation of the plastic after autoclaving can be very difficult.

**A final radioactive survey should be made of the spill area, dust pan, and squeegee with a Geiger counter, or a smear should be taken and counted in a liquid scintillation counter.*

IX. A SECONDARY RESERVOIR AND FILTRATION APPARATUS FOR VACUUM SYSTEMS

The aspiration of tissue culture media from monolayer cultures and of supernatants from centrifuged samples into collection vessels or reservoirs is a common procedure in many laboratories. To prevent the accidental contamination by aerosols or fluids of house vacuum systems or laboratory pumps, some investigators have installed side arm flasks containing cotton, sulfuric acid or decontaminant between the reservoir and the vacuum line. Cotton is not completely effective as a filtering agent,

[1] Changes in procedures have been starred and italicized.

sulfuric acid will corrode pipes, and contaminants may lose their inactivating ability upon standing. The introduction of a cartridge-type filter that is moisture resistant and has a rated capacity to remove particles 350 nm (0.35u) or larger in size provides an effective barrier to virus aerosols.

The secondary reservoir and filtration apparatus can be assembled from readily available units as shown in Figure 1. A length of plastic tubing ¼ inch I.D x 1/16 inch wall is attached at one end of the reservoir and at the other end to the lower arm of a filtration and media storage flask. These flasks vary in capacity from 250 to 4000 ml, the choice of flask depending on available space and amount of fluid that could be accidentally aspirated. A second tube of the same dimensions is attached from the upper arm of the flask to the inlet port of the disposable filter assembly. The third tube is attached from the filter assembly to a vacuum source. The tubes are securely held to the filter by fittings supplied with the filter and the other tubing connections can be secured by worm drive hose clamps.

Ideally the flask should be placed higher than the reservoir of collection vessel. If fluid is accidentally drawn into the flask, the liquid can drain back into the reservoir by gravity if the connection at the vacuum line is broken. This prevents the loss of fluid which the investigator needs to retain.

Should the flask be used only for the recovery and storage of waste fluids, then the addition of a few grams of Dow Corning Antifoam A to the flask will reduce violent foaming of fluids aspirated into it. Such fluids can be decontaminated by introducing into the reservoir a final 5% concentration of an iodophor or other appropriate decontaminant, holding for 30 minutes and draining as above.

If the filter becomes contaminated or requires changing, the filter and flask can be safely removed by clamping the line between filter and vacuum source. The filter and flask should be autoclaved before the filter is discarded. A new filter can then be installed and the assembly replaced.

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Figure 1
A SECONDARY RESERVOIR AND FILTRATION APPARATUS

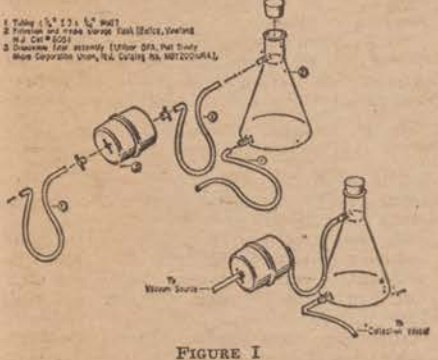

FIGURE I

X. PACKAGING AND SHIPPING

A. *Introduction.* Federal regulations and carrier tariffs have been promulgated to ensure the safe transport of hazardous biological materials. The NIH Guidelines specify that all DNA recombinant materials will be packaged and shipped in containers that meet the requirements of these regulations and carrier tariffs. In addition when any portion of the recombinant DNA material is derived from an etiologic agent listed in paragraph (c) of 42 CFR 72.25 (which is included at the end of this section, page D-85) the labeling requirements in these regulations and carrier tariffs shall apply.

B. *Packaging of recombinant DNA materials.* 1. *Volume less than 50 ml.* Material shall be placed in a securely closed, watertight container [primary container (test tube, vial, etc.)] which shall be enclosed in a second, durable watertight container (secondary container). Several primary containers may be enclosed in a single secondary container, if the total volume of all the primary containers so enclosed does not exceed 50 ml. The space at the top, bottom, and sides between the primary and secondary containers shall contain sufficient nonparticulate absorbent material to absorb the entire contents of the primary container(s) in case of breakage or leakage. Each set of primary and secondary containers shall then be enclosed in an outer shipping container constructed of corrugated fiberboard, cardboard, wood, or other material of equivalent strength.

If dry ice is used as a refrigerant, it must be placed outside the secondary container(s). er(s).

Descriptions of this packaging method are given in Table III.

