DEPARTMENT OF LABOR

Occupational Safety and Health Administration

29 CFR Parts 1910, 1915 and 1926

[Docket No. H–041]

RIN 1218–AA83

Occupational Exposure to 1,3-Butadiene

AGENCY: Occupational Safety and Health Administration (OSHA), Department of Labor.

ACTION: Final rule.

SUMMARY: This final standard amends the Occupational Safety and Health Administration's (OSHA) occupational standard that regulates employee exposure to 1,3-Butadiene (BD). The basis for this action is a determination by the Assistant Secretary, based on animal and human data, that OSHA's current permissible exposure limit (PEL) which permits employees to be exposed to BD in concentrations up to 1,000 parts BD per million parts of air (1,000 ppm) as an eight-hour time-weighted average (TWA) does not adequately protect employee health. OSHA's new limits reduce the PEL for BD to an 8-hour TWA of 1 ppm and a short term exposure limit (STEL) of 5 ppm for 15 minutes. An ''action level'' of 0.5 ppm as an 8-hour TWA is included in the standard as a mechanism for exempting an employer from some administrative burdens, such as employee exposure monitoring and medical surveillance, in instances where the employer can demonstrate that the employee's exposures are consistently at very low levels. In order to reduce exposures and protect employees, OSHA's BD standard includes requirements such as engineering controls, work practices and personal protective equipment, measurement of employee exposures, training, medical surveillance, hazard communication, regulated areas, emergency procedures and recordkeeping.

DATES: The effective date of these amendments is February 3, 1997. Start-up date for engineering controls is November 4, 1998, and for the exposure goal program November 4, 1999. Affected parties do not have to comply with the information collection requirements in § 1910.1051(d) exposure monitoring, § 1910.1051(f) methods of compliance, § 1910.1051(g) exposure goal program, § 1910.1051(h) respiratory protection, § 1910.1051(j) emergency situations, § 1910.1051(k) medical screening and surveillance, § 1910.1051(l) communication of BD hazards to employees; and § 1910.1051(m) recordkeeping until the Department of Labor publishes a Federal Register notice informing the public that OMB has approved these information requirements under the Paperwork Reduction Act of 1995.

Other Dates: Written comments on the paperwork requirements of this final rule must be submitted on or before January 3, 1997.

ADDRESSES: In accordance with 28 U.S.C. 2112(a), the Agency designates the following party to receive petitions for review of this regulation: Associate Solicitor for Occupational Safety and Health, Office of the Solicitor, Room S–4004, U.S. Department of Labor, 200 Constitution Ave., NW., Washington, DC 20210. These petitions must be filed no later than the 59th calendar day following promulgation of this regulation; see section 6(f) of the Occupational Safety and Health Act of 1970 (OSH Act), 29 CFR 1911.18(d), and *United Mine Workers of America* v. *Mine Safety and Health Administration*, 900 F.2d 384 (D.C. Circ. 1990).

Comments regarding the paperwork burden of this regulation, which are being solicited by the Agency as required by the Paperwork Reduction Act of 1995, are to be submitted to the Docket Office, Docket No. ICR 96–13, U.S. Department of Labor, Room N–2625, 200 Constitution Ave., NW., Washington, DC 20210, telephone (202) 219–7894. Written comments limited to 10 pages or less in length may also be transmitted by facsimile to (202) 219–5046.

FOR FURTHER INFORMATION CONTACT: Ms. Anne Cyr, OSHA Office of Public Affairs, United States Department of Labor, Room N–3641, 200 Constitution Avenue, NW., Washington, DC. 20210, Telephone (202) 219–8151. Copies of the referenced information collection request are available for inspection and copying in the Docket Office and will be mailed to persons who request copies by telephoning Vivian Allen at (202) 219–8076. For electronic copies of the 1,3–Butadiene Information Collection Request, contact OSHA's WebPage on Internet at http://www.osh.gov/.

I. Collection of Information; Request for Comment

This final 1,3–Butadiene standard contains information collection requirements that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act (PRA95) 44 U.S.C. 3501 *et seq.* (see also 5 CFR part 1320). PRA95 defines collection of information to mean, ''the obtaining, causing to be obtained, soliciting, or requiring the disclosure to third parties or the public of facts or opinions by or for an agency regardless of form or format.'' (44 U.S.C. 3502(3)(A))

The title, the need for and proposed use of the information, a summary of the collections of information, description of the respondents, and frequency of response required to implement the required information collection is described below with an estimate of the annual cost and reporting burden (as required by 5 CFR 1320.5(a)(1)(iv) and 1320.8(d)(2)). Included in the estimate is the time for reviewing instructions, gathering and maintaining the data needed, and completing and reviewing the collection of information.

OSHA invites comments on whether the proposed collection of information:

- Ensures that the collection of information is necessary for the proper performance of the functions of the agency, including whether the information will have practical utility;
- Estimates the projected burden accurately, including whether the methodology and assumptions used are valid;
- Enhances the quality, utility, and clarity of the information to be collected; and
- Minimizes the burden of the collection of information on those who are to respond, including the use of appropriate automated, electronic, mechanical, or other technological collection techniques or other forms of information technology, e.g., permitting electronic submissions of responses.

Title: 1,3–Butadiene, 29 CFR 1910.1051.

Description: The final 1,3-Butadiene (BD) Standard is an occupational safety and health standard that will minimize occupational exposure to BD. The standard's information collection requirements are essential components that will protect employees from occupational exposure. The information will be used by employers and employees to implement the protection required by the standard. OSHA will use some of the information to determine compliance with the standard.

Summary of the Collection of Information: The collections of information contained in the standard include the provisions concerning objective data; exposure monitoring records and employee notification of exposure monitoring results; written plans for compliance, respiratory protection, exposure goal, emergency situations; information to the physician; employee medical exams and medical

records; respirator fit-testing records; record of training program; employee access to monitoring and medical records; and transfer of records to NIOSH.

Respondents: The respondents are employers whose employees may have occupational exposure to BD above the action level. The main industries affected are 1,3-Butadiene Polymer Production, Monomer purification of 1,3-Butadiene, Stand-Alone Butadiene Terminals, and Crude 1,3-Butadiene Producers.

Frequency of Response: The frequency of monitoring and notification of monitoring results will be dependent on the results of the initial and subsequent monitoring events and the number of different job classifications with BD exposure. The Compliance Plan is required to be established and updated as necessary and reviewed at least annually. The Exposure Goal Program, Respiratory Protection Program, and Emergency Plans are required to be established and updated as necessary. For those using respirators, respirator fit testing is required initially, and at least annually thereafter. The frequency of the medical examinations will be dependent on the number of employees who will be exposed at or above the action level, or in emergency situations. A record of the training program is required to be maintained. Those employers using objective data in lieu of monitoring must maintain records of the objective data relied upon. The employer must maintain exposure monitoring and medical records, which includes information provided to the physician or other licensed health care professional, in accordance with 29 CFR 1910.20. Fit-Test records must be maintained for respirator users until the next fit test is administered.

Total Estimated Cost: First Year $820,388; Second Year $658,949; and Third and Recurring Years $75,890.

Total Burden Hours: The total burden hours for the first year is estimated to be *8,077;* for the second year, the burden is estimated to be *5,342;* and for the third and recurring years, the burden is estimated to be *1,587.* The Agency has submitted a copy of the information collection request to OMB for its review and approval. Interested parties are requested to send comments regarding this information collection to the OSHA Docket Office, Docket No. ICR 96–13, U.S. Department of Labor, Room N–2625, 200 Constitution Avenue, NW, Washington, DC 20210. Written comments limited to 10 pages or fewer may also be transmitted by facsimile to (202) 219–5046.

Comments submitted in response to this notice will be summarized and included in the request for Office of Management and Budget approval of the final information collection request; they will also become a matter of public record.

Copies of the referenced information collection request are available for inspection and copying in the OSHA Docket Office and will be mailed to persons who request copies by telephoning Vivian Allen at (202) 219–8076. Electronic copies of the 1,3-Butadiene information collection request are available on the OSHA WebPage on the Internet at http://www.osha.gov/.

Federalism

This standard has been reviewed in accordance with Executive Order 12612, 52 FR 41685 (October 30, 1987), regarding Federalism. This Order requires that agencies, to the extent possible, refrain from limiting State policy options, consult with States prior to taking any actions only when there is clear constitutional authority and the presence of a problem of national scope. The Order provides for preemption of State law only if there is a clear Congressional intent for the Agency to do so. Any such preemption is to be limited to the extent possible.

Section 18 of the Occupational Safety and Health Act (OSH Act), expresses Congress' clear intent to preempt State laws with respect to which Federal OSHA has promulgated occupational safety or health standards. Under the OSH Act, a State can avoid preemption only if it submits, and obtains Federal approval of, a plan for the development of such standards and their enforcement. Occupational safety and health standards developed by such State Plan-States must, among other things, be at least as effective in providing safe and healthful employment and places of employment as the Federal standards. Where such standards are applicable to products distributed or used in interstate commerce, they may not unduly burden commerce and must be justified by compelling local conditions. (See section 18(c)(2).)

The final BD standard is drafted so that employees in every State will be protected by general, performance-oriented standards. States with occupational safety and health plans approved under section 18 of the OSH Act will be able to develop their own State standards to deal with any special problems which might be encountered in a particular state. Moreover, the performance nature of this standard, of and by itself, allows for flexibility by States and employers to provide as much leeway as possible using alternative compliance.

This final rule of BD addresses a health problem related to occupational exposure to BD which is national in scope.

Those States which have elected to participate under section 18 of the OSH Act would not be preempted by this regulation and will be able to deal with special, local conditions within the framework provided by this performance-oriented standard while ensuring that their standards are at least as effective as the Federal Standard.

State Plans

The 23 States and 2 territories with their own OSHA-approved occupational safety and health plans must adopt a comparable standard within 6 months of the publication of this final standard for occupational exposure to 1,3-butadiene or amend their existing standards if it is not ''at least as effective'' as the final Federal standard. The states and territories with occupational safety and health state plants are: Alaska, Arizona, California, Connecticut (for State and local government employees only), Hawaii, Indiana, Iowa, Kentucky, Maryland, Michigan, Minnesota, Nevada, New Mexico, New York (for State and local government employees only), North Carolina, Oregon, Puerto Rico, South Carolina, Tennessee, Utah, Vermont, Virginia, the Virgin Islands, Washington, and Wyoming. Until such time as a State standard is promulgated, Federal OSHA will provide interim enforcement assistance, as appropriate, in these states and territories.

SUPPLEMENTARY INFORMATION:

I. Table of Contents

The preamble to the final standard on occupational exposure to BD discusses events leading to the final rule, physical and chemical properties of BD, manufacture and use of BD, health effects of exposure, degree and significance of the risk presented, an analysis of the technological and economic feasibility, regulatory impact and regulatory flexibility analysis, and the rationale behind the specific provisions set forth in the proposed standard. The discussion follows this outline:

I. Table of Contents
II. Pertinent Legal Authority
III. Events Leading to the Final Standard
IV. Chemical Identification, Production, and Use
A. Monomer
B. Polymers
V. Health Effects

A. Introduction
B. Carcinogenicity
1. Animal Studies
2. Epidemiologic Studies
C. Reproductive Effects
D. Other Relevant Studies
VI. Quantitative Risk Assessment
VII. Significance of Risk
VIII. Summary of the Final Economic Analysis
IX. Environmental Impact
X. Summary and Explanation of the Proposed Standard
A. Scope and Application
B. Definitions
C. Permissible Exposure Limits
D. Exposure Monitoring
E. Regulated Areas
F. Methods of Compliance
G. Exposure Goal Program
H. Respiratory Protection
I. Personal Protective Equipment
J. Emergency Situations
K. Medical Screening and Surveillance
L. Hazard Communication
M. Recordkeeping
N. Dates
O. Appendices
XI. Final Standard and Appendices
Appendix A: Substance Safety Data Sheet for 1,3-Butadiene
Appendix B: Substance Technical Guidelines for 1,3-Butadiene
Appendix C: Medical Screening and Surveillance for 1,3-Butadiene
Appendix D: Sampling and Analytical Method for 1,3-Butadiene
Appendix E: Respirator Fit Testing Procedures
Appendix F: Medical Questionnaires

II. Pertinent Legal Authority

The purpose of the Occupational Safety and Health Act, 29 U.S.C. 651 *et seq.* (''the Act'') is to ''assure so far as possible every working man and woman in the nation safe and healthful working conditions and to preserve our human resources.'' 29 U.S.C. 651(b). To achieve this goal, Congress authorized the Secretary of Labor to promulgate and enforce occupational safety and health standards. U.S.C. 655(a) (authorizing summary adoption of existing consensus and federal standards within two year of Act's enactment), 655(b) (authorizing promulgation of standards pursuant to notice and comment), 654(b) (requiring employers to comply with OSHA standards.)

A safety or health standard is a standard ''which requires conditions, or the adoption or use of one or more practices, means, methods, operations, or processes, reasonably necessary or appropriate to provide safe or healthful employment or places of employment.'' 29 U.S.C. 652(8).

A standard is reasonably necessary or appropriate within the meaning of Section 652(8) if it substantially reduces or eliminates significant risk, and is economically feasible, technologically feasible, cost effective, consistent with prior Agency action or supported by a reasoned justification for departing from prior Agency actions, supported by substantial evidence, and is better able to effectuate the Act's purposes than any national consensus standard it supersedes. See 58 FR 16612–16616 (March 30, 1993).

The Supreme Court has noted that a reasonable person would consider a fatality risk of 1/1000 over a 45-year working lifetime to be a significant risk. Industrial Union *Dep't* v. *American Petroleum Institute, 448 U.S. 607,* 646 (1980) (benzene standard). OSHA agrees that a fatality risk of 1/1000 over a working lifetime *is well within the range of risk that* reasonable people would consider significant. See e.g., *International Union, UAW* v. *Pendergrass,* 878 F.2d 389 (D.C. Cir. 1989) (formaldehyde standard); *Building and Constr. Trades Dep't, AFL–CIO* v. *Brock,* 838 F.2d 1258, 1265 (D.C. Cir. 1988) (asbestos standard).

A standard is technologically feasible if the protective measures it requires already exist, can be brought into existence with available technology, or can be created with technology that can reasonably be expected to be developed. *American Textile Mfrs. Institute* v. *OSHA,* 452 U.S. 490, 513 (1981) (''ATMI''), *American Iron and Steel Institute* v. *OSHA,* 939 F.2d 975, 980 (D.C. cir. 1991) (''AISI'').

A standard is economically feasible if industry can absorb or pass on the cost of compliance without threatening its long term profitability or competitive structure. See *ATMI,* 452 U.S. at 530 n. 55; *AISI,* 939 F. 2d at 980.

A standard is cost effective if the protective measures it requires are the least costly of the available alternatives that achieve the same level of protection. ATMI, 453 U.S. at 514 n. 32; *International Union, UAW* v. *OSHA,* 37 F. 3d 665, 668 (D.C. Cir. 1994) (''LOTO III'').

All standards must be highly protective. See 58 FR 16614–16615; *LOTO III,* 37 F. 3d at 668. However, health standards must also meet the ''feasibility mandate'' of Section 6(b)(5) of the Act, 29 U.S.C. 655(b)(5). Section 6(b)(5) requires OSHA to select ''the most protective standard consistent with feasibility'' that is needed to reduce significant risk when regulating health hazards. *ATMI,* 452 U.S. at 509.