2. *Volumes of 50 ml or Greater.* Material shall be placed in a securely closed, watertight container (primary container) which shall be enclosed in a second, durable watertight container (secondary container). Single primary containers shall not contain more than 500 ml. of material. However, two or more primary containers whose combined volumes do not exceed 500 ml. may be placed in a single secondary container. The space at the top, bottom, and sides between the primary and secondary containers shall contain sufficient non-particulate absorbent material to absorb the entire contents of the primary container(s) in case of breakage or leakage. Each set of primary and secondary containers shall then be enclosed in an outer shipping container constructed of corrugated fiberboard, cardboard, wood, or other material of equivalent strength. A shock absorbent material, in volume at least equal to that of the absorbent material between the primary and secondary containers, shall be placed at the top, bottom, and sides between the secondary container and the outer shipping container. Not more than eight secondary shipping containers may be enclosed in a single outer shipping container. (The maximum amount of materials which may be enclosed within a single outer shipping container should not exceed 4,000 ml.).

If dry ice is used as a refrigerant, it must be placed outside the secondary container(s). If dry ice is used between the secondary container and the outer shipping container, the shock absorbent material shall be placed so that the secondary container does not become loose inside the outer shipping container as the dry ice sublimates.

Descriptions of packages which comply with the regulations of the Department of Transportation (DOT) are given in Table IV.

C. Labeling of packages containing recombinant DNA naterials. 1. Materials which do not contain any portion of an etiologic agent listed in paragraph (c) of 42 CFR 72.25.

Material data forms, letters, and other information identifying or describing the material should be placed around the outside of the secondary container. Place only the address label on the outer shipping container.

DO NOT USE THE LABEL FOR ETIOLOGIC AGENTS/BIOMEDICAL MATERIAL.

2. Materials which contain any portion of an etiologic agent listed in paragraph (c) of 42 CFR 72.25.

Material data forms, letters, and other information identifying or describing the material should be placed around the outside of the secondary container. In addition to the address label, the label for Etiologic Agents/Biomedical Material must be affixed to the outer shipping container. This label is described in paragraph (c)(4) of 42 CFR 72.25.

3. Materials which contain any portion of a plant pest (plant pathogens) which are so defined by the Department of Agriculture (USDA).

Material data forms, letters, and other information identifying or describing the material should be placed around the outside of the secondary container. In addition to the address label, the shipping labels furnished by the USDA as part of the General, Courtesy, or Special Permits required for research with and shipment of such agents shall be affixed to the outer shipping container.

D. *Additional shipipng requirements and limitations for recombinant DNA materials.*—1. *Domestic Transportation.* Civil Aeronautics Board Rule No. 82 (Air Transport Association Restricted Articles Tariff 6-D) requires that a Shipper's Certificate, depicted below, be completed and affixed to all shipments which bear the ETIOLOGIC AGENT/BIOMEDICAL MATERIALS label required under the provisions of the Interstate Quarantine regulations (42 CFR 72.25(c)). The Certificate must be completed in duplicate and affixed to the outer shipping container.

This is to certify that the contents of this consignment are properly classified, described by proper shipping name and are packed, marked and labelled and are in proper condition for carriage by air according to all applicable carrier and government regulations. (For international shipments add "and to the IATA Restricted Articles Regulations".) This consignment is within the limitations prescribed for: PASSENGER AIRCRAFT/CARGO ONLY (cross out nonapplicable).

Number of Packages	Specify Each Article Separately (Proper Shipping Name)	Classification	Net Quantity per Package
	ETIOLOGIC AGENT, n.o.s.	ETIO. AG.	

Shipper:

Date _____

_____
(Signature of Shipper)

Shipments of recombinant DNA Materials exceeding 50 ml in volume and containing any portion of an etiologic agent listed in paragraph (c) of 42 CFR 72.25 are restricted, by DOT regulations, to transport by cargo only aircraft. When the volume of a single primary container exceeds the 50 ml limitation, this restriction must be indicated on the Shipper's Certificate by crossing out "Passenger Aircraft".

When dry ice is used as a refrigerant an "ORA—Group A—DRY ICE LABEL" should be affixed to the outer shipping container. The amount of dry ice used and the date packed should be designated on the label.

2. *International Transportation.*—In addition to the packaging and labeling requirements of the regulations previously cited, international shipments of recombinant DNA materials in which any portion of the material is derived from an etiologic agent listed in paragraph (c) of 42 CFR 72.25 must have one or more of the following documents—depending on the country of destination:

(1) Parcel Post Customs Declaration (PS 2966) tag.

(2) Parcel Post Customs Declaration (PS 2966–A) label.

(3) International Parcel Post—Instructions Given by Sender (POD 2922) label.

(4) Dispatch note (POD 2972) tag.

(5) "Violet Label"

(6) Shipper's Certificate specified in the current International Air Transport Association Tariff. Individual country requirements are listed in "International Postage Rates and Fees" (USPO Publication 51).

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TABLE III

Description of Packages for Material in Volumes less than 50 ml.

Volume (ml)	Primary Container	Packing	Secondary Container	Packing	Outer Shipping d/ Container
15 max.	Sealed vial(s) or small glass test tube, screw cap* or stopper, taped	a/	Metal can 1" diam. x 7" O.D. metal screw cap	None Required	Fiberbody; metal screw cap, top and bottom; 1-1/2" diam. x 7 to 7-1/2" O.D.
50 or less	One 20 x 150 mm test tube, taped* stopper or multiple small vials	a/	Metal can 2-1/2" diam. x 6-1/2" high O.D. screw cap	None Required	Fiberbody; metal screw cap, top and bottom; 3-1/4" diam. x 7 to 7-1/2" O.D.
50 or less	Plastic* screw cap* bottle or Pyrex glass with skirt rubber stopper	a/	Metal can 2-1/2" diam. x 6-1/2" high O.D. screw cap	None Required	Fiberbody; metal screw cap, top and bottom; 3-1/4" diam. x 7 to 7-1/2" O.D.
50 or less	Multiple watertight vials or * tubes, taped stoppers	a/	One or more friction-seal tin cans b/ 306 x 400 or larger	c/	Fiberboard box

*The flexibility of the plastic bottle requires that a stopper or screw cap be secured in place by adhesive tape. The usual equivalent-size glass flat-sided prescription bottle is too fragile for use. For air transport, all stoppers, corks, and caps on primary containers must be secured in place with wire, tape, or other means, and all screw-capped containers of unfrozen liquid must be placed in 5 or 6 mil polyvinyl tubing heat-sealed at both ends to prevent atmospheric decompression that may result in leakage past the screw cap.

O.D. = outside dimensions.

a/ Nonparticulate absorbent material at top, bottom and sides that will completely absorb contents of the primary container(s).

b/ 610 x 708 and 804 x 908 are trade designations for outside dimensions of 6-10/16 inches diameter x 7-8/16" height, and 8-4/16" x 9-8/16".

c/ None required, but with the 306 x 400 cans or larger cans use sufficient nonparticulate shock-absorbent material to prevent rattling.

d/ If materials are to be refrigerated, it is recommended that an overpack be used to contain the refrigerant and the secured (original) outer shipping container. A leak proof outer container must be used for water ice. If dry ice is used the outer container must permit release of carbon dioxide. Interior supports must be provided to hold the container(s) in the original position(s) after wet or dry ice has dissipated.

TABLE IV

Description of Packages for Material in Volumes of 50 ml or greater

Volume (ml)	Primary Container	Packing	Secondary Container	Packing: With Refrigerant	Packing: Without Refrigerant	Outer Shipping Container: With Refrigerant	Outer Shipping Container: Without Refrigerant
51 to 100 ml	Plastic* or Pyrex glass screw cap* bottle; rubber or skirt rubber stopper, taped*	a/	Consists of metal container & outer container specified in Table III	Styrofoam box shock-absorbent insulation	c/	Fiberboard box closely fitting the styrofoam box, taped shut	Corrugated fiberboard or cardboard box, taped shut
100 max.	One 100 ml plastic* screw cap* narrow neck bottle or Pyrex glass, taped*	a/	No. 3 crimp seal tin can 404 x 700 or a 1-gallon friction-seal tin can, 610 x 708, top soldered or clipped at 4 points b/	Styrofoam box shock-absorbent insulation	c/	Fiberboard box closely fitting the styrofoam box, taped shut	V3C cardboard box PS3 type, 9-3/16" x 9-3/16" x 11-1/4" high O.D. taped shut with 3" type PS3 tape
200 max.	Two 100 ml plastic* screw cap* bottles or Pyrex glass, taped	a/	No. 3 crimp seal tin can 404 x 700 or a 1-gallon friction-seal tin can, 610 x 708, top soldered or clipped at 4 points b/	Styrofoam box shock-absorbent insulation	c/	Fiberboard box closely fitting the styrofoam box, taped shut	V3C cardboard box PS3 type, 9-3/16" x 9-3/16" x 11-1/4" high O.D. taped shut with 3" type PS3 tape
250 max.	One 250 ml, plastic* narrow mouth screw cap* bottle or Pyrex glass skirted rubber stopper, taped*	a/	No. 3 crimp seal tin can 404 x 700 or a 1-gallon friction-seal tin can, 610 x 708, top soldered or clipped at 4 points b/	Styrofoam box shock-absorbent insulation	c/	Fiberboard box closely fitting the styrofoam box, taped shut	V3C cardboard box PS3 type, 9-3/16" x 9-3/16" x 11-1/4" high O.D. taped shut with 3" type PS3 tape
500 max.	Two 250 ml plastic* screw cap* bottles or Pyrex glass bottles, taped*	a/	2-gallon friction-seal tin can, 804 x 908, top soldered or clipped at 4 points b/	Styrofoam box shock-absorbent insulation	c/	Fiberboard box closely fitting the styrofoam box, taped shut	V3C cardboard box 12-1/4" x 12-1/4" x 10-3/16" high O.D. taped shut with 3" wide PS3 tape.
500 max.	500 ml Pyrex glass bottle, rubber-skirt stopper, taped, or 500 ml plastic* bottle, narrow or wide mouth, screw cap*, taped	a/	No. 12 crimp seal tin can 603 x 810 2-gallon friction-seal tin can, 804 x 908, top soldered or clipped at 4 points b/	Styrofoam box shock-absorbent insulation	c/	Fiberboard box closely fitting the styrofoam box, taped shut	V3C cardboard box 12-1/4" x 12-1/4" x 10-3/16" high O.D. taped shut with 3" wide PS3 tape. For the No. 12 can a cardboard box is ok taped shut