Section 6(b)(5) also directs OSHA to base health standards on ''the best available evidence,'' including research, demonstrations, and experiments. 29 U.S.C. 655(b)(5). OSHA shall consider ''in addition to the attainment of the highest degree of health and safety protection * * * the latest scientific data * * * feasibility and experience gained under this and other health and safety laws.'' *Id.*

Section 6(b)(7) of the Act authorizes OSHA to include among a standard's requirements labeling, monitoring, medical testing and other information gathering and transmittal provisions. 29 U.S.C. 655(b)(7).

Finally, whenever practical, standards shall ''be expressed in terms of objective criteria and of the performance desired.'' *Id.*

III. Events Leading to the Final Standard

The standard adopted for BD by OSHA in 1971 pursuant to Section 6(a) of the OSH Act, 29 U.S.C. 655 from an existing Walsh-Healey Federal Standard required employers to assure that employee exposure does not exceed 1,000 ppm determined as an 8-hour TWA (29 CFR 1910.1000, Table Z–1). The source of the Walsh-Healey Standard was the Threshold Limit Value (TLV) for BD developed in 1968 by the American Conference of Governmental Industrial Hygienists (ACGIH). This TLV was adopted by the ACGIH to prevent irritation and narcosis.

In 1983, the National Toxicology Program (NTP) released the results of an animal study indicating that BD causes cancer in rodents. (Ex. 20) Based on the strength of the results of this animal study, ACGIH in 1983 classified BD as an animal carcinogen and in 1984 recommended a new TLV of 10 ppm. (Ex. 2–4) Based on the same evidence, on February 9, 1984, the National Institute for Occupational Safety and Health (NIOSH) published a Current Intelligence Bulletin (CIB) recommending that BD be regarded as a potential occupational carcinogen, teratogen and a possible reproductive hazard. (Ex. 23–17) On January 5, 1984, OSHA published a Request for Information (RFI) jointly with the Environmental Protection Agency. (EPA) (49 FR 844) EPA also announced the initiation of a 180 day review under the authority of section 4(f) of the Toxic Substance Control Act (TSCA) (49 FR 845) to determine ''whether to initiate appropriate action to prevent or reduce the risk from the chemical or to find that the risk is not unreasonable.'' Comments were to be submitted to OSHA by March 5, 1984. On April 4, 1984, OSHA extended the comment period until further notice. (49 FR 13389)

Petitions for an Emergency Temporary Standard (ETS) of 1 ppm or less for workers' exposure to BD were submitted to OSHA on January 23, 1984, by the United Rubber, Cork, Linoleum and

Plastic Workers of America (URW), the Oil, Chemical and Atomic Workers (OCAW), the International Chemical Workers Union (ICWU), and the American Federation of Labor and Congress of Industrial Organizations (AFL–CIO). (Ex. 6–4) On March 7, 1984, OSHA denied the petitions on the ground that the Agency was still evaluating the health data to determine whether regulatory action was appropriate.

Based on its 180-day review of BD, EPA published, on May 15, 1984, an Advance Notice of Proposed Rulemaking (ANPR) (49 FR 20524) to announce the initiation of a regulatory action by the EPA to determine and implement the most effective means of controlling exposures to the chemical BD under the TSCA. EPA was working with OSHA because available evidence indicated that exposure to BD occurs primarily within the workplace.

Information received in response to this ANPR was used by EPA to develop risk assessments. Subsequently, EPA identified BD as a probable human carcinogen (Group B2) according to EPA's classification of carcinogens, and concluded that current exposures during the manufacturing of BD and its processing into polymers presented an unreasonable risk of injury to human health. (Ex. 17–4) Additionally, EPA determined that the risks associated with exposure to BD may be reduced to a sufficient extent by action taken under the OSH Act. Following these findings, EPA, in accordance with section 9(a) of TSCA, on October 10, 1985 (50 FR 41393), referred BD to OSHA to give this Agency an opportunity to regulate the chemical under the OSH Act. EPA requested that OSHA determine whether the risks described in the EPA report may be prevented or reduced to a sufficient extent by action taken under the OSH Act and then if such a determination is made, OSHA issue an order declaring whether the manufacture and use of BD described in the EPA report present the risk therein described. EPA asked OSHA to respond within 180 days, by April 8, 1986. (50 FR 41393)

On December 27, 1985, OSHA published a notice soliciting public comments on EPA's referral report. (50 FR 52952) Based on all the available information, OSHA, on April 11, 1986, responded to the EPA referral report by making a preliminary determination (50 FR 12526) that a revised OSHA standard limiting occupational exposure to BD could prevent or reduce the risk of exposure to a sufficient extent and that such risks had been accurately described by EPA in the report. On October 1, 1986, OSHA published an ANPR (51 FR 35003) to initiate a rulemaking within the meaning of section 9(a) of TSCA. The Agency requested that comments be submitted by December 30, 1986. Twenty-four comments, some of them containing new information, were received in response to the ANPR. (Ex. 28–1 to 28–24) Six additional comments were received after the deadline. (Ex. 29–1 to 29–6)

OSHA reviewed the available data and conducted risk assessment, regulatory impact and flexibility analyses. These analyses demonstrate that the proposed standard was technologically and economically feasible and substantially reduced the significant risk of cancers and other adverse health effects.

On August 10, 1990, OSHA published its proposed rule to regulate occupational exposure to 1,3-butadiene. (55 FR 32736) Based on the Agency's review of studies of exposed animals and epidemiologic studies and taking into account technologic and economic feasibility considerations, OSHA proposed a permissible exposure limit (PEL) of 2 ppm as an 8-hour time-weighted average and a short term exposure limit (STEL) of 10 ppm for a 15 minute sampling period. Also included in the proposal was an ''action level'' of 1 ppm which triggered certain provisions of the standard such as medical surveillance and training.

OSHA convened public hearings in Washington, DC., on January 15–23, 1991, and in New Orleans, Louisiana, on February 20–21, 1991. The post-hearing period for the submission of briefs, arguments and summations was to end July 22, 1991, but was extended by the Administrative Law Judge to December 13, 1991, in order to give participants time to review new data on low-dose exposures submitted by NTP and a quantitative risk assessment done by NIOSH. The comment period closed February 10, 1992.

In the Fall of 1992, the International Agency for Research on Cancer (IARC) published the results of the Working Group on the Evaluation of Carcinogenic Risks to Humans, which reviewed the carcinogenic potential of BD and concluded that:

> There is limited evidence for the carcinogenicity in humans of 1,3-butadiene * * * There is sufficient evidence for the carcinogenicity in experimental animals * * * (Ex. 125)

IARC stated that its overall evaluation led it to conclude that ''1,3-butadiene is probably carcinogenic to humans (Group 2A).'' (Ex. 125)

To assist OSHA in issuing a final rule for BD, representatives of the major unions and industry groups involved in the production and use of BD submitted the outline of a voluntary agreement reached by the parties dated January 29, 1996, outlining provisions that they agreed upon and recommended be included in the final rule. The letter transmitting the agreement was signed by J.L. McGraw for the International Institute of Synthetic Rubber Producers (IISRP), Michael J. Wright for the United Steelworkers of America (USWA), and Michael Sprinker (CWU). The committee that worked on the issues also included Joseph Holtshouser of the Goodyear Tire and Rubber Company, Carolyn Phillips of the Shell Chemical Company, representing the Chemical Manufacturers Association, Robert Richmond of the Firestone Synthetic Rubber and Latex Company, and Louis Beliczky (formerly of the URW) and James L. Frederick of the SWA.

The agreement proposed a change in the permissible exposure limits, additional provisions for exposure monitoring, and an exposure goal program designed to reduce exposures below the action level. It also set forth other modifications to the scope, respiratory protection, communication of hazards, medical surveillance, and start-up dates sections of the final rule.

On March 8, 1996 OSHA published the labor/industry joint recommendations and re-opened the record for 30 days to allow the public to comment. (61 FR 9381) In response to requests from the parties to the agreement, the comment period was extended to April 26, 1996. (61 FR 15205)

At the beginning of the comment period, OSHA placed in the rulemaking record an epidemiologic study of BD exposed workers by Delzell, et al. sponsored by IISRP, along with IARC volume 127 ''Butadiene and Styrene Assessment of Health Hazards,'' a published paper by Santos-Burgoa, et al. entitled ''Lymphohematopoietic Cancer in Styrene-Butadiene Polymerization Workers,'' and abstracts from a symposium entitled ''Evaluation of Butadiene and Isoprene Health Risks.'' (Ex. 117–1; 117–2; 117–3; 117–4) The epidemiological study had also been submitted to the EPA in compliance with provisions of the Toxic Substances Control Act.

In response to the re-opening of the BD record, 18 sets of comments were received. The parties to the labor/industry agreement submitted a draft regulatory text which put their recommendations into specific requirements. The outline and the

subsequent draft regulatory text are solely the work product of the negotiating committee. OSHA was neither a party to nor present at the negotiations.

While the responses to the record re-opening helped clarify the intent of the negotiating parties, the rationales behind several of the changes were not fully explained.

On September 16, 1996, Judge John M. Vittone, for Judge George C. Pierce who presided over the BD hearings, closed the record of the public hearing on the proposed standard for 1,3-butadiene and certified it to the Assistant Secretary of Labor. (Ex. 135)

IV. Chemical Identification, Production and Use

A. Monomer

The chemical 1,3-butadiene (BD) (Chemical Abstracts Registry Number 106–99–0) is a colorless, noncorrosive, flammable gas with a mild aromatic odor at standard ambient temperature and pressure. It has a chemical formula of C_4H_6, a molecular weight of 54.1, and a boiling point of −4.7 °C at 760 mm Hg, a lower explosive limit of 2%, and an upper explosive limit of 11.5%. Its vapor density is almost twice that of air. It is slightly soluble in water, somewhat soluble in methanol and ethanol, and readily soluble in less polar organic solvents such as hexane, benzene, and toluene. (Ex. 17–17) It is highly reactive, dimerizes to 4-vinylcyclohexene, and polymerizes easily. Because of its low odor threshold, high flammability and explosiveness, BD has been handled with extreme care in the industry.

In the United States BD has been produced commercially by three processes: Catalytic dehydrogenation of n-butane and n-butene, oxidative dehydrogenation of n-butene, and recovery as a by-product from the C_4 co-product stream from the steam cracking process used to manufacture ethylene, which is the major product of the petrochemical industry. For economic reasons, almost all BD currently made in the U.S. is produced by the ethylene co-product process.

In the steam cracking process for ethylene, a hydrocarbon feedstock is diluted with steam then heated rapidly to a high temperature by passing it through tubes in a furnace. The output stream, containing a broad mixture of hydrocarbons from the pyrolysis reactions in the cracking tubes plus unreacted components of feedstock, is cooled and then processed through a series of distillation and other separation operations in which the various products of the cracking operation are separated for disposal, recycling or recovery.

The cracking process produces between 0.02 to 0.3 pounds of BD per pound of ethylene, depending upon the composition of the feedstock. BD is recovered from the C_4 stream by the separation operations. The C_4 stream contains from 30 to 50% BD plus butane, butenes and small fractions of other hydrocarbons. This crude BD stream from the ethylene unit may be refined in a unit on site, or transferred to another location, a monomer plant, owned by the same or a different company, to produce purified BD.

Regardless of the source of the crude BD-ethylene co-product, (dehydrogenation, or blending of C_4 streams from other sources), the processes used by different companies to refine BD for subsequent use in polymer production are similar. Extractive distillation is used to effect the basic separation of BD from butanes and butenes and fractional distillation operations are used to accomplish other related separations. A typical monomer plant process is described below.

C_3 and C_4 acetylene derivatives, present in the C_4 co-product stream, are converted to olefins by passing the stream through a hydrogenation reactor. The stream is then fed to an extractive distillation column to separate the BD from butanes and butenes. Several different solvents have been employed for this operation, including n-methylpyrrolidone, dimethylformamide, furfural, acetonitrile, dimethylacetamide, and cuprous ammonium acetate solution. The BD, extracted by the solvent, is stripped from it in the solvent recovery column, then fed to another fractionation column, the methylacetylene column, to have residual acetylene stripped out. The bottom stream from the methylacetylene column, containing the BD, is fed to the BD rerun column, from which the purified BD product is taken off overhead. The solvent, recovered in the solvent recovery column, is recycled to the extractive distillation column with part of it distilled to keep down the level of polymer. (Ex. 17–17)

A stabilizer is added to the monomer to inhibit formation of polymer during storage. It is stored as a liquid under pressure, sometimes refrigerated to reduce the pressure, generally stored in a tank farm in diked spheres. It is shipped to polymer manufacturers and other users by pipeline, barge, tank car, or tank truck.

BD is a major commodity product of the petrochemical industry. Total U.S. production of BD in 1991 was 3.0 billion pounds. Although BD is a toxic flammable gas, its simple chemical structure with low molecular weight and high chemical reactivity make it a useful building block for synthesizing other products. In ''1,3-Butadiene Use and Substitutes Analysis,'' EPA identified 140 major, minor and potential uses of BD in the chemical industry. (Ex. 17–15)

Over 60% of the BD consumed in the United States is used in the manufacture of rubber, about 12% in making adiponitrile which in turn is used to make hexamethylenediamine (HMDA), a component of Nylon, approximately 8% in making styrene-butadiene copolymer latexes, approximately 7% in producing polychloroprene, and about 6% in producing acrylonitrile-butadiene-styrene (ABS) resins. Lesser amounts are consumed in the production of rocket propellants, specialty copolymer resins and latexes for paint, coatings and adhesive applications, and hydrogenated butadiene-styrene polymers used as lubricating oil additives. Some nonpolymer applications include the manufacture of the agricultural fungicides, Captan and Captofol, the industrial solvent sulfolane, and anthroquinone dyes.

B. Polymers

BD based synthetic elastomers are manufactured by polymerizing BD by itself, by polymerizing BD with other monomers to produce copolymers, and by producing mixtures of these polymers. The largest-volume product is the copolymer of styrene and BD, styrene-butadiene rubber, followed in volume by polybutadiene, polychloroprene, and nitrile rubber. Polybutadiene is the polymer of BD monomer by itself. Polychloroprene is made by polymerizing chloroprene, produced by chlorination of BD. Nitrile rubbers are copolymers of acrylonitrile and BD.

Four general types of processes are used in polymerizing BD and its copolymers: emulsion, suspension, solution and bulk polymerization. In emulsion and suspension polymerization, the monomers and the many chemicals used to control the reaction are finely dispersed or dissolved in water. In solution polymerization, the monomers are dissolved in an organic solvent such as hexane, pentane, toluene. In bulk polymerization, the monomer itself serves as solvent for the polymer. The polymer product, from which end-use products are manufactured, is produced in the form of polymer crumb (solid particles), latex (a milky suspension in water), or cement (a solution).

Emulsion polymerization is the principal process used to make synthetic rubber. A process for the manufacture of styrene-butadiene crumb is typical of emulsion processes. Styrene and BD are piped to the process area from the storage area. The BD is passed through a caustic soda scrubber to remove the inhibitors which were added to prevent premature polymerization. The fresh BD monomer streams are mixed with styrene, aqueous emulsifying agents, activator, catalyst, and modifier, and then fed to the first of a train of reactors. The reaction proceeds stepwise in the series of reactors to around 60% conversion of monomer to polymer. In the cold process, the reactants are chilled and the reactor temperature is maintained at 4°C to 7°C (40°F to 45°F) and pressure at 0 to 15 psig; in the hot rubber process, temperature and pressure are around 50°C (122°F) and 40 to 60 psig, respectively.

The latex from the reactor train is flashed to evaporate unreacted BD which is compressed, condensed and recycled. Uncondensed vapors are absorbed in a kerosene absorber before venting and the absorbed BD is steam stripped or recovered from the kerosene by some other operation. The latex stream is passed through a steam stripper, operated under vacuum, to remove and recover unreacted styrene. The styrene and water in the condensate are separated by decanting. The styrene phase is recycled to the process. Noncondensibles from the stripping column contain some BD and are directed through the BD recovery operations.

Stripped latex, to which an antioxidant has been added, is pumped to coagulation vessels where dilute sulfuric acid and sodium chloride solution are added. The acid and brine mixture breaks the emulsion, releasing the polymer in the form of crumb. Sometimes carbon black and oil are added during the coagulation step since better dispersion is obtained than by mixing later on.

The crumb and water slurry from the coagulation operation is screened to separate the crumb. The wet crumb is pressed in rotary presses to squeeze out most of the entrained water then dried with hot air on continuous dry belt dryers. The dried product is baled and weighed for shipment.

Production of styrene-butadiene latex by the emulsion polymerization process is similar to that for crumb but is usually carried out on a smaller scale with fewer reactors. For some but not all products, the reaction is run to near completion, monomer removal is simpler and recovery may not be practiced.

Polybutadiene rubber is usually produced by solution polymerization. Inhibitor is removed from the monomer by caustic scrubbing. Both monomer and solvent are dried by fractional distillation, mixed in the desired ratio and dried in a desiccant column. Polymerization is conducted in a series of reactors using initiators and catalysts and is terminated with a shortstop solution. The solution, called rubber cement, is pumped to storage tanks for blending. Crumb is precipitated by pumping the solution into hot water under violent agitation. Solvent and monomer are recovered by stripping and distillation similar to those previously described. The crumb is screened, dewatered, dried and baled.

Polychloroprene (neoprene) elastomers are manufactured by polymerizing chloroprene in an emulsion polymerization process similar to that used for making styrene-butadiene rubber. The monomer, chloroprene (2-chloro-BD), is made by chlorination of BD to make 3,4-dichlorobutene, and dehydrochlorination of the latter.

Nitrile rubbers, copolymers of acrylonitrile and BD, are produced by emulsion polymerization similar to that used to make styrene-butadiene rubber.

Substantial amounts of BD are used in the production of two other large volume polymers: Nylon resins and ABS resin. Dupont manufactures adiponitrile from BD and uses the product to make hexamethylenediamine which is polymerized in making Nylon resins and fibers, including Nylon 6,6. Acrylonitrile, BD and styrene are the monomers used to make ABS resin which is a major thermoplastic resin. Chemically complex emulsion, suspension and bulk polymerization processes are used by different producers to make ABS polymer.

V. Health Effects

A. Introduction

The toxicity of BD was long considered to be low and non-cumulative. Thus, the OSHA standard for BD was 1,000 ppm on the basis of its irritation of mucous membranes and narcosis at high levels of exposure. However, in the 1980s, carcinogenicity studies indicated BD is clearly a carcinogen in rodents. In 1986, the American Conference of Governmental Industrial Hygienists (ACGIH) was prompted by these studies to lower the workplace threshold limit value (TLV) from 1,000 to 10 ppm. (Ex. 2–5)

Rodent studies are now conclusive that BD is an animal carcinogen. Further, a consistent body of epidemiologic studies have also shown increased mortality from hematopoietic cancers associated with BD exposure among BD-exposed production and styrene/BD rubber polymer workers. Complementary studies of metabolic products and genotoxicity support these cancer findings. OSHA was also concerned about evidence that BD affects the germ cell as well as the somatic cell, and what potential reproductive toxicity might result from exposure to BD. Since BD itself does not appear to be carcinogenic, but must be metabolized to an active form, OSHA also reviewed studies on the metabolism of BD to determine wether they might help explain the observed differences in cancer incidence among species.

The following sections discuss the effects of BD exposure, both in human and animal systems.

B. Carcinogenicity

1. Animal Studies

In the proposed BD rule, OSHA discussed the results of two lifetime animal bioassays, one on the Sprague-Dawley rat and one in the B6C3F$_1$ mouse. (55 FR 32736 at 32740) Both studies found evidence of BD carcinogenicity, with the greater response in the mouse. The rat study involved exposure levels of 0, 1000, or 8000 ppm BD, starting at five weeks of age, to groups of 100 male and 100 female Sprague-Dawley rats for 6 hours per day, five days per week, for 105 weeks. Mortality was increased over controls in the 1,000 ppm exposed female rats and in both of the male rat exposure groups. Significant tumor response sites in the male rats included exocrine adenomas and carcinomas (combined) of the pancreas in the highest exposure group (3, 1, and 11 tumors in the 0, 1000, and 8000 ppm groups, respectively); and Leydig-cell tumors of the testis (0, 3, and 8 in the same groups, respectively). In the female rats, the significantly increased tumor response also occurred in the highest exposure group; cancers seen included follicular-cell adenomas and carcinomas (combined) of the thyroid gland (0,4, and 11 tumors in the three exposure groups, respectively), and benign and malignant (combined) mammary gland tumors (50, 79, and 81 in the same exposure groups). To a lesser degree there were also sarcomas of the uterus (1, 4, 5 tumors in the three exposure groups), and Zymbal gland (0, 0, 4 tumors in the same exposure groups, respectively). While only high

exposure group tumor response for some of these sites was statistically significant, trend tests were also significant.

In contrast to the generally less than 10% increase in tumor response seen in the Sprague-Dawley rat at levels far above BD metabolic saturation, the carcinogenic response to BD in the $B6C3F_1$ mouse in the National Toxicology Program study (NTP I) was extensive. (Ex. 23–1) In this study, groups of 50 male and 50 female mice were exposed via inhalation to 0, 625 or 1250 ppm BD for 6 hours per day, 5 days per week in a study originally designed to last 2 years. However, the high carcinogenic response included multiple primary cancers, with short latent periods, and led to early study termination (60–61 weeks) due to high cancer mortality in both the 625 ppm and 1250 ppm exposure groups of both sexes. This mortality was due mainly to lymphocytic lymphomas and hemangiosarcomas of the heart, both of which were typically early occurring and quickly fatal. This large and rapidly fatal carcinogenic response led to both the NTP and industry to undertake additional studies to better understand the mechanisms involved.

Some commenters have associated qualitative or quantitative differences in mouse and rat BD carcinogenicity with the differences in rat and mouse BD metabolism. Many studies published and submitted to the BD record since the proposed rule have sought to better characterize the metabolic, distributional, and elimination processes involved, and some have attributed species differences (at least in part) to the metabolic differences. These will be addressed separately in the metabolism section.

Another factor hypothesized to account for differences between mouse and rat BD carcinogenicity was the role of activation of ecotropic retrovirus in hematopoietic tissues on tumor response in the $B6C3F_1$ mouse. This virus is endogenous to the $B6C3F_1$ mouse and was hypothesized to potentiate the BD lymphoma response in this strain. To study this hypothesis Irons and co-workers exposed both (60) $B6C3F_1$ male (those with the endogenous virus) and (60) NIH Swiss male (those without the endogenous virus) mice to either 0 or 1250 ppm BD, for 6 hours./day, 5 days per week for 52 weeks. (Ex. 32–28D) A third group of 50 $B6C3F_1$ male mice received 1250 ppm for 12 weeks only and was observed until study termination at 52 weeks. The results of the study showed significantly increased thymic lymphomas in all exposed groups but significantly greater response in the $B6C3F_1$ mouse—1 tumor/60 (2%) in the control (zero exposure) group, 10/48 (21%) in the 12 week exposure group, and 34/60 (57%) in the 52 week exposure group—vs. the NIH Swiss mice, which developed 0 tumors/60 in the control group, and 8 tumors/57 (14%) in the BD exposed group. Hemangiosarcomas of the heart were also observed in both strains exposed to BD for 52 weeks—5/60 (8%) in the $B6C3F_1$ mice vs. 1/57 in the NIH Swiss mice. (Ex. 32–28D). The $B6C3F_1$ response was very similar to the NTP I high exposure group response, verifying that earlier study. The qualitatively similar lymphoma responses of the two strains also confirmed that the mouse hematopoietic system is highly susceptible to the carcinogenic effects of BD, although quantitatively the strains may differ. The 21% 1-year lymphoma response in the 12-week stop-exposure $B6C3F_1$ group also increased concerns about high concentration, short duration exposures.

NTP II Study

Concurrent with the industry studies, the NTP, in order to better characterize the dose-response and lifetime experience, conducted a second, much larger research effort over a much broader dose range. (Ex. 90; 96) These toxicology and carcinogenesis studies included a 100-fold lower (6.25 ppm) low exposure group than NTP I, several intermediate exposure groups, a study of dose-rate effects using several high-concentration partial lifetime (stop-) exposure groups, and planned interim sacrifice groups. Other parts of the study included clinical pathology studies (with the 9- and 15-month interim sacrifices, metabolism studies, and examination of tumor bearing animals for activated oncogenes).

For the lifetime carcinogenesis studies, groups of 70 $B6C3F_1$ mice of each sex were exposed via inhalation to BD at levels of 0, 6.25, 20, 62.5, 200, or 625 ppm (90 of each sex in this highest group) for 6 hours per day, 5 days per week for up to 2 years. Up to 10 randomly selected animals in each group were sacrificed after 9 and 15 months of exposure, and these animals were assessed for both carcinogenicity and hematologic effects.

For the stop-exposure study, different groups of 50 male mice were exposed 6 hours per day, 5 days per week to concentrations of either 200 ppm for 40 weeks, 625 ppm for 13 weeks, 312 ppm for 52 weeks, or 625 ppm for 26 weeks. Following the BD exposure period, the exposed animals were then observed for the remainder of the 2-year study. The first two stop-exposure groups received a total exposure (concentration times duration) of 8,000 ppm-weeks, while the latter two groups received approximately 16,000 ppm-weeks of exposure. For the analysis discussed below, groups are compared both with each other for dose-rate effects and with the lifetime (2 year) exposure groups for recovery effects.

Methodology

Male mice were 6–8 weeks old and female mice were 7–8 weeks old when the exposures began. Animals were exposed in individual wire mesh cage units in stainless steel Hazelton 2000 chambers (2.3 m^3). The exposure phase extended from January, 1986 to January, 1988. Animals were housed individually; water was available *ad libitum;* NIH–07 diet feed was also available *ad libitum* except during exposure periods. Animals were observed twice daily for moribundity and mortality; animals were weighed weekly for the first 13 weeks and monthly thereafter. Hematology included red blood cell count (RBC), and white blood cell count (WBC). The study was conducted in compliance with the Food and Drug Administration (FDA) Good Laboratory Practice Regulations with retrospective quality assurance audits.

The results of the study are presented below for the two-year and stop-exposure study. Between study group comparisons are made where it is deemed appropriate. Emphasis is placed on the neoplastic effects.

Results

Two-Year Study

While body weight gains in both exposed male and female mice were similar to those of the control groups, exposure related malignant neoplasms were responsible for decreased survival in all exposure groups of both sexes exposed to concentrations of 20 ppm or above. Excluding the interim sacrificed animals, the two-year survival decreased uniformly with increasing exposure for females (37/50, 33/50, 24/50, 11/50, 0/50, 0/70), and nearly uniformly for males (35/50, 39/50, 24/50, 22/50, 4/50, 0/70). As with the earlier NTP study, all animals in the 625 ppm group were dead by week 65, mostly as a result of lymphomas or hemangiosarcomas of the heart. The 200 ppm exposure groups of both sexes also had much higher mortality, but significantly less than that of the 625 ppm group. The survival of the lowest exposure group (6.25 ppm) was slightly better than controls for the male mice, slightly less for the female mice. Mean

survival for the males was an exposure-related 597, 611, 575, 558, 502, and 280 days; for the females it was similarly 608, 597, 573, 548, 441, and 320 days. This decreased survival with increasing exposure was almost totally due to tumor lethality.

Carcinogenicity

Nine different sites showed primary tumor types associated with butadiene exposures, seven in the male mice and eight in the female mice. These were lymphoma, hemangiosarcoma of the heart, combined alveolar-bronchiolar adenoma and carcinoma, combined forestomach papilloma and carcinoma, Harderian gland adenoma and adenocarcinoma, preputial gland adenoma and carcinoma (males only), hepatocellular adenoma and carcinoma, and mammary and ovarian tumors (females only). These are shown in Table V–1 adapted from Melnick et al. (Ex. 125) From this table it is seen that six of these tumor sites are statistically significantly increased in the highest exposed males and five were statistically significantly increased in the highest exposed females. Two additional sites which showed significant increases at lower exposures showed decline at the highest exposures because other tumors were more rapidly fatal. At 200 ppm preputial gland adenoma and carcinoma combined were significantly increased in males ($p<.05$; 0/70 (0%) control vs. 5/70 (7%) in the 200 ppm group) and hepatocellular adenoma and carcinoma were increased for both exposed males and females. At the lowest exposure concentration, 6.25 ppm, only female mouse lung tumors (combined adenoma and carcinoma) showed statistical significance ($p<.05$; 4/70 (6%) in controls vs. 15/70 (21%) in the 6.25 ppm group); these tumors in female mice showed a monotonic increase with increasing exposure up to 200 ppm. At 20 ppm female mouse lymphomas and liver tumors also reached statistical significance (lymphomas, $p<.05$; 10/70 (15%) in controls vs. 18/70 (26%) in the 20 ppm group; liver tumors, $p<.05$; 17/70 (24%) in controls vs. 23/70 (33%) in the 20 ppm group), and at 62.5 ppm, tumors at several other sites were also significantly increased. In general, while there were some differences in amount of tumor response between the male and female mice, there is fairly consistent pattern of tumor type in mice of both sexes for the six non-sexual organ sites.

TABLE V–1.—TUMOR INCIDENCES (I) AND PERCENTAGE MORTALITY-ADJUSTED TUMOR RATES (R) IN MICE EXPOSED TO 1,3-BUTADIENE FOR UP TO 2 YEARS.

[Adapted from Ex. 125]

Tumor	Sex	Exposure concentration (ppm)											
		0		6.25		20		62.5		200		625	
		I	R[c]	I	R	I	R	I	R	I	R	I	R
Lymphoma	M	4/70	8	3/70	6	8/70	19	11/70	[a]25	9/70	[a]27	69/90	[a]97
	F	10/70	20	14/70	30	[a]18/70	41	10/70	26	19/70	[a]58	43/90	[a]89
Heart—Hemangiosarcoma	M	0/70	0	0/70	0	1/70	2	5/70	[a]13	20/70	[a]57	6/90	[a]53
	F	0/70	0	0/70	0	0/70	0	1/70	3	20/70	[a]64	26/90	84
Lung—Alveolar-bronchiolar adenoma and carcinoma.	M	22/70	46	23/70	48	20/70	45	33/70	[a]72	42/70	[a]87	12/90	[a]73
Forestomach—Papilloma and carcinoma	F	4/70	8	15/70	[a]32	19/70	[a]44	27/70	[a]61	32/70	[a]81	25/90	[a]83
Harderian gland—Adenoma and adenocarcinoma	M	1/70	2	0/70	0	1/70	2	5/70	13	12/70	[a]36	13/90	[a]75
	F	2/70	4	2/70	4	3/70	8	4/70	12	7/70	[a]31	28/90	[a]85
Preputial gland—Adenoma and carcinoma	M	6/70	13	7/70	15	11/70	25	24/70	[a]53	33/70	[a]77	7/90	[a]58
	F	9/70	18	10/70	21	7/70	17	16/70	[a]40	22/70	[a]67	7/90	48
Liver—Hepatocellular adenoma and carcinoma	M	0/70	0	0/70	0	0/70	0	0/70	0	5/70	[a]17	0/90	0
Mammary gland—Adenocarcinoma	M	31/70	55	27/70	54	35/70	68	32/70	69	40/70	[a]87	12/90	75
Ovary—Benign and malignant granulosa-cell tumors.	F	17/70	35	20/70	41	23/70	[a]52	24/70	[a]60	20/70	[a]68	3/90	28
	F	0/70	0	2/70	4	2/70	5	6/70	[a]16	13/70	[a]47	13/90	[a]66
	F	1/70	2	0/70	0	0/70	0	9/70	[a]24	11/70	[a]44	6/90	44

[a] Increased compared with chamber controls (0 ppm), $p < 0.05$, based on logistic regression analysis.
[b] The Working Group noted that the incidence in control males and females was in the range of that in historical controls (Haseman et al., 1985).
[c] Mortality adjusted tumor rates are adjusted for competing causes of mortality, such as death due to other tumors, whose rates differ by exposure group.