*The flexibility of the plastic bottle requires that a stopper or screw cap be secured in place by adhesive tape. The usual equivalent-size glass flat-sided prescription bottle is too fragile for use. For air transport, all stoppers, corks, and caps on primary containers must be secured in place with wire, tape, or other means, and all screw-capped containers of unfrozen liquid must be placed in 5 or 6 mil polyvinyl tubing heat-sealed at both ends to prevent atmospheric decompression that may result in leakage past the screw cap.

O.D. = outside dimensions.

a/ Nonparticulate absorbent material at top, bottom and sides that will completely absorb contents of the primary container(s).

b/ 610 x 708 and 804 x 908 are trade designations for outside dimensions of 6-10/16 inches diameter x 7-8/16" height, and 8-4/16" x 9-8/16".

c/ Shock absorbent material, in volume at least equal to that between the primary and secondary container(s), at the top, bottom, and sides between the secondary container and the outer shipping container. The shock absorbent material shall be so placed that the secondary container(s) does not become loose inside the outer shipping container as the water ice or dry ice is dissipated.

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ATTACHMENT I

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
CENTER FOR DISEASE CONTROL
ATLANTA, GEORGIA 30333
Telephone: (404) 633-3311, Ext. 3783

TITLE 42—PUBLIC HEALTH

Chapter I—Public Health Service, Department of Health, Education, and Welfare

SUBCHAPTER F—QUARANTINE, INSPECTION, LICENSING

PART 72—INTERSTATE QUARANTINE

Subpart C—Shipment of Certain Things

Section 72.25 of Part 72, Title 42, Code of Federal Regulations, is amended to read as follows:

§ 72.25 Etiologic agents.[1]

(a) *Definitions.* As used in this section:

(1) An "etiologic agent" means a viable microorganism or its toxin which causes, or may cause, human disease.

(2) A "diagnostic specimen" means any human or animal material including, but not limited to, excreta, secreta, blood and its components, tissue, and tissue fluids being shipped for purposes of diagnosis.

(3) A "biological product" means a biological product prepared and manufactured in accordance with the provisions of 9 CFR Part 10, Licensed Veterinary Biological Products, 42 CFR Part 73, Licensed Human Biological Products, 21 CFR 130.3, *New drugs for investigational use in humans*, 9 CFR Part 103, Biological Products for Experimental Treatment of Animals, or 21 CFR 130.3(a), *New drugs for investigational use in animals*, and which, in accordance with such provisions, may be shipped in interstate traffic.

(b) *Transportation; etiologic agent minimum packaging requirements.* No person may knowingly transport or cause to be transported in interstate traffic, directly or indirectly, any material, including but not limited to, diagnostic specimens and biological products, containing, or reasonably believed by such person to contain, an etiologic agent unless such material is packaged to withstand leakage of contents, shocks, pressure changes, and other conditions incident to ordinary handling in transportation.

(c) *Transportation; etiologic agents subject to additional requirements.* No person may knowingly transport or cause to be transported in interstate traffic, directly or indirectly, any material, other than diagnostic specimens and biological products, containing, or reasonably believed by such person to contain, one or more of the following etiologic agents unless such material is packaged in accordance with the requirements specified in paragraph (b) of this section, and unless, in addition, such material is packaged and shipped in accordance with the requirements specified in subparagraphs (1)–(6) of this paragraph:

BACTERIAL AGENTS

Actinobacillus—all species.
Arizona hinshawii—all serotypes.
Bacillus anthracis.
Bartonella—all species.
Bordetella—all species.
Borrelia recurrentis, B. vincenti.
Brucella—all species.
Clostridium botulinum, Cl. chauvoei, Cl. haemolyticum, Cl. histolyticum, Cl. novyi, Cl. septicum, Cl. tetani.
Corynebacterium diphtheriae C, equi, C. haemolyticum, C. pseudotuberculosis, C. pyogenes, C. renale.
Diplococcus (Streptococcus) pneumoniae.
Erysipelothrix insidiosa.
Escherichia coli, all enteropathogenic serotypes.
Francisella (Pasteurella) tularensis.
Haemophilus ducreyi, H. influenzae.
Herellea vaginicola.
Klebsiella—all species and all serotypes.
Leptospira interrogans—all serotypes.
Listeria—all species.
Mima polymorpha.
Morazella—all species.
Mycobacterium—all species.
Mycoplasma—all species.
Neisseria gonorrhoeae, N. meningitidis.
Pasteurella—all species.
Pseudomonas pseudomallei.
Salmonella—all species and all serotypes.
Shigella—all species and all serotypes.
Sphaerophorus necrophorus.
Staphylococcus aureus.
Streptobacillus moniliformis.
Streptococcus pyogenes.
Treponema caretcum, T. pallidum, and *T. pertenue.*
Vibrio fetus, V. comma, including biotype El Tor, and *V. parahemolyticus.*
Yersenia (Pasteurella) pestis.