Hemangiosarcoma of the heart, with metastases to other organs was first observed at 20 ppm in 1 male (the historical controls for this strain are 1/2373 in males and 1/2443 in females), in 5 males and 1 female at 62.5 ppm and in 20 males and 20 females at 200 ppm; at 625 ppm these tumor rates leveled off as other tumors, especially lymphomas became dominant. Lymphatic lymphomas increased to statistical significance first in females at 20 ppm and were usually rapidly fatal, the first tumor appearing at week 23, most likely preempting some of the later appearing tumors in the higher exposure groups. Because of the plethora of primary tumors and the different time patterns observed to onset of each type, several tumor dose-response trends do not appear as strong as they would otherwise be.

Non-Neoplastic Effects

Several non-cancer toxic effects were noted in the exposed groups, reflecting many of the same target sites for which the neoplastic effects were seen. (Ex. 90; 96; 125).

Although the reported numbers differ slightly in the different exhibits, generally dose-related increases in hyperplasia were observed in the heart, lung, forestomach, and Harderian gland, both in the two-year study (both sexes) and in the stop-exposure study (conducted in males only). In addition, testicular atrophy was observed in both the two-year and stop-exposure male mice, but remained in the 6%–10% range except for the 2-year, 625 ppm

group where it was 74%. Ovarian germinal hyperplasia (2/49 (control), 3/49 (6.25 ppm), 8/48 (20 ppm), 15/50 (62.5 ppm), 15/50 (200 ppm), 18/79 (625 ppm), ovarian atrophy (4/49, 19/49, 32/48, 42/50, 43/50, 69/79), and uterine atrophy (1/50, 0/49, 1/50, 1/49, 8/50, 41/78) were also dose related, with ovarian atrophy significantly increased at the lowest BD exposure of 6.25 ppm. These toxic effects to the reproductive organs are discussed in greater detail in the reproductive effects section of this preamble. Bone marrow atrophy was noted only in the highest exposure groups, occurring in 23/73 male mice and 11/79 female mice.

Stop-Exposure Study

As with the 2-year study, the body weights of the four treated groups in the stop-exposure study were similar to controls. All exposure groups exhibited markedly lower survival than controls, and only slightly better survival than that of the comparable full lifetime exposure groups. Mortality appeared to be more related to total dose than to exposure concentration. Most deaths were caused by tumors.

Neoplastic Effects

All of these stop-exposure groups exhibited a very similar tumor profile to that of the lifetime high exposure groups, with the lone exception of liver tumors, which were increased only in the lifetime exposure group; all the other multiple primary tumors were observed at significantly increased levels in both the stop- and lifetime-exposure groups, Table V–2. (Ex. 125) In addition, the 625 ppm, 26 week exposure group had higher rates for several of the tumor types compared to the lifetime 625 ppm group, possibly because of the shorter exposure group's slightly better survival. The most prevalent tumor type, lymphoma, also showed a dose-rate effect, as the tumor incidence was greater for exposure to short-term higher concentrations compared with a lower long-term exposure (p=.01; 24/50 at 625 ppm for 13 weeks vs. 12/50 at 200 ppm for 40 weeks: p<.0001; 37/50 at 625 ppm for 26 weeks vs. 15/50 at 312 ppm for 52 weeks). The same pattern was seen with forestomach tumors and preputial gland carcinomas. Conversely, the hemangiosarcomas of the heart and alveolar-bronchiolar tumors showed an opposite trend, as lower exposures for a longer time yielded a significantly higher incidence of these tumors than the same cumulative exposures over a shorter time (survival-adjusted, as opposed to the raw incidence lung tumor rates actually suggest no dose-response trends). These inconsistent trends with the different tumor sites may be the result of multiple mechanisms of carcinogenicity or partially due to the rapid fatality caused by lymphocytic lymphomas in the short-term high-exposure groups. As with the lifetime study, angiosarcomas of the heart and lymphomas presented competing risks in the highly exposed mice.

TABLE V–2.—TUMOR INCIDENCES (I) AND PERCENTAGE MORTALITY-ADJUSTED TUMOR RATES (R) IN MALE MICE EXPOSED TO 1,3-BUTADIENE IN STOP-EXPOSURE STUDIES. (AFTER EXPOSURES WERE TERMINATED, ANIMALS WERE PLACED IN CONTROL CHAMBERS UNTIL THE END OF THE STUDY AT 104 WEEKS.)

[Adapted from Ex. 125]

Tumor	Exposure									
	0		200 ppm, 40 wk		625 ppm, 13 wk		312 ppm, 52 wk		625 ppm, 26 wk	
	I	R[c]	I	R	I	R	I	R	I	R
Lymphoma	4/70	8	12/50	[a]35	24/50	[a]61	15/50	[a]55	37/50	[a]90
Heart—Hemang-iosarcoma	0/70	0	7/50	[a]47	7/50	[a]31	33/50	[a]87	13/50	[a]76
Lung—Alveolar-bronchiolar adenoma and carcinoma	22/70	46	35/50	[a]88	27/50	[a]87	32/50	[a]88	18/50	[a]89
Forestomach—Squamous-cell papilloma and carcinoma	1/70	2	6/50	[a]20	8/50	[a]33	13/50	[a]52	11/50	[a]63
Harderian gland—Adenoma and adenocarcinoma	6/70	13	27/50	[a]72	23/50	[a]82	28/50	[a]86	11/50	[a]70
Preputial gland—Carcinoma	0/70	0	1/50	3	5/50	[a]21	4/50	[a]21	3/50	[a]31
Kidney—Renal tubular adenoma	0/70	0	5/50	[a]16	1/50	5	3/50	[a]15	1/50	11

From Melnick et al (1990).

AA[a]Increased compared with chamber controls (0ppm), p<0.05, based on logistic regression analysis.

[c]Mortality adjusted tumor rates are adjusted for competing causes of mortality, such as death due to other tumors, whose rates differ by exposure group.

Activated Oncogenes

The presence of activated oncogenes in the exposed groups which differ from those seen in tumors in the control group can help in identifying a mechanistic link for BD carcinogenicity. Furthermore, certain activated oncogenes are seen in specific human tumors and K-*ras* is the most commonly detected oncogene in humans. In independent studies, tumors from this study were evaluated for the presence of activated protooncogenes. (Ex. 129) Activated K-*ras* oncogenes were found in 6 of 9 lung adenocarcinomas, 3 of 12 hepatocellular cancers and 2 of 11 lymphomas in BD exposed mice. Nine of these 11 K-*ras* mutations, including all six of those seen in lung tumors, were G to C conversions in codon 13. Activation of K-*ras* genes by codon 13 mutations has not been detected in lung or liver tumors or lymphomas in unexposed $B6C3F_1$ mice, but activation by codon 12 mutation was observed in 1 of 10 lung tumors in unexposed mice. (Ex. 129)

Conclusion

All of the four animal bioassays (one rat, three mouse) find a clear carcinogenic response; together they provide sufficient evidence to declare BD a known animal carcinogen and a probable human carcinogen. The three mouse studies, all with a positive lymphoma response, further support a finding that the mouse is a good model for BD related lymphatic/hematopoietic and other site tumorigenicity. The most recent NTP II study confirms and strengthens the previous NTP I and Irons et al. mouse studies, and presents clear evidence that BD is a potent multisite carcinogen in $B6C3F_1$ mice of both sexes. (Ex. 23–1;32–28D, Irons) The finding of lung tumors at exposures as low as 6.25 ppm, 100 fold lower than the lowest exposure of the NTP I study and a level that is in the occupational exposure range, increases concern for workers' health. Two other concerns

raised by both the second NTP and the Irons et al. studies are, (1) substantial carcinogenicity is found with less-than-lifetime exposures (as low as 12 or 13 weeks) for lymphomas and hemangiosarcomas, at least at higher concentrations, and, (2) for lymphomas and at least two other sites, there appears to be a dose-rate effect, where exposure to higher concentrations for a shorter time yields higher tumor response (by a factor of as much as 2–3) than a comparable total exposure spread over a longer time. These findings suggest that even short-term exposures should be as low as possible. Positive studies for genotoxicity and the detection of activated K-*ras* oncogenes in several of these tumors induced in mice, including lymphomas, liver, and lung, suggest a mutagenic mechanism for carcinogenicity, and support reliance on a linear low-dose extrapolation procedure (on the basis of the multistage mutagenesis theory of carcinogenicity), at least for these tumor sites. The finding of activated K-*ras* oncogenes in these mouse tumors may also be relevant to humans, because K-*ras* is the most commonly detected oncogene in humans.

The different dose-rate trends for different tumor sites suggest that different mechanisms are involved at different sites. The observation of a highly nonlinear exposure-response for lymphomas at exposure levels of 625 ppm and above suggests a secondary high-exposure mechanism as well, not merely a metabolic saturation, as is suspected with the high-exposure saturation seen in Sprague-Dawley rats. (Ex. 34–6, Owen and Glaister) The picture emerges of BD as a potent genotoxic multisite carcinogen in mice, far more potent in mice than in rats.

With respect to appropriate tumor sites for risk extrapolation from mouse to humans, Melnick and Huff have presented information comparing animal tumor response for five known or suspected human carcinogens—BD, benzene, ethylene oxide, vinyl chloride, and acrylonitrile. (Ex. 117–2) BD, benzene, and ethylene oxide all have strong occupational epidemiology evidence of increased lymphatic/hematopoietic cancer (LHC) mortality and all three cause both LHC, lung, Harderian gland, and mammary gland tumors in mice, plus several other primary tumors (see Table V–3). Only BD and vinyl chloride cause mouse hemangiosarcomas, BD in the heart and vinyl chloride in the liver. In rats, while all five carcinogens cause tumors at multiple sites, only brain and Zymbal gland tumors are associated with as many as four of the compounds. In general mice and rats are affected at different tumor sites by these carcinogens. LHC, lung, Harderian gland, mammary gland and, possibly hemangiosarcomas are sites in mice which correlate well with human LHC. This suggests that mice, rats and humans may have different target sites for the same carcinogen, but that compounds which are multisite carcinogens in the mouse and rat are likely to be human carcinogens as well. Based on BD's strong LHC association in humans, and its multisite carcinogenicity in the mouse, including occurrence at several of the same target sites seen with other carcinogens, OSHA concludes that the mouse is a good animal model for predicting BD carcinogenesis in humans.

TABLE V–3.—SITES AT WHICH NEOPLASMS ARE CAUSED BY 1,3-BUTADIENE IN MICE AND RATS: COMPARISON WITH RESULTS OF STUDIES WITH BENZENE, ETHYLENE OXIDE, VINYL CHLORIDE AND ACRYLONITRILE

[From Ex. 117–2]

Site	1,3–Butadiene		Benzene		Ethylene oxide		Vinyl chloride		Acrylonitrile	
	Mice	Rats	Mice	Rats	Mice	Rats	Mice	Rats	Mice	Rats
Lymphatic/hematopoietic	•		•		•	•			NS	
Lung	•		•		•		•			
Heart	[f]•									
Liver	•		•				[a]•	[a]•		
Forestomach	•		•	•				•		•
Harderian gland	•		•		•					
Ovary	•		•							
Mammary gland	•	•	•		•		•			•
Preputial gland	•		•							
Brain		•				•		•		•
Zymbal gland		•	•	•				•		•
Uterus		•		•	•					
Pancreas		•								
Testis		•								
Thyroid gland		•								

NS, not studied.
Hemangiosarcoma.

2. Epidemiologic Studies

(i) *Introduction*. OSHA has concluded that the epidemiologic studies contained in this record, as well as the related hearing testimony and record submissions, show that occupational exposure to BD is associated with an increased risk of death from cancers of the Lymphohematopoietic (LH) system. However, in contrast to the available toxicologic data, our understanding of BD epidemiology is based on observational studies, not experimental ones. In other words, the investigators who conducted these epidemiologic studies did not have control over the exposure status of the individual workers. They were, nonetheless, able to select the worker populations and the observational study design.

Cohort and case control studies are two types of observational study designs. Each of these designs has strengths and weaknesses that should be considered when the results are interpreted. Cohort studies, for example, have the advantages of decreasing the chance of selection bias regarding exposure status and providing a more complete description of all health outcomes subsequent to exposure. The disadvantages of cohort studies include the large number of subjects that are needed to study rare diseases and the potentially long duration required for follow-up. By comparison, case control studies are well suited for the study of rare diseases and they require fewer

subjects. The disadvantages of case control studies, however, include the difficulty of selecting an appropriate control group(s), and the reliance on recall or records for information on past exposures. Regardless of the selected observational study design, the greatest limitation of occupational epidemiologic studies is their ability to measure and classify exposure.

In spite of the inherent limitations of observational epidemiologic studies, guidelines have been developed for judging causal association between exposure and outcome. Criteria commonly used to distinguish causal from non-causal associations include: Strength of the association as measured by the relative risk ratio or the odds ratio; consistency of the association in different populations; specificity of the association between cause and effect; temporal relationship between exposure and disease which requires that cause precede effect; biologic plausibility of the association between exposure and disease; the presence of a dose-response relationship between exposure and disease; and coherence with present knowledge of the natural history and biology of the disease. These criteria have been considered by OSHA in the development of its conclusion regarding the association between BD and cancer of the LH system.

As stated previously, each type of epidemiologic study design has strengths and weaknesses. Since epidemiologic studies are observational and not experimental, each study will also have inherent strengths and weaknesses; there is no perfect epidemiologic study. The most convincing evidence of the validity and reliability of any epidemiologic study comes with replication of the study's results.

There are six major epidemiologic studies in the record that have examined the relationship between occupational exposure to BD and human cancer. These studies include: A North Carolina study of rubber workers (Ex. 23–41; 23–42; 23–4; 2–28; 23–27; 23–3); a Texaco study of workers at a BD production facility in Texas (Ex. 17–33; 34–4; 34–4); a NIOSH study of two plants in the styrene-butadiene rubber (SBR) industry (Ex. 2–26; 32–25); the Matanoski cohort study of workers in SBR manufacturing (Ex. 9; 34–4); the nested case-control study of workers in SBR manufacturing conducted by Matanoski and Santos-Burgoa (Ex. 23–109); and a follow-up study of synthetic rubber workers recently completed by Delzell et al. (Ex. 117–1). Several comments in the record have concluded that these studies demonstrate a positive association between occupational exposure to BD and LH cancers. However, OSHA has been criticized by the Chemical Manufacturers Association (CMA) and the International Institute of Synthetic Rubber Producers, Inc. (IISRP) for its interpretation of these studies as showing a positive association; the chief criticisms will be discussed below. (Ex. 112 and 113)

OSHA's final consideration of the BD epidemiologic studies is organized and presented according to what have been identified as key issues. These are the epidemiologic issues that were raised and considered throughout the rulemaking. They are also the issues most pertinent to OSHA's conclusions. These key issues surrounding BD exposure and LH cancer are: Evidence of an association; observation of a dose-response relationship; observation of short latency periods; the potential role of confounding exposures and the observed study results; the biological basis for grouping related LH cancers; relevance of subgroup analyses; and appropriateness of selected reference populations.