FUNGAL AGENTS

Actinomycetes (including *Nocardia* species, *Actinomyces* species and *Arachnia propionica*).
Blastomyces dermatitidis.
Coccidioides immitis.
Cryptococcus neoformans.
Histoplasma capsulatum.
Paracoccidioides brasiliensis.

VIRAL, RICKETTSIAL, AND CHLAMYDIAL AGENTS

Adenoviruses—human—all types.
Arboviruses.
Coxiella burnetii.
Coxsackie A and *B viruses*—all types.
Cytomegaloviruses.
Dengue virus.
Echoviruses—all types.
Encephalomyocarditis virus.
Hemorrhagic fever agents, including *Crimean hemorrhagic fever (Congo), Junin*, and *Machupo viruses*, and others as yet undefined.
Hepatitis-associated antigen.
Herpesvirus—all members.
Infectious bronchitis-like virus.
Influenza viruses—all types.
Lassa virus.
Lymphocytic choriomeningitis virus.
Marburg virus.
Measles virus.
Mumps virus.
Parainfluenza viruses—all types.
Polioviruses—all types.
Poxviruses—all members.
Psittacosis - Ornithosis - Trachoma-Lymphogranuloma group of agents.
Rabies virus—all strains.
Reoviruses—all types.
Respiratory syncytial virus.
Rhinoviruses—all types.
Rickettsia—all species.
Rubella virus.
Simian viruses—all types.
Tick-borne encephalitis virus complex, including *Russian spring-summer encephalitis, Kyasanur forest disease, Omsk hemorrhagic fever*, and *Central European encephalitis viruses.*
Vaccinia virus.
Varicella virus.
Variola major and *Variola minor viruses.*
Vesicular stomatis virus.
Yellow fever virus.

(1) *Volume less than 50 ml.* Material shall be placed in a securely closed, watertight container (primary container (test tube, vial, etc.)) which shall be enclosed in a second, durable watertight container (secondary container). Several primary containers may be enclosed in a single secondary container, if the total volume of all the primary containers so enclosed does not exceed 50 ml. The space at the top, bottom, and sides between the primary and secondary containers shall contain sufficient nonparticulate absorbent material to absorb the entire contents of the primary container(s) in case of breakage or leakage. Each set of primary and secondary containers shall then be enclosed in an outer shipping container constructed of corrugated fiberboard, cardboard, wood, or other material of equivalent strength.

(2) *Volume 50 ml. or greater.* Packaging of material in volumes of 50 ml. or more shall include, in addition, a shock absorbent material, in volume at least equal to that of the absorbent material

[1] The requirements of this section are in addition to and not in lieu of any other packaging or other requirements for the transportation of etiologic agents in interstate traffic prescribed by the Department of Transportation and other agencies of the Federal Government.

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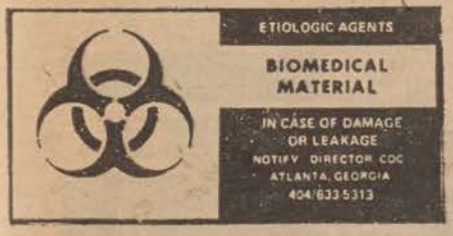
between the primary and secondary containers, at the top, bottom, and sides between the secondary container and the outer shipping container. Single primary containers shall not contain more than 500 ml. of material. However, two or more primary containers whose combined volumes do not exceed 500 ml. may be placed in a single, secondary container. Not more than eight secondary shipping containers may be enclosed in a single outer shipping container. (The maximum amount of etiologic agent which may be enclosed within a single outer shipping container shall not exceed 4,000 ml.)

(3) *Dry ice.* If dry ice is used as a refrigerant, it must be placed outside the secondary container(s). If dry ice is used between the secondary container and the outer shipping container, the shock absorbent material shall be so placed that the secondary container does not become loose inside the outer shipping container as the dry ice sublimates.

(4) *Labels.* The label for Etiologic Agents/Biomedical Material, except for size and color, must be as shown:



(i) The color of material on which the label is printed must be white and the symbol and printing in red.

(ii) The label must be a rectangle measuring 51 mm. (2 inches) high by 102.5 mm. (4 inches) long.