(ii) *Evidence of an Association Between BD and LH Cancer.* Each of the studies listed above contributes to the epidemiologic knowledge upon which OSHA's conclusion regarding the relationship of BD exposure and LH cancer has been developed.

(a) *North Carolina Studies.* This series of studies was undertaken to examine work-related health problems of a population of workers in a major tire manufacturing plant. They were not designed to look specifically at the health hazards of BD. (Tr. 1/15/91, p. 117) However, in a work area that involved the production of elastomers, including SBR, relative risks of 5.6 for lymphatic and hematopoietic malignancies and 3.7 for lymphatic leukemia were found among workers employed for more than five years. The International Agency for Research on Cancer (IARC) evaluation concluded that this study suggests an association between lymphatic and hematopoietic malignancy and work in SBR manufacturing. (Tr. 1/15/91, p. 117) However, the IISRP asserted that these studies do not provide ''meaningful evidence of an association between butadiene and cancer.'' (Ex. 113, p. A–23) OSHA recognizes that the researchers who conducted these studies acknowledged that the workers may have had exposures to organic solvents, including benzene, a known leukemogen, as pointed out by the IISRP. (Ex. 113, p. A–24)

(b) *Texaco Study.* The two Texaco studies examined mortality of a population of workers in a BD manufacturing facility in Texas. (Ex. 17–33; 34–4 Vol. III, H–2; Divine 34–4, Vol. III, H–1) A qualitative method of exposure classification, based on department codes and expert consensus judgement, was used in the Downs study. (Ex. 17–33; 34–4, Vol. III, H–2) From this methodology four exposure groups were defined: Low exposure, which included utility workers, welders, electricians, and office workers; routine exposure, which included process workers, laboratory personnel, and receiving, storage and transport workers; non-routine exposure, which included skilled maintenance workers; and unknown exposure, which included supervisors and engineers. It is OSHA's opinion that although this is a crude approach to exposure classification, there are important findings in this study that contribute to our understanding of BD epidemiology.

In the Downs study (Ex. 34–4, Vol. III, H–2) the standardized mortality ratio (SMR) for all causes of death in the entire study cohort was low (SMR 80; $p < .05$) when compared to national population rates. However, a statistically significant excess of deaths was observed for lymphosarcoma and reticulum cell sarcoma combined (SMR 235; 95% confidence interval (CI) = 101,463) when compared with national population rates. (The issue of reference population selection is discussed below in paragraph (viii).)

When analyzed by duration of employment, the SMR for the category of all LH neoplasms was higher in workers with less than five years employment (SMR = 167) than for those with more than five years employment (SMR = 127). (Ex. 34–4, Vol. III, H–2) However, neither of these findings was statistically significant. Alternatively, it has been suggested that perhaps the short-term workers were wartime workers, and that these workers were actually exposed to higher levels of BD, albeit for a shorter time. (Tr. 1/15/91, p. 119)

Analyses of the four exposure groups also showed elevated but not statistically significant SMRs. The routine exposure group had a SMR of 187 for all LH neoplasms, explained primarily by excesses in Hodgkin's disease (SMR = 197) and other lymphomas (SMR = 282). (Ex. 34–4, Vol. III, H–2) Those workers in the non-routine exposure group also had an elevated SMR for all LH neoplasms (SMR = 167), with excess mortality for Hodgkin's disease (SMR = 130), leukemias (SMR = 201), and other

lymphomas (SMR = 150) (Ex. 34–4, Vol. III, H–2).

These data were updated by Divine by extending the period of follow-up from 1979 through 1985. (Ex. 34–4, Vol. III, H–1) The SMR for all causes of mortality remained low (SMR = 84, 95% CI = 79,90), as it did for mortality from all cancers (SMR = 80, 95% CI = 69,94). (Ex. 34–4, Vol. III, H–1) However, the SMR for lymphosarcoma and reticulosarcoma combined was elevated and statistically significant (SMR = 229, 95% CI = 104,435). This finding was consistent with the previous analyses done by Downs. (Tr. 1/15/91, p. 120).

Exposure group analyses were also consistent with the previous findings by Downs. The highest levels of excess mortality from lymphatic and hematopoietic malignancy were again seen in the routine and non-routine exposure groups. The routine exposure group that was ''ever employed'' had a statistically significant excess of lymphosarcoma (SMR = 561, 95% CI = 181,1310), that accounted for most of the LH excess. (Ex. 34–4, Vol. III, H–1) The cohort of workers employed before 1946 (wartime workers) also demonstrated a statistically significant excess of mortality due to lymphosarcoma and reticulosarcoma combined (SMR = 269, 95% CI = 108,555). (Ex. 34–4, Vol. III, H–2)

In summary, the Texaco study provides several notable results. The first of these is the consistently elevated mortality for lymphosarcoma. This finding is consistent with excess lymphomas observed in experimental mice. (Ex. 23–92) Second, the excess risk of mortality was found in the routine and non-routine exposure groups. Based on the types of jobs held by workers in these two exposure groups, this finding suggests that the incidence of lymphatic malignancy is highest in the groups with the heaviest occupational exposure to BD. (Tr. 1/15/91, p. 121) The third notable result of this study was the significantly elevated rate of malignancy in workers employed for fewer than 10 years.

(c) *NIOSH Study.* The NIOSH study was undertaken in January 1976 in response to the report of deaths of two male workers from leukemia. (Ex. 2–26; 32–25) These workers had been employed in two adjacent SBR facilities (Plant A and Plant B) in Port Neches, Texas. The hypothesis tested by this study is that:

> Employment in the SBR production industry was associated, specifically, with an increased risk of leukemia and, more generally, with an increased risk of other malignancies of hematopoietic and lymphatic tissue. (Ex. 2–26)

This study did not specifically examine the association between BD and all LH cancers. Thus, OSHA agrees with the criticism that this study by itself did not demonstrate that occupational exposure to BD *causes* cancer. (Ex. 113, pp. A–13, A–19) However, the findings in this study are consistent with the patterns observed in the other epidemiologic studies discussed in this section. In Plant A, the overall mortality was significantly decreased (SMR=80, $p<0.05$). (Ex. 2–26) The SMR for all malignant neoplasms was also decreased (SMR=78), but this result was not statistically significant. (Ex. 2–26) The SMR for LH cancers was elevated (SMR=155), as it was for lymphosarcoma and reticulum cell sarcoma (SMR=181) and leukemia (SMR=203), but none of these results was statistically significant. (Ex. 2–26)

The pattern of mortality for a subgroup of wartime workers was also examined for the Plant A population. For this subgroup of white males, employed at least six months between the beginning of January 1943 and the end of December 1945, there was an elevated SMR for lymphatic and hematopoietic neoplasms (SMR = 212) that was statistically significant at the level of $0.05<p<0.1$. (Ex. 2–26) Likewise, the SMR for leukemia was increased (SMR=278), also with statistical significance at the level of $0.05<p<0.1$. (Ex. 2–26)

At Plant B, the overall mortality was low (SMR=66, $p<0.05$), as was death from all malignant neoplasms (SMR=53, $p<0.05$). (Ex. 2–26) The SMR for LH cancer was also low (SMR=78), but this finding was not statistically significant. (Ex. 2–26)

When this study was updated, the mortality patterns remained unchanged. (Ex. 32–25) The most remarkable findings of the NIOSH study are the excess mortality for malignancies of the LH system, and the excess of these cancers in workers employed during the wartime years.

(d) *Matanoski Cohort Study.* The cohort study conducted by Matanoski et al. is comprised of two follow-up periods: In the original study, completed in June 1982, the cohort was followed from 1943 to 1979; and in the update, completed in March 1988, the cohort follow-up period was extended to 1982. (Ex. 9; 23–39; 34–4, Vol. III, H–3 and H–6, respectively) The original study analyzed mortality data for 13,920 male workers employed for more than one year in eight SBR production plants in the United States and Canada. Although historical quantitative exposure data were not available, creation of a job dictionary made it possible to designate four general work activities as surrogates for exposure: Production; utilities; maintenance; and a combined category of all other jobs. The work activities with the highest BD exposures were production and maintenance. (Ex. 16–39) The total duration worked was measured by the dates of first and last employment.

The mortality experience for the original study cohort, as compared with death rates for males in the United States, was low for all causes (SMR=81) and all cancers (SMR=84). (Ex. 9; 23–39) The SMR for all LH cancers was also low (SMR=85). (Ex. 9; 23–39) The mortality rate for Hodgkin's disease was slightly elevated (SMR=120), but it was not statistically significant. (Ex. 9; 23–39) In fact, there were no statistically significant excesses in mortality from cancer at any site found in this original cohort study.

These initial data were also analyzed according to major work area. There were not any elevations of mortality rates for the category of all LH cancers. (Ex. 9; 23–39) For production workers, the SMR for other lymphatic cancers was elevated (SMR=202), but it was not statistically significant. (Ex. 9; 23–39) The SMR for leukemia in the utilities work group was also elevated (SMR=198), but it was based on only two deaths and was not statistically significant. (Ex. 9; 23–39) Slight excesses, none of which was statistically significant, were seen for Hodgkin's disease in each of the four work group categories. (Ex. 9; 23–39)

OSHA has been criticized for its opinion, expressed in the preamble of the BD proposed rule, that the original Matanoski cohort study did not have sufficient power to detect a difference in the cancer SMR if one actually existed. (Ex. 113, pp. A–10–11) Statistical power of at least 80% is the accepted rule-of-thumb for epidemiologic research study design. Calculations provided by Matanoski indicate that, for the outcomes of greatest concern to OSHA, statistical power was often below the 80% level. (Ex. 9) For leukemia, statistical power to detect 25% and 50% increases in mortality was only 27% and 62%, respectively. (Ex. 9) The power to detect a 25% increase in mortality for all lymphohematopoietic cancers was only 49%. (Ex. 9) However, the study did have a statistical power of 93% to detect a SMR of 150 for all LH cancers. (Ex. 9) Thus, for the cancers of most interest to OSHA, this study had limited statistical power to detect mortality excesses that were less than two-fold. OSHA does not consider this to be an ''unrealistically strict standard of acceptability,'' as alleged by the

IISRP, but rather part of a thorough critique of an epidemiologic study with purportedly ''negative results.'' (Ex. 113, p. A–11)

The update of Matanoski's original study extends the period of cohort follow-up from 1979 to 1982, providing a full 40 years of mortality experience for analysis. The update study cohort differed from the original cohort in two additional ways: Canadian workers with relatively short-term exposure were removed from the cohort; and the proportion of workers lost to follow-up was reduced. The extension of follow-up resulted in findings of excess mortality from lymphatic and hematopoietic cancers that had not been observed in the original analyses. (Ex. 34–4, Vol. III, H–6)

The SMR for all causes of mortality remained low (SMR=81, 95% CI=78,85), as it did for death from all cancers (SMR=85, 95% CI=78,93). (Ex. 34–4, Vol. III, H–6) For lymphatic and hematopoietic cancers, the overall SMR for white males was not increased (SMR=92, 95% CI=68,123). (Ex. 34–4, Vol. III, H–6) However, for black males, the SMR for all LH cancers was elevated (SMR=146, 95% CI=59,301). (Ex. 34–4, Vol. III, H–6) Specific increases were also found for lymphosarcoma (SMR=132), leukemia (SMR=218, 95% CI=59,560), and other lymphatic neoplasms (SMR=116, 95% CI=14,420). (Ex. 34–4, Vol. III, H–6) These increases were based on small numbers of observed deaths.

Analyses conducted on the four exposure groups also produced some evidence of excess mortality. For the total cohort of production workers, an elevated SMR was observed for all lymphopoietic cancers (SMR=146, 95% CI=88,227). (Ex. 34–4, Vol. III, H–6) For white production workers, the SMR for that category was 110, explained principally by excess mortality from other lymphatic neoplasms (SMR=230, 95% CI=92,473). (Ex. 34–4, Vol. III, H–6) Although based on small numbers, the results for black production workers were more pronounced and statistically significant: The SMR for all lymphatic and hematopoietic cancers was 507 (95% CI=187,1107). (Ex. 34–4, Vol. III, H–6) That overall increase in black workers reflected excess mortality from lymphosarcoma (SMR=532), leukemia (SMR=656, 95% CI=135,1906), and other lymphatic cancers (SMR=482, 95% CI=59,1762). (Ex. 34–4, Vol. III, H–6)

A pattern of excess mortality for all LH cancers was also seen in utility workers (SMR=203, 95% CI=66,474). (Ex. 34–4, Vol. III, H–6) That elevated SMR may be explained by elevated rates for leukemia (SMR=192, 95% CI=23,695) and other lymphatic cancers (SMR=313, 95% CI=62,695). (Ex. 34–4, Vol. III, H–6) No increases in LH malignancy were seen in the other exposure groups, i.e., maintenance or other workers.

From these study results Matanoski et al. concluded:

> Deaths from cancers of the hematopoietic and lymphopoietic system are higher than expected in production workers with significant excesses for leukemias in black workers and other lymphomas in all (production) workers. (Ex. 34–4, Vol. III, H–6, p. 116)

In response to criticism from the IISRP that OSHA placed too much emphasis on the findings in the group of black production workers, OSHA is aware of the statement offered by the researchers that because of the potential for bias from misclassification of race: ''* * * the total SMRs are probably the most correct representation of risk.'' (Ex. 34–4, Vol. III, H–6) However, OSHA also agrees with the authors that the risk of death from LH cancers seems to be higher in this SBR industry population than in the general population, and these causes of death seem to be associated with different work areas. These cohort study findings stimulated the design and implementation of the Santos-Burgoa and Matanoski nested case-control study.

(e) *Santos-Burgoa and Matanoski Nested Case-Control Study.* To further investigate the findings of the cohort study, Santos-Burgoa and Matanoski et al. designed and conducted a case-control study of LH cancers in workers in the styrene-butadiene polymer manufacturing industry. (Ex. 23–109; 34–4, Vol. III, H–4) The specific questions addressed by this research study are: ''Is there a risk of any lymphatic or hematopoietic cancer which is associated with exposure to (BD) or styrene or both?''; and ''is there a risk of these cancers related to exposure to jobs within the industry?'' (Ex. 34–4, Vol. III, H–4) This is the first study to specifically investigate the association between LH cancers and individual worker exposure to BD, which is why, contrary to the opinion of IISRP, OSHA places so much ''weight'' on these results. (Ex. 113, pp. A–25–34)

The subjects in this case-control study were ''nested,'' or contained, within the population of the original cohort study. ''Cases'' in this study were defined as males who worked one year or more at any of eight synthetic rubber polymer producing plants and who died of or with a lymphopoietic cancer. These cancers included: Lymphosarcoma and reticulum cell sarcoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, all leukemias, multiple myeloma, polycythemia vera, and myelofibrosis. Sixty-one cases were identified, but two cases were omitted from data analyses, resulting in a total of 59 cases. One case was omitted because he could not be matched to controls, and the other case lacked job records from which exposure could be identified.

Eligible ''controls'' included workers who were either alive or had died of any cause other than malignant neoplasms, who had been employed at one of the eight SBR plants, and who had not been lost to follow-up. These controls were individually matched to cases on the following criteria: Plant; age; hire year; employment as long or longer than the case; and survival to the death of the case. The study aim was to select four controls per case. Even though this was not always possible, there were, on average, just over three controls per case in each group of lymphopoietic cancer. The total number of controls was 193.

Unlike the previous studies, in this research study an exposure measurement value for BD (and also for styrene) was determined for each case and control. This value was determined by a multi-step process. First, the job records of each subject were reviewed and the number of months that each job was held was determined. Second, the level of BD (and styrene) associated with the job was estimated by a panel of five industrial experts, i.e., engineers with long term experience in SBR production. The exposure level for BD (and styrene) for each job was based on a scale of zero to ten, with ten being the rank given to the job with the highest exposure. The next step in the development of each individual job-exposure matrix was to add all of the exposures to the chemicals for all the months a specific job was held and then sum the exposures over a working lifetime. This procedure resulted in a cumulative BD exposure value for each case and control.

The distribution of the cumulative exposure estimates for the study population was not normally distributed, i.e., there were some extreme values. In order to approximate a normal distribution, a required assumption for many statistical analyses, a logarithmic transformation of these values was done. (Ex. 34–4, Vol. III, H–4) Exposure was analyzed as a dichotomous variable, i.e., ever/never exposed. ''Exposed'' workers were defined as those with a log rank cumulative exposure score above the mean of the scores for the entire population of cases and controls within

a cancer subtype; ''non-exposed'' workers were those with a score below the mean.

There were several important findings in this study. First, in the unmatched analysis of cases and controls, the leukemia subgroup had a significant excess risk of 6.8 fold for exposure to BD among cases compared to controls (Odds Ratio (OR)=6.82, 95% CI=1.10,42.23). (Ex. 34–4, Vol. III, H–4) The results were even stronger in the matched-pair analyses. In that analysis for exposure to BD, the OR was 9.36 (95% CI=2.05,22.94) in the leukemia subgroup. (Ex. 34–4, Vol. III, H–4) This result can be interpreted to mean that cases with leukemia were more than nine times as likely as their controls to be exposed to BD. Additionally, the data in this analysis indicate that BD exposure above the group mean is 2.3 times (OR=2.30, 95% CI=1.13,4.71) more common among cases with all lymphopoietic cancers when compared to a similar exposure in the controls. (Ex. 34–4, Vol. III, H–4)

This case-control study has been the subject of criticism that has centered on both validity and reliability. (Ex. 23–68; 113) For example, the data from this study have been criticized as being ''inconsistent'' with the results of the Matanoski cohort study. (Ex. 23–68; 113, p. A–25) Further, it has been suggested that ''the study results are not reliable and should not be relied upon by OSHA.'' (Ex. 113, p. A–25) OSHA rejects these criticisms for the reasons discussed below.

First, regarding the issue of inconsistency, a nested case control study does not test the same hypotheses or make the same comparisons as a cohort study. (Ex. 32–24; Tr. 1/15/91, p. 161; Tr. 1/16/91, p. 347) In fact, as presented in the above discussions of the studies, they ask and answer different research questions. For example, the cohort study asked whether all of the SBR workers have a different risk of leukemia from the general population, and the case control study asked whether workers with leukemia have different exposures within the industrial setting from workers without leukemia. (Ex. 32–24) Thus, the criticism that the results of these two studies are incompatible, and therefore invalid, is not relevant. (Ex. 32–24)

Second, the challenge directed at the reliability of the case-control study does not hold up under close scrutiny. This criticism is based on four issues: Log transformation of the exposure data; instability of the results; irregular dose-response pattern; and selection criteria for ''controls.'' (Ex. 113, A–29–34) Regarding the log transformation of the exposure data, the IISRP asserts that there is not a sound rationale for this approach to data analyses. (Ex. 113, A–29–30) However, Santos-Burgoa offered the following explanation of this procedure in his testimony:

> For analysis, exposures were categorized in advance above and below the mean of the cumulative exposure for the study subjects. This cutpoint was defined from the very beginning of the analysis design as follows. The total cumulative exposures, as happens in most environmental exposures, showed a skewed distribution with many observations at the low levels and few at the high levels. Since the geometric mean is the best estimate of the central tendency point in log normal data, such as exposure data, the cumulative exposures were transformed by the logarithm, and then the mean was calculated. (Ex. 40, pp. 12–13)

It is OSHA's opinion that, given the log normal distribution of the exposure data, Santos-Burgoa chose the best approach for data analyses.

The case-control study has also been criticized for producing ''highly unstable and therefore unreliable'' results. (Ex. 113, A–30) For example, the leukemia subgroup (matched-pair analysis) OR of 9.36 with a 95% confidence interval of 2.05–22.94 has been used to illustrate statistical instability of the data. (Ex. 113, A–31) However, as previously discussed, the disease category of ''all lymphopoietic cancers'' (matched-pair analysis) had an OR of 2.30 with a confidence interval of 1.13–4.71. Thus, it is OSHA's opinion that, while some specific odds ratios may have wide confidence intervals, the study results as a whole are not ''unreliable.''

The IISRP has also criticized the case-control study for ''* * * fail(ing) to demonstrate a dose-response relationship * * *'' (Ex. 113, A–32) However, the test for linear trend, i.e., test for dose-response, shows a statistically significant, but irregular, trend in the odds of leukemia with increasing levels of exposure to BD. Specifically, as exposure levels increase the pattern of odds ratios is: 7.2; 4.9; 13.0; 2.5; and 10.3. (Ex. 23–109, Table 10) Although this is not a compelling linear dose-response, in OSHA's opinion, it is suggestive of a pattern of increasing disease risk at increasing exposure levels.

Inconsistent application of the control selection criteria is the final criticism directed at the case-control study by the IISRP. (Ex. 113, A–33) However, careful review of docket exhibits related to the case-control study reveals this criticism to be unfounded. In his dissertation, Santos-Burgoa clearly states the protocol for control selection:

> All cohort subjects were arranged into groups by plants, date of birth, date of hire, duration of work and duration of follow-up. A two and a half year period around each time variable was relaxed in a few instances when no more controls were available. One lymphosarcoma case was lost since no match was found for his date of birth, even allowing for three and a half years around the date. This was the only case lost to analysis because of lack of a matched control. (Ex. 32–25, p. 80)

With only 59 cases, Santos-Burgoa was correctly concerned about loss of valuable data should any additional cases need to be eliminated due to lack of a match. Also, regarding the potential for bias, abstractors were blinded to case or control status when employment data were being collected. (Ex. 34–4, Vol. III, App. H–5) Thus, it is most likely that any misclassification bias would be nondifferential, biasing the study results towards the null.

(f) *Delzell et al. Follow-up Study for the IISRP.* The most recent study of synthetic rubber workers was conducted by Delzell et al. (Ex. 117–1) This study updated and expanded the research on SBR workers conducted by NIOSH, Matanoski et al., and Santos-Burgoa. More specifically, the Delzell et al. study consists of workers at seven of eight plants previously studied by The Johns Hopkins University (JHU) investigators, and the two plants included in the NIOSH study.

This retrospective cohort study evaluated the associations between occupational exposure to BD, styrene, and benzene and mortality from cancer and other diseases among the SBR workers. There were five study objectives:

> (1) To evaluate the overall and cause-specific mortality experience of SBR workers relative to that of the USA and Canadian general populations;
>
> (2) To assess the cancer incidence experience of Canadian synthetic rubber workers relative to that of the general population of Ontario;
>
> (3) To determine if overall and cause-specific mortality patterns vary by subject characteristics such as age, calendar time, plant, period of hire, duration of employment, time since hire and payroll status (hourly or salaried);
>
> (4) To examine relationships between work areas within the SBR study plants and cause-specific mortality patterns;
>
> (5) To evaluate the relationship between exposure to BD and [styrene] and the occurrence of leukemia and other lymphopoietic cancers among SBR workers. (Ex. 117–1 p. 10)

The study population for this investigation included 17,964 male synthetic rubber workers employed in one of eight plants in either the USA or Canada. In order to be eligible for

inclusion, a worker had to be employed for a total of at least one year before the closing date of the study, January 1, 1992. Additional eligibility criteria were developed for selected plants due to limitations in availability of plant records and follow-up of subjects. The eligibility criteria in this study were considered by the investigators to be more restrictive than in either the JHU or NIOSH studies. (Ex. 117–1, p. 13) Most of the exclusions were based on less than one year of employment. During the study period of 1943 through 1991, there were 4,665 deaths in the study population.

The methods used in this study included development of work history information and retrospective quantitative exposure estimates for individual members of the study population. Complete work history information was available for approximately 97% of the study cohort. There was a total of 8,281 unique ''work area/job'' combinations for all of the plants combined, with a range of 199 to 4,850 in specific plants. Additionally, 308 work area groups were defined based on individual plant information regarding production, maintenance, and other operations, as well as jobs and tasks within each type of operation. Five ''process groups'' and seven ''process subgroups'' were derived from the work area groups. The process groups include: Production of SBR, solution polymerization (SP), liquid polymerization (LP), and latex production; maintenance; labor; laboratories; and other operations.

Six plants had sufficiently detailed individual work history information for use in development of retrospective quantitative exposure estimates for BD and styrene. The process used to produce these exposure estimates included: In-depth walk-through surveys of each plant; meetings with plant management; interviews with key plant experts, such as individuals with long-term employment. The interviews were used to collect information regarding the production process, specific job tasks, and exposure potential. Additionally, the results of industrial hygiene monitoring from these plants were obtained. The actual exposure estimation was based on:

Specification of the exposure model; the estimation of exposure intensities for specific tasks in different time periods; the estimation of exposure intensities for generic (nonspecific) job titles (e.g., ''laboratory worker'') in different time periods; validation of exposure intensity estimates; the computation of job- and time period specific summary indices; and the compilation of job-exposure matrices (JEMs) for BD, [styrene], and [benzene] and linkage with subjects' work histories. (Ex. 117–1, pp. 27–28)

A limited validation of the quantitative exposure estimations was conducted, which resulted in revision of the estimates used in analyses presented in the Delzell et al. study. (Ex. 117–1)

The major findings of this study have been reported by Delzell et al. in five categories: General mortality patterns; mortality among USA subjects compared to state populations; cancer incidence; mortality patterns by process group; and mortality patterns by estimated monomer exposure. Key results from each of these categories, especially as they relate to leukemia and other LH cancers, are briefly presented.

First, regarding general mortality patterns, there were deficits in both all causes (SMR=87, 95% CI=85,90) and all cancers (SMR=93, 95% CI=87,99) for the entire cohort. (Ex. 117–1, p. 53) Of the LH cancers, excess mortality was only observed for leukemia (SMR=131, 95% CI=97–174). (Ex. 117–1, p. 53) In a cohort subgroup having 10 or more years of employment and 20 or more years since hire, the excess of leukemia deaths was even greater (SMR=201, 95% CI=134,288). (Ex. 117–1, p. 54)

Analyses were also conducted to explore the possibility of racial differences in the general mortality patterns. Regarding mortality from leukemia, the SMRs were higher for blacks than for whites. In a subgroup of ''ever hourly'' workers with 10 or more years of work and 20 or more years since hire, the SMRs for leukemia were 192 (95% CI=119,294) for whites and 436 (95% CI=176,901) for blacks. (Ex. 117–1, p. 55)

Additionally, analyses were done by specific groups of LH cancers: Lymphosarcoma; leukemia; and other lymphopoietic cancer. For the overall cohort, there was an excess of mortality from lymphosarcoma in those members who died in 1985 and beyond (SMR=215, 95% CI=59,551). (Ex. 117–1, p. 116) This excess was observed in ''ever hourly'' white men; there were no lymphosarcoma deaths in blacks. (Ex. 117–1, p. 119)

In the ''other lymphopoietic cancer'' category, the overall cohort had a slight deficit of mortality (SMR=97, 95% CI=70,132). (Ex. 117–1, p. 116) When analyzed according to racial groups, whites were also observed to have a deficit of mortality from this group of cancers (SMR=91, 95% CI=63,127). (Ex. 117–1, p. 118) Blacks, however, had an increase in mortality from ''other lymphopoietic'' cancers (SMR=142, 95% CI=61,279). (Ex. 117–1, p. 120)

The analyses for leukemia mortality in the overall cohort showed a modest increase (SMR=131, 95% CI=97,174). (Ex. 117–1, p. 116) The increase in mortality was found primarily in the subgroups of workers who died in 1985 or later, those that worked for 10 or more years, and those with 20 or more years since hire. A dose-response type of pattern was observed among ''ever hourly'' subjects in the analysis of the relationship of leukemia and duration of employment: Less than 10 years worked, the SMR=95 (95% CI=53,157); 10–19 years worked, the SMR=170 (95% CI=85,304); and 20 or more years worked, the SMR=204 (95% CI=123,318). (Ex. 117–1, p. 117)

Leukemia mortality was also analyzed for racial difference among ''ever hourly'' men. Overall, the SMR was higher for black subjects (SMR=227, 95% CI=104,431) than for white (SMR=130, 95% CI=91,181). (Ex. 117–1, p. 122) In fact, there were statistically significant elevations in the leukemia SMR for black ''ever hourly'' men with 20 or more years worked (SMR=417, 95% CI=135,972), and 20 to 29 years since hire (SMR=446, 95% CI=145,1042). (Ex. 117–1, p. 122)

Second, Delzell et al. analyzed the mortality data of the USA cohort subgroup using both state general population rates and USA general population rates for comparison. The overall pattern of these analyses was that of ''slightly lower'' SMRs when the state general population rates were used. (Ex. 117–1, p. 60) For example, in the analysis for leukemia mortality, the SMR using the USA rates was 131 (95% CI not provided), and it decreased to 129 (95% CI=92,176) when state rates were applied. (Ex. 117–1, pp. 61, 136)

Third, the results of the Delzell et al. study include an analysis of the cancer incidence in the Canadian plant (plant 8). Regardless of whether the cancer experience of terminated workers was included or excluded, the overall cancer incidence was not elevated in this cohort subgroup (SIR=105, 95% CI=93,117; SIR=106, 95% CI=94,119, respectively). (Ex. 117–1, pp. 61–62) However, analysis of this cohort subgroup, with the terminated workers included, ''revealed an excess of leukemia cases before 1980 (overall cohort, 6 observed/3.0 expected; ever hourly, 6 observed/2.9 expected)'' (further data were not provided). (Ex. 117–1, p. 62)

Fourth, Delzell et al. examined mortality patterns by work process group. These analyses produced elevated SMRs for both lymphosarcoma and leukemia. There was excess lymphosarcoma mortality in field maintenance workers (SMR=219, 95% CI=88,451), production laborers

(SMR=263, 95% CI=32,951), and maintenance laborers (SMR=188, 95% CI=39,548). (Ex. 117–1, pp. 65–66) However, these results were not statistically significant, and may be due to chance. For leukemia, the results were more striking: Polymerization workers had a SMR of 251 (95% CI=140,414); workers in coagulation had a SMR of 248 (95% CI=100,511); maintenance labor workers had a SMR of 265 (95% CI=141,453); and workers in laboratories had a SMR of 431 (95% CI=207,793). (Ex. 117–1, pp. 66,151) It should be noted that excess mortality by work process group was also observed for other cancers, i.e., lung cancer and larynx cancer.