(iii) The red symbol measuring 38 mm. (1½ inches) in diameter must be centered in a white square measuring 51 mm. (2 inches) on each side.

(iv) Type size of the letters of label shall be as follows:

ETIOLOGIC AGENT	10 pt. rev.
BIOMEDICAL MATERIAL	14 pt.
IN CASE OF DAMAGE OR LEAKAGE	10 pt. rev.
NOTIFY DIRECTOR CDC ATLANTA, GA	8 pt. rev.
404 633 5313	10 pt. rev.

(5) *Damaged packages.* Carriers shall promptly, upon discovery of damage to the package that indicates damage to the primary container, isolate the package and notify the Director, Center for Disease Control, 1600 Clifton Road NE., Atlanta, GA 30333 (telephone (404) 633-5313), and the sender.

(6) *Registered mail or equivalent system.* Transportation of the following etiologic agents shall be by registered mail or an equivalent system which requires or provides for sending notification to the shipper immediately upon delivery:

Actinobacillus mallei.
Coccidioides immitis.
Francisella (Pasteurella) tularensis.
Hemorrhagic fever agents, including, but not limited to, *Crimean hemorrhagic fever (Congo), Junin, Machupo viruses.*
Herpesvirus simiae (B virus).
Histoplasma capsulatum.
Lassa virus.
Marburg virus.
Pseudomonas pseudomallei.
Tick-borne encephalitis virus complex, including, but not limited to, *Russian spring-summer encephalitis, Kyasanur forest disease, Omsk hemorrhagic fever,* and *Central European encephalitis viruses, Variola minor* and *Variola major.*
Yersenia (Pasteurella) pes:

(d) *Notice of delivery, failure to receive.* When notice of delivery of agents containing, or suspected of containing, etiologic agents listed in paragraph (c) (6) of this section is not received by the sender within 5 days following anticipated delivery of the package, the shipper shall notify the Director, Center for Disease Control, 1600 Clifton Road NE., Atlanta, GA 30333 (telephone (404) 633-5313).

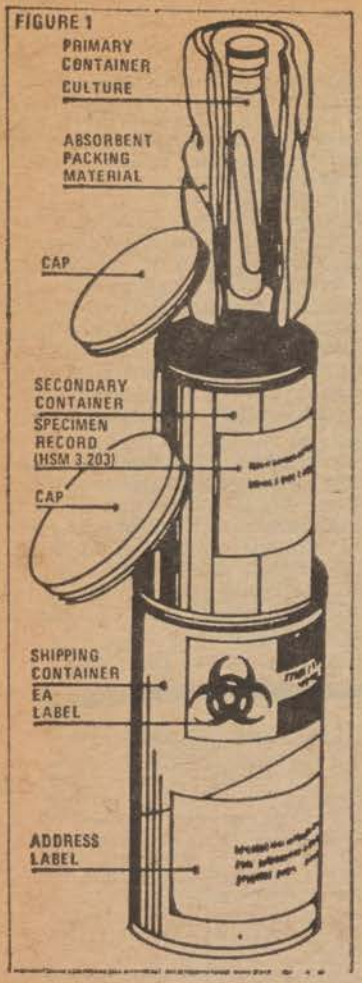
(e) *Requirements; variations.* The Administrator may approve variations from the requirements of this section if, upon review and evaluation, he finds that such variations provide protection at least equivalent to that provided by compliance with the requirements specified in this section and makes such findings a matter of official record.

(Sec. 361, 58 Stat. 703; 42 U.S.C. 264)

[redacted]

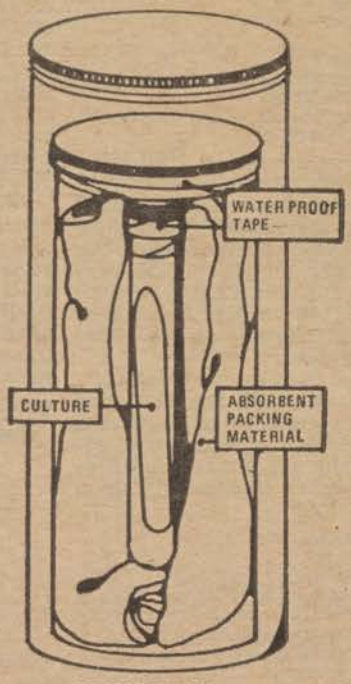
Effective July 30, 1972

FIGURE 1



PACKAGING AND LABELING OF ETIOLOGIC AGENTS

FIGURE 2



CROSS SECTION OF PROPER PACKING

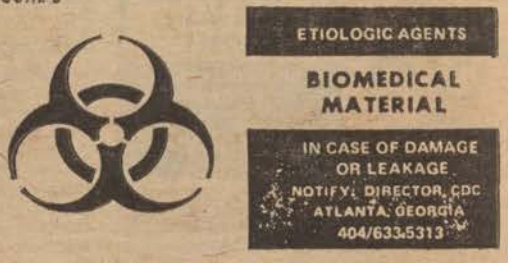
The Interstate Quarantine Regulations (42 CFR, Part 72 25 Etiologic Agents) was revised July 31, 1972 to provide for packaging and labeling requirements for etiologic agents and certain other materials shipped in interstate traffic.