Fifth, the final set of analyses performed by Delzell et al. was designed to examine mortality patterns by estimated monomer exposure, i.e., BD, styrene, and benzene. Poisson regression analyses conducted to explore the association between ''BD ppm-years'' and leukemia indicated a positive dose-response relationship, after controlling for styrene ''ppm-years'', age, years since hire, calendar period, and race. Specifically, in the cohort group that included all person-years and leukemia coded as either underlying or contributing cause of death, the rate ratios (RRs) were: 1.0, 1.1 (95% CI=0.4,5.0), 1.8 (95% CI=0.6,5.4), 2.1 (95% CI=0.6,7.1), and 3.6 (95% CI=1.0,13.2) for BD ppm-year exposure groups of 0, >0–19, 20–99, 100–199, and 200+, respectively. (Ex. 117–1, pp. 68–69; 158) Poisson regression analyses were also conducted using varying exposure categories of BD ppm-years. These analyses demonstrated a stronger and more consistent relationship between BD and leukemia than between styrene and leukemia. (Ex. 117–1, p. 69, 159) Although a clearly positive relationship between BD ''peak-years'' and leukemia was observed from additional Poisson regression analyses, even after controlling for BD ppm-years, styrene ppm-years, and styrene peak-years, the dose-response relationship was less clear. (Ex. 117–1, pp. 71, 162)

In summary, one of the most important findings of the research of Delzell et al. was strong and consistent evidence that employment in the SBR industry produced an excess of leukemia. In the authors own words:

> This study found a positive association between employment in the SBR industry and leukemia. The internal consistency and precision of the result indicate that the association is due to occupational exposure. The most likely causal agent is BD or a combination of BD and [styrene]. Exposure to [benzene] did not explain the leukemia excess. (Ex. 117–1, p. 85)

(g) *Summary*. These studies provide a current body of scientific evidence regarding the association between BD and LH cancers. As previously discussed, two of the criteria commonly used to determine causal relationships are consistency of the association and strength of the association. The consistency criterion for causality refers to the repeated observation of an association in different populations under different circumstances. Consistency is perhaps the most striking observation to be made from this collection of studies: ''[E]very one of these studies to a greater or lesser extent finds excess rates of deaths from tumors of the lymphatic and hematopoietic system.'' (Tr. 1/15/91, p. 129)

Strength of the association is determined by the magnitude and precision of the estimate of risk. In general, the greater the risk estimate, e.g., SMR or odds ratio, and the narrower the confidence intervals around that estimate, the more probable the causal association. In the nested case-control study, although the confidence intervals were wide, the odds ratios provide evidence of a strong association between leukemia and occupational exposure to BD.

(iii) *Observation of a Dose-Response Relationship*. A dose-response relationship is present when an increase in the measure of effect (response), e.g., SMR or odds ratio, is positively correlated with an increase in the exposure, i.e., estimated dose. When such a relationship is observed, it is given serious consideration in the process of determining causality. However, the absence of a dose-response relationship does not necessarily indicate the absence of a causal relationship.

OSHA has been criticized for its conclusion that the epidemiologic data suggest a dose-response relationship. (Ex. 113) The IISRP offers a different interpretation of the data. In their opinion, the data provide a ''consistent finding of an inverse relationship between duration of employment and cancer mortality.'' (Ex. 113, A–34) This observation is further described by John F. Acquavella, Ph.D., Senior Epidemiology Consultant, Monsanto Company, as ''the paradox of butadiene epidemiology.'' (Ex. 34–4, Vol. I, Appendix A) This interpretation assumes that cumulative occupational exposure to BD will increase with duration of employment, and, thus, cancer mortality will increase with increasing duration of employment. (Ex. 113, A–35–39)

In OSHA's opinion, this is an erroneous assumption; the epidemiologic data for BD tell a different story. For the workers in these epidemiologic studies, it is unlikely that occupational exposure to BD was constant over the duration of employment. According to Landrigan, BD exposures were most likely higher during the war years than they were in subsequent years. (Tr. 1/15/91, p.146) It is logical that exposures would be especially intense during this time period because of wartime production pressures, the process of production start-up in a new industry, and the general lack of industrial hygiene controls during that phase of industrial history. Unfortunately, without quantitative industrial hygiene monitoring data, the true levels of BD exposure for wartime workers cannot be ascertained. In the absence of such data, however, OSHA believes it is reasonable to consider wartime workers as a highly exposed occupational subgroup. (Tr. 1/15/91, p. 121; Tr. 1/16/91, pp. 225–227) Thus, the excess mortality seen among these workers provides another piece of the evidence to support a dose-response relationship between occupational exposure to BD and LH cancers.

Additional support that excess mortality, among workers exposed to BD, is dose-related can be found in the analyses of the work area exposure groups. The studies by Divine, Matanoski, and Matanoski and Santos-Burgoa all provide evidence that excess mortality is greatest among production workers. (Ex. 34–4, Vol. III, H–1; 34–4, Vol. III, H–6; 23–109, respectively) Production workers are typically the most heavily exposed workers to potentially toxic substances. (Ex. 34–4)

The most compelling data that support the existence of a dose-response relationship for occupational exposure to BD and LH cancers are those in the study by Delzell et al. (Ex. 117–1) Analysis of the cumulative time-weighted BD exposure in ppm-years indicates a relative risk for all leukemias that increases positively with increasing exposure. This relationship is present even with statistical adjustment for age, years since hire, calendar period, race, and exposure to styrene. It is OSHA's opinion that identification of a positive dose-response in an epidemiologic study is a very powerful observation in terms of causality.

(iv) *Observation of Short Latency Periods*. Short latency periods, i.e., time from initial BD exposure to death, were seen in two epidemiologic studies. In the NIOSH study, three of the six leukemia cases had a latency period from three to four years. (Ex. 2–26) Additionally, five of these six workers were employed prior to 1945. (Ex. 2–26)

In the Texaco study update, a latency of less than 10 years was seen in four of the nine non-Hodgkin's lymphoma (lymphosarcoma) cases, and seven of these workers were also employed during the wartime years. (Ex. 34–4, Vol. III, H–1)

According to OSHA's expert witness, Dr. Dennis D. Weisenburger,

> these findings are contrary to the accepted belief that, if a carcinogen is active in an environment, one should expect the * * * SMRs to be higher for long-term workers than for short-term workers (i.e., larger cumulative dose). (Ex. 39, p. 9)

Thus, it has been argued that these findings appear to lack coherence with what is known of the natural history and biology of LH cancers. (Ex. 113, A–40–42) Furthermore, these findings have been interpreted as evidence against a causal association between BD and these LH cancers. (Ex. 113, A–42)

In OSHA's opinion, there are other possible explanations for these observations. First, as proffered by Dr. Weisenburger, a median latency period of about seven years has been found for leukemia in studies of atomic bomb victims, radiotherapy patients, and chemotherapy patients who have received high-dose, short-term exposures. (Ex. 39) In contrast, Dr. Weisenburger points out that low-dose exposure to an environmental carcinogen, such as benzene, has a median latency period for leukemia of about 15–20 years. (Ex. 39) He concludes that short-term, high-dose exposures may be associated with a short latency period, whereas long-term, low-dose exposures may be associated with a long latency period.

Second, the occurrence of short latency periods for LH cancer mortality in these two studies was concentrated in workers first employed during the wartime years. As previously discussed, it is possible that exposure to BD during the wartime years was greater than in subsequent years. (Ex. 39; Tr. 1/15/91, p. 121) Dr. Weisenburger suggests that the ''short latency periods for LH cancer in these studies may be explained by intense exposures to BD over a relatively short time period.'' (Ex. 39, p. 10)

In his testimony, Dr. Landrigan, another OSHA expert witness, makes the point that ''duration of employment is really only a crude surrogate for total cumulative exposures, not itself a measure of exposure.'' (Tr. 1/15/91, p. 121) In other words, it is possible that short-term workers employed during the wartime years may have actually had heavier exposures to BD than long-term workers. (Tr. 1/15/91, pp. 115–205) On cross-examination, Dr. Landrigan cautioned against ''assuming that duration of exposure directly relates to total cumulative exposure.'' (Tr. 1/15/91, p. 180) He also emphatically stated that an increased cancer risk in short-term workers would not be inconsistent with a causal association. (Tr. 1/15/91, p. 204)

(v) *The Potential Role of Confounding Exposures and Observed Results.* In epidemiologic studies ''confounding'' may lead to invalid results. Confounding occurs when there is a mixing of effects. More specifically, confounding may produce a situation where a measure of the effect of an exposure on risk, e.g., SMR, RR, is distorted because of the association of the exposure with other factors that influence the outcome under study.

For example, the IISRP has suggested that confounding exposures from other employment were responsible for the LH cancers observed in the studies of BD epidemiology. (Ex. 113, A–43) This argument is based on the past practice of using petrochemical industry workers, who may have also been exposed to benzene, to start up the SBR and BD production plants. The IISRP finds support for this position in the observation of elevated SMRs in short-term workers employed during the wartime years, precisely those most likely to be cross-employed. (Ex. 113, A–43)

However, there are a number of research methods in occupational epidemiology that are available to control potential confounding factors. Research methods that eliminate the effect of confounding variables include: Matching of cases and controls; adjustment of data; and regression analyses. In the nested case-control study, for example, cases and controls were matched on variables that otherwise might have confounded the study results. In the testimony provided by Santos-Burgoa, he states that the ''matching scheme allowed us to control for potential confounders and concentrate only on exposure variations.'' (Ex. 40, p. 12)

On cross-examination, Landrigan also addressed the potential role of confounding exposures and the observed study results. First, he observed that Dr. Philip Cole, Professor, Department of Epidemiology, School of Public Health, University of Alabama at Birmingham, one of the outspoken critics of OSHA's proposed rule, found no evidence for confounding in his review of the Matanoski study. (Tr. 1/15/91, p. 178) Second, Dr. Landrigan dismissed the notion of previous exposure to benzene as the causative agent for the observed results in the short-term workers. (Tr. 1/15/91, p. 178–179)

In their analyses of mortality patterns by estimated monomer exposure, Delzell et al. used Poisson regression to control for potential confounding factors. (Ex. 117–1) As previously stated, the analyses conducted to determine the association between BD ppm-years and leukemia indicated a positive dose-response relationship, even after controlling for styrene ppm-years, age, years since hire, calendar period, and race. In the opinion of the investigators, benzene exposure did not explain the excess of leukemia risk, and BD is the most likely causal agent. (Ex. 117–1, p. 85)

(vi) *The Biological Basis for Grouping Related LH Cancers.* The epidemiologic studies that have examined the association between occupational exposure to BD and excess mortality have grouped related LH cancers in their analyses. This approach has been criticized as evidence of a lack of ''consistency with respect to cell type'' which ''argues against a common etiologic agent.'' (Ex. 113, A–45) In other words, these critics suggest that the relationship between BD and excess mortality does not meet the specificity of association requirement for a causal relationship. This requirement states that the likelihood of a causal relationship is strengthened when an exposure leads to a single effect, not multiple effects, and this finding also occurs in other studies.

More specifically, OSHA has been criticized for its position that ''broad categories such as 'leukemia' or 'all LHC' should be used to evaluate the epidemiologic data.'' (Ex. 113, A–46) Dr. Cole, for example, commented that:

> It is a principle of epidemiology—and of disease investigation in general—that entities should be divided as finely as possible in order to maximize the prospect that one has delineated a homogeneous etiologic entity. Entities may be grouped for investigative purposes only when there is substantial evidence that they share a common etiology. (Ex. 63, p. 11)

It is Dr. Cole's opinion that LH cancers are ''distinct diseases'' with ''heterogeneous and multifactorial'' etiologies. (Ex. 63, p. 47)

Dr. Weisenburger, OSHA's expert in hematopathology, provided testimony to the contrary. (Ex. 39, pp. 7–8) According to Dr. Weisenburger, ''LH (cancer) cannot be readily grouped into 'etiologic' categories, since the precise etiologies and pathogenesis of LH (cancer) are not well understood.'' (Ex. 39, p. 7) In his opinion, because LH cancers are ''closely related to one

another and arise from common stem cells and/or progenitor cells, it is valid to group the various types of LH (cancer) into closely-related categories for epidemiologic study.'' (Ex. 39, p.7)

The issue of grouping related LH cancers to observe a single effect was also addressed by Dr. Landrigan in his testimony. (Tr. 1/15/91, pp. 131–133) The first point raised by Dr. Landrigan is that the ''diagnostic categories [for LH cancers] are imprecise and * * * overlapping.'' (Tr. 1/15/91, p. 131) For example, he explained that in clinical practice transitions of lymphomas and myelomas into leukemias may be observed. In such a case, one physician may record the death as due to lymphoma and another may list leukemia as the cause of death. (Tr. 1/15/91, p. 131–132) Additionally, Dr. Landrigan testified that ''some patients with lymphomas or multiple myeloma may subsequently develop leukemia as a result of their treatments with radiation or cytotoxic drugs.'' (Tr. 1/15/91, p. 132)

These recordings of disease transition are further complicated by the historical changes that have occurred in nomenclature and The International Classification of Diseases (ICD) coding. According to Dr. Landrigan,

> certain lymphomas and * * * leukemias, such as chronic lymphatic leukemia are now considered by some investigators * * * to represent different clinical expressions of the same neoplastic process. There have been recent immunologic and cytogenetic studies which indicate that there are stem cells which appear to have the capacity to develop variously into all the various sorts of hematopoietic cells including T-lymphocytes, plasma cells, granulocytes, erythrocytes, and monocytes. (Tr. 1/15/91, p. 132)

Dr. Landrigan summarized his testimony on this issue by stating that ''these different types of cells share a common ancestry * * * there is good biologic reason to think that they would have etiologic factors in common.'' (Tr. 1/15/91, pp. 132–133)

OSHA maintains the opinion, which is well supported by the record, that there is a biological basis and a methodologic rationale for grouping related LH cancers. Furthermore, OSHA rejects the criticism that the observation of different subtypes of LH cancers argues against the consistency and specificity of the epidemiologic findings.

(vii) *Relevance of Worker Subgroup Analyses.* OSHA has been criticized for focusing on and emphasizing the ''few positive results'' seen in the results of worker subgroup analyses. (Ex. 113, A–48) It has been pointed out, for example, that in the update of the Matanoski cohort study ''there were hundreds of SMRs computed in that study and it's not surprising that one or two or even more would be found to be statistically significant even when there is in fact nothing going on.'' (Tr. 1/22/91, p. 1444) Additionally, it has been suggested that OSHA has ignored the ''clearly overall negative results'' of the epidemiologic studies. (Ex. 113, A–48)

OSHA agrees with the observation that when many statistical analyses are done on a database, it is possible that some positive results may be due to chance. However, OSHA rejects criticism that the Agency has inappropriately concentrated on the positive results and disregarded the negative results. It is OSHA's opinion that there is a compelling pattern of results in the epidemiologic studies.

Furthermore, a reasonable explanation for the elevated SMR for black production workers in the update of the Matanoski cohort study is that this subset of the population actually had heavy exposure to BD. Support for this explanation can be found in the industrial hygiene survey results of Fajen et al. (Ex. 34–4) In this case, then, the risk for excess mortality would be concentrated in a small subset of otherwise very healthy and unexposed workers that would be diluted when analyses are based on the entire group being studied. The only way to observe the risk in the most highly exposed subset would be to analyze the data by subgroups of the population.

(viii) *Appropriateness of Selected Reference Populations.* OSHA also has been criticized for ''ignor[ing] the fact that most of the epidemiologic studies of butadiene-exposed workers only used U.S. cancer mortality rates for comparison to worker mortality.'' (Ex. 113, A–49) The significance of this criticism is based on the observation by Downs that ''use of local (mortality) rates (for comparison) tended to bring the SMRs closer to 100.'' (Ex. 17–33, p.14) This finding results from cancer rates along the Texas Gulf coast that are higher than national rates. (Ex. 17–33) In other words, it has been argued that national comparison rates artificially inflate the SMRs, while local rates provide a more accurate picture of the mortality experience of workers with occupational exposure to BD. (Ex. 113, A–50)

Dr. Landrigan captured the essence of this issue in his testimony on cross-examination,

> This is a perennial debate in epidemiology of whether to use local comparison rates or regional or national, and there's [sic] arguments [to] go both ways. (Tr. 1/15/91, p. 154)

He presented several arguments for using national rates. First, U.S. mortality rates are based on the entire population, so they are more stable. Second, national rates are more commonly used, so it is easier to compare results from different studies.