Figures 1 and 2 diagram the packaging and labeling of etiologic agents in volumes of less than 50 ml. in accordance with the provisions of subparagraph (C) (1) of the cited regulation. Figure 3 illustrates the color and size of the label, described in subparagraph (C) (4) of the regulations, which shall be affixed to all shipments of etiologic agents.

For further information on any provision of this regulation contact:

Center for Disease Control
Attn: Biohazards Control Office
1600 Clifton Road
Atlanta, Georgia 30333
Telephone: 404 633 3311

FIGURE 3



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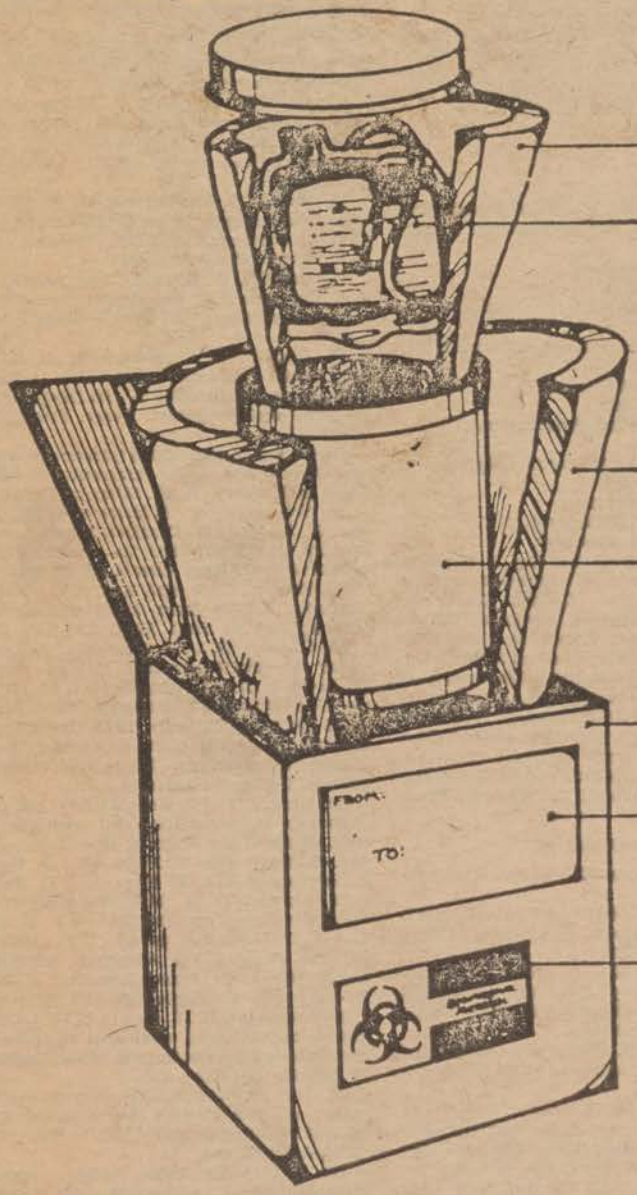
PACKAGING AND LABELING OF ETIOLOGIC AGENTS



ABSORBENT PACKING MATERIAL

PRIMARY CONTAINER *(Bottle, blood bag, etc.)**

*NOTE: Single primary containers may not exceed 500 ml. of material. Two or more primary containers whose combined volumes do not exceed 500 ml. may be enclosed in a single, secondary container. The maximum volume of etiologic agent which may be enclosed in a single outer shipping container shall not exceed 4000 ml.

SHOCK ABSORBENT MATERIAL

SECONDARY CONTAINER *(Gasketed screwcap with waterproof tape or hermetically sealed can)*

OUTER SHIPPING CONTAINER

MAILING LABEL

ETIOLOGIC AGENT LABEL

The Interstate Quarantine Regulations (42 CFR, Part 72.25, Etiologic Agents) was revised July 31, 1972, to provide for packaging and labeling requirements for etiologic agents and certain other materials shipped in interstate traffic. The illustration shows acceptable packaging and labeling of etiologic agents in accordance with subparagraphs (c) (2) and (4) of the cited regulation.

For further information on any provision of this regulation contact:

Center for Disease Control
Attn: Biohazards Control Office
1600 Clifton Road
Atlanta, Georgia 30333

Telephone: 404-633-3311

XI. TRAINING AIDS, MATERIALS AND COURSES

A. *Slide-tape cassettes.* 1. Assessment of Risk in the Cancer Virus Laboratory ($10).

2. Effective Use of The Laminar Flow Biological Safety Cabinet ($10).

3. Formaldehyde Decontamination of Laminar Flow Biological Safety Cabinets ($10).

4. Certification of Class II (Laminar Flow) Biological Safety Cabinets ($13).

5. Hazard Control in the Animal Laboratory ($10).

6. Basic Principles of Contamination Control (In preparation).

7. Selection of a Biological Safety Cabinet (In preparation).

These slide tape cassettes are available for purchase from the National Audiovisual Center. The price for each is given above after the title. Send your order prepaid with a check or money order made payable to National Archives Trust Fund and mail to: Sales Branch, National Audiovisual Center (GSA), Washington, D.C. 20409.

8. Research Laboratory Safety.

This slide tape cassette, stock number 176.79, is available for $75 from the National Safety Council, 425 North Michigan Avenue, Chicago, Illinois 60611.

B. *Films.* 1. Air Sampling for Microbiological Particulates (M–926).

2. Handling the Laboratory Guinea Pig (T2618–X).

3. Handling the Laboratory Mouse (T2617–X).

4. Infectious Hazards of Bacteriological Techniques (M–382).

5. Laboratory Design for Microbiological Safety (M–1091).

6. Plastic Isolators: New Tools for Medical Research (M–599).

7. Safe Handling of Laboratory Animals (M–455).

8. Surface Sampling for Microorganisms (Rodac Method) (M–924).

9. Surface Sampling for Microorganisms (Swab Method) (M–925).

These films are available on loan without charge from: Media Resources Branch, National Medical Audiovisual Center (Annex), Station K, Atlanta, Georgia 30324. The same films (except 2 and 3) can be rented or bought from: National Audiovisual Center (GSA), (Rental Branch)—(Sales Branch), Washington, D.C. 20409.

C. *Courses.* 1. Biohazard and Injury Control in the Biomedical Laboratory. Presented by the University of Minnesota, School of Public Health and the National Cancer Institute, Office of Research Safety. Direct inquiries to Dr. Donald Vesley, University of Minnesota, School of Public Health, 1325 Mayo Memorial Building, Minneapolis, Minnesota 55455. June 22–24, 1976, Los Angeles, CA; October 26–28, 1976, Boston, MA; December 7–9, 1976, Bethesda, MD.

2. Biohazard Containment and Control for Recombinant DNA Molecules. Presented by the University of Minnesota, School of Public Health and the National Cancer Institute, Office of Research Safety. Direct inquires as above. September 8–9, 1976, Stanford, CA; September 21–11, 1976, Cold Spring Harbor, NY.

3. Safety in Laboratory. Presented by National Institute of Occupational Safety and Health, Division of Training and Manpower Development, by special arrangement. Robert A. Taft Laboratories, 4676 Columbia Parkway, Cincinnati, Ohio 45226.

4. Laboratory Safety Management. Presented by the Laboratory and Training Division, Bureau of Laboratories, Center for Disease Control, Atlanta, Georgia, September 14–16, 1976 and September 13–15, 1977.

XII. OUTLINE OF A SAFETY AND OPERATION MANUAL FOR A P4 FACILITY

A. *Purpose.*

B. *Policy.*

C. *Responsibility and Authority.* 1. Management.

2. Supervisor.

3. Each Employee.

4. Facility Safety Officer.

5. Biohazard Safety Committee.

D. *Facility Assignment Procedures.*

E. *Reporting of Major and Minor Accidents and Injuries, Exposure to Toxic or Infectious Materials, Unsafe Conditions and Property Damages, and Rendering First-Aid.*

F. *General Laboratory Safety.* 1. Fire.

2. Equipment.

3. Physical.

4. Chemical.

5. Radiological.

G. *Safety Procedures Associated with Biohazard Activities of the Laboratory.* 1. Personnel Practices.

2. Operational Practices.

H. *Medical Surveillance.*

I. *Facility Operations.* 1. Personnel Access Procedures.

2. Access Procedures for Equipment Materials and Supplies.

3. Maintenance and Support.

4. Zone Classification.

5. Facility Monitoring Procedures.

6. Housekeeping.

J. *Others.* 1. Packaging and Shipment of Biohazardous Materials.

2. Emergency Procedures.

3. Insect and Rodent Control.

4. Orientation and Training.

Appendix D was prepared by a Working Group Consisting of: W. Emmett Barkley (Chairman), National Cancer Institute, NIH; Manuel S. Barbeito, National Cancer Insitute, NIH; Everett Hanel, Jr., Frederick Cancer Research Center; George S. Michaelsen, School of Public Health, University of Minnesota; Vinson R. Oviatt, Division of Research Services, NIH; Warren V. Powell, Division of Research Services, NIH; John Richardson, Center for Disease Control; James F. Sullivan, National Animal Disease Laboratories; and Arnold G. Wedum, Frederick Cancer Research Center.

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