On the other hand, the argument in favor of using local rates centers on the fact that people in a local area may truly be different from the total population or a regional population(s). Thus, comparing a local subpopulation with the entire local population may provide more accurate results. However, the weakness in this argument was highlighted by Dr. Landrigan when he said that,

> * * * if there are factors acting in the local population, such as environmental pollution that may elevate rates in the local area so that they are closer to the rates in the occupationally exposed population, then theoretically at least one could argue that the local population is overmatched, too similar to the employee population and that the use of the national comparison group actually give [sic] a better reflection of reality. (Tr. 1/15/91, p. 155)

In fact, he went on to point out that the BD plants have been identified by the Environmental Protection Agency (EPA) as ''major'' polluters of the local environment with BD. (Tr. 1/15/91, p. 155)

OSHA acknowledges that there are pros and cons to both approaches of reference population selection. However, in the study by Delzell et al. mortality data of the USA cohort subgroup were analyzed using both state, i.e., local, general population rates and USA general population rates. (Ex. 117–1) As previously stated, there was little difference in the overall pattern of these analyses. (Ex. 117–1, p. 60) Additionally, the Santos-Burgoa and Matanoski nested case control study used the most appropriate comparison group of all: Those employed at the same facilities. (Ex. 23–109 and 34–4, Vol. III, H–4) Thus, given the available data in the record, OSHA is of the opinion that it cannot ignore the findings of excess mortality that are based on national comparison rates.

(ix) *Summary and Conclusions.* (a) *Summary.* Table V–4 lists the criteria that can be used to judge the presence of a causal association between occupational exposure to BD and cancer of the lymphohematopoietic system. When the available epidemiologic study results are examined in this way, there is strong evidence for causality. The data fulfill all of the listed criteria: Temporal relationship; consistency;

strength of association; dose-response relationship; specificity of association; biological plausibility; and coherence.

In his testimony, OSHA's epidemiologist expert witness agreed that there is ''definite evidence for the fact that occupational exposure to 1,3–Butadiene can cause human cancer of the hematopoietic and lymphatic organs.'' (Tr. 1/15/91, p. 133) Dr. Weisenburger, OSHA's expert witness in hematopathology, also concluded that ''it would be prudent to treat BD as though it were a human carcinogen.'' (Ex. 39, p. 11)

TABLE V–4.—EVIDENCE THAT 1,3-BUTADIENE IS A HUMAN CARCINOGEN

Criterion for causality	Met by BD
Temporal relationship	Yes.
Consistency	Yes.
Strength of association	Yes.
Dose-response relationship	Yes.
Specificity of association	Yes.
Biological plausibility	Yes.
Coherence	Yes.

(b) *Conclusion.* On the basis of the foregoing analysis, OSHA concludes that there is strong evidence that workplace exposure to BD poses an increased risk of death from cancers of the lymphohematopoietic system. The epidemiologic findings supplement the findings from the animal studies that demonstrate a dose-response for multiple tumors and particularly for lymphomas in mice exposed to BD.

C. Reproductive Effects

In addition to the established carcinogenic effects of BD exposure, various reports have led to concern about the potential reproductive and developmental effects of exposure to BD. The term reproductive effects refers to those on the male and female reproductive systems and the term developmental refers to effects on the developing fetus.

Male reproductive toxicity is generally defined as the occurrence of adverse effects on the male reproductive system that may result from exposure to chemical, biological, or physical agents. Toxicity may be expressed as alterations to the male reproductive organs and/or related endocrine system. For example, toxic exposures may interfere with spermatogenesis (the production of sperm), resulting in adverse effects on number, morphology, or function of sperm. These may adversely affect fertility. Human males produce sperm from puberty throughout life and thus the risk of disrupted spermatogenesis is of concern for the entire adult life of a man.

Female reproductive toxicity is generally defined as the occurrence of adverse effects on the female reproductive system that may result from exposure to chemical, biological, or physical agents. This includes adverse effects in sexual behavior, onset of puberty, ovulation, menstrual cycling, fertility, gestation, parturition (delivery of the fetus), lactation or premature reproductive senescence (aging).

Developmental toxicity is defined as adverse effects on the developing organism that may result from exposure prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Developmental effects induced by exposures prior to conception may occur, for example, when mutations are chemically induced in sperm. If the mutated sperm fertilizes an egg, adverse developmental effects may be manifested in developing fetuses. Mutations may also be induced in the eggs. The major manifestations of developmental toxicity include death of the developing fetus, structural abnormality, altered growth and function deficiency.

To determine whether an exposure condition presents a developmental or reproductive hazard, there are two categories of research studies on which to rely: Epidemiologic, or studies of humans, and toxicologic, or experimental studies of exposed animals or other biologic systems.

Many outcomes such as early embryonic loss or spontaneous abortion are not easily detectable in human populations. Further, some adverse effects may be quite rare and require very large study populations in order to have adequate statistical power to detect an effect, if in fact one is present. Often, these populations are not available for study. In addition, there are fewer endpoints which may be feasibly measured in humans as compared to laboratory animals. For example, early embryonic loss is difficult to measure in the study of humans, but can be measured easily in experimental animals. There are no human studies available to address reproductive and developmental effects of BD exposure to workers. Thus, evidence on the reproductive and developmental toxicity of BD comes from toxicologic studies performed using primarily mice.

Animal studies have proved useful for studying reproductive/developmental outcomes to predict human risk. A very important advantage to the toxicological approach is the ability of the experimenter to fully quantitate the exposure concentration and conditions of exposure. Although extrapolation of risk to humans on a qualitative basis is accepted, quantitative extrapolation of study results is more complex.

In his testimony, OSHA's witness, Dr. Marvin Legator, an internationally recognized genetic toxicologist from the University of Texas Medical Branch in Galveston, cautioned that in assessing risk ''humans in general have proven to be far more sensitive than animals * * * to agents characterized as developmental toxicants.'' (Ex. 72) He also noted that ''of the 21 agents considered to be direct human developmental toxins, in 19 * * * the human has been shown to be more sensitive than the animal * * *'' He also pointed to the possibility that sub-groups of the human population may be even more highly sensitive than the population average.

OSHA believes that the animal inhalation studies designed to determine the effect of BD on the reproduction and development of these animals indicate that BD causes adverse effects in both the male and female reproductive systems and produces adverse developmental effects. These studies are briefly summarized and discussed below.

Toxicity to Reproductive Organs

In the first NTP bioassay, an increased incidence of testicular atrophy was observed in male mice exposed to BD atmospheric concentrations of 625 ppm. (Ex. 23–1) In female mice, an increased incidence of ovarian atrophy was observed at 625 and 1,250 ppm. These adverse effects were confirmed in reports of the second NTP study, which used lower exposure concentrations. The latter lifetime bioassay exposed male and female B3C6F1 mice to 0, 6.25, 20, 62.5, 200, and 625 ppm BD. (Ex. 114, p 115) See Table V–5. Testicular atrophy in males was significantly increased at the highest dose tested, 625 ppm, and reduced testicular weight was observed from BD exposures of 200 ppm. (Ex. 96) These latter data are not shown in the Table. In female mice at terminal sacrifice, 103 weeks, ovarian atrophy was significantly increased at all exposure levels including the lowest dose tested, 6.25 ppm, compared with controls. Evidence of ovarian toxicity was also seen during interim sacrifices, but in these cases was the result of higher exposure levels. After 65 weeks of exposure, 90% of the mice exposed to 62.5 ppm experienced ovarian atrophy.

TABLE V–5.—OVARIAN AND TESTICULAR ATROPHY IN MICE EXPOSED TO BD

Lesion	Weeks of exposure	Exposure concentration (ppm)					
		0	6.25	20	62.5	200	625
		Incidence (%)					
Testicular atrophy	40	0/10(0)	NE	NE	NE	0/10(0)	6/10(60)
	65	0/10(0)	NE	NE	NE	0/10(0)	4/7(57)
	103	1/50(2)	3/50(6)	4/50(8)	2/48(4)	6/49(12)	53/72(74)
Ovarian atrophy	40	0/10(0)	NE	NE	0/10(0)	9/10(90)	8/8(100)
	65	0/10(0)	0/10(0)	1/10(10)	9/10(90)	7/10(70)	2/2(100)
	103	4/49(8)	19/49(39)	32/48(67)	42/50(84)	43/50(86)	69/79(87)

NE, not examined microscopically.
Source: Ex. 114.

Extensive comments on the BD induced ovarian atrophy were received from Dr. Mildred Christian, a toxicologist who offered testimony on behalf of the Chemical Manufacturers Association. She questioned the relevance of using the data from studies of mice to extrapolate risk of ovarian atrophy to humans because most of the evidence was observed among the animals who were sacrificed after the completion of the species reproductive life and only after prolonged exposure to 6.25 ppm and 20 ppm (Ex. 118–13, Att 3, p. 4) On the other hand, Drs. Melnick and Huff, toxicologists from the National Institute of Environmental Health Sciences stated that: ''Even though ovarian atrophy in the 6.25 ppm group was not observed until late in the study when reproductive senescence likely pertains, the dose-response data clearly establish the ovary as a target organ of 1,3-butadiene toxicity at concentrations as low as 6.25 ppm, the lowest concentration studied.'' (Ex. 114, p. 116) In addition, it should be noted that an elevated incidence of ovarian atrophy was observed at periods of interim sacrifice of female mice exposed to 20 ppm that took place at the 65 week exposure period, a time prior to the ages when senescence would be expected to have occurred. NIOSH also accepted Dr. Melnick's view that mice exposed to 6.25 ppm BD demonstrated ovarian atrophy. (Ex. 32–35) OSHA remains concerned about the ovarian atrophy demonstrated at low exposure levels in the NTP study. Thus, OSHA concludes that exposure to relatively low levels of BD resulted in the induction of ovarian atrophy in mice.

Sperm-Head Morphology Study

NTP/Battelle investigators also described sperm head morphology findings using $B6C3F_1$ mice exposed as described in the dominant lethal study mentioned below, e.g., exposures to 200, 1000 and 5000 ppm BD. The mice were sacrificed in the fifth week post-exposure and examined for gross lesions of the reproductive system. (Ex. 23–75) The study authors chose this interval as having the highest probability for detecting sperm abnormalities. Epididymal sperm suspensions were examined for morphology. The percentage of morphologically abnormal sperm heads was significantly increased in the mice exposed at 1,000 ppm and 5,000 ppm, but not for those exposed to 200 ppm. The study authors concluded that ''these significant differences in the percentage of abnormalities between control mice and males exposed to 1000 and 5000 ppm [BD] indicated that their late spermatogonia or early spermatocytes were sensitive to this chemical.'' (Ex. 23–75, p. 16)

In reviewing this study, Dr. Mildred Christian stated that these results are not necessarily correlated with developmental abnormalities or reduced fertility and are ''reversible in nature'' and that the observed differences are ''biologically insignificant.'' (Ex. 76, p. 14) In its submission, the Department of Health Services of California said: ''A conclusion as to the reproductive consequences of these abnormalities cannot be made from this study.'' (Ex. 32–168) In reviewing Dr. Christian's comments, OSHA is in agreement that the observation of a significant excess of sperm head abnormalities as a result of BD exposure is not necessarily correlated with the development of abnormal fetuses or of reduced fertility; however, the Anderson study, which did evaluate fetal abnormality and reduced fertility, demonstrated a significant excess of both fetal abnormality plus early and late fetal mortality as a result of male mice exposure to BD. (Ex. 117–1, P. 171) These observations of fetal mortality could only occur as a result of an adverse effect on the sperm. In response to Dr. Christian's comment that the sperm head abnormality observed in the study is reversible, the reversibility would be dependent upon cessation of exposure. Since workers may be exposed to BD on a daily basis, the significance of reversibility may be moot.

Developmental Toxicity

Dominant Lethal Studies

A dominant lethal study was conducted by Battelle/NTP to assess the effects of a 5-day exposure of male CD–1 mice to BD atmospheric concentrations of 0, 200, 1,000 and 5,000 ppm BD for 6 hours per day on the reproductive capacity of the exposed males during an 8-week post-exposure period. (Ex 23–74) If present, dominant lethal effects are expressed as either a decrease in the number of implantations or as an increase in the incidence of intrauterine death, or both, in females mated to exposed males. Dominant lethality is thought to arise from lethal mutations in the germ cell line that are dominantly expressed through mortality to the offspring. In this study, the only evidence of toxicity to the adult male mouse was transient and occurred over a 20 to 30 minute period following exposure at 5,000 ppm. Males were then mated to a different female weekly for 8 weeks. After 12 days, females were killed and examined for reproductive status. Uteri were examined for number, position and status of implantation. Females mated to the BD-exposed males during the first 2 weeks post-exposure were described as more likely than control animals to have increased numbers of dead implantations per pregnancy.

For week one, the percentage of dead implantations in litters sired by males exposed to 1,000 ppm was significantly higher than controls. There were smaller increases at 200 ppm and 1000 ppm that were not statistically significant. The percentage of females with two or more dead implantations was significantly higher than the control value for all three exposure groups. For week two, the numbers of dead implantations per

pregnancy in litters sired by males exposed to 200 ppm and 1000 ppm were also significantly increased, but not for those exposed to 5000 ppm. No significant increases in the end points evaluated were observed in weeks three to eight. These results suggested to the authors that the more mature cells (spermatozoa and spermatids) may be adversely altered by exposure to BD. (Ex. 23–74)

The State of California Department of Health Services concluded that the above mentioned study showed no adverse effect from exposure to BD, with the possible exception of the increase in intrauterine death seen as a result of male exposures to 1000 ppm BD at the end of one week post exposure. (Ex. 32–16) Since values for the 5000 ppm exposure group were not significantly elevated for this same period of follow up, the California Department of Health thought the biological significance of the results of the 1000 ppm exposure was questionable. (Ex. 32–16) On the other hand, Dr. Marvin Legator stressed the low sensitivity of the dominant lethal assay which, he felt was due to the endpoint-lethality. He expressed the opinion that the studies were ''consistent with an effect on mature germ cells.'' (Ex. 72) He felt that since an effect was observable in this relatively insensitive assay that only the ''tip of the iceberg'' was observed, and that ''[t]ransmissible genetic damage, displaying a spectrum of abnormal outcomes can be anticipated at concentrations (of BD) below those identified in the dominant lethal assay procedure.'' (Ex. 72, p. 17)

The dominant lethal effect of BD exposure was more recently confirmed by Anderson et al. in 1993. (Ex. 117–1, p. 171) They studied CD–1 mice using a somewhat modified study design. Two exposure regimens were used. In the first, ''acute study,'' male mice were exposed to 0 (n=25), 1250 (n=25), or 6250 (n=50) ppm BD for 6 hours only. Five days later they were caged with 2 untreated females. One female was allowed to deliver her litter and the other was killed on day 17 of gestation and examined for the number of live fetuses, number of early and late post-implantation deaths and the number and type of any gross malformation. The authors stated that sacrifice on day 17 (rather than the standard days 12 through 15) allowed examination of near-term embryos for survival and abnormalities. The mean number of implants per female was reduced compared with controls at both concentrations of BD, but was statistically significant only at 1250 ppm. Neither post-implantation loss nor fetal abnormalities were significantly increased at either concentration. The authors concluded that ''a single 6-hour acute exposure to butadiene was insufficient to elicit a dominant lethal effect.'' (Ex. 117–1, p. 171)

In the second phase of the study, the ''subchronic study,'' CD–1 mice were exposed to 0 (n=25), 12.5 (n=25), or 1250 (n=50) ppm BD for 6 hours per day, 5 days per week, for 10 weeks. They were then mated. The higher 1250 ppm BD exposure resulted in significantly reduced numbers of implantations and in significantly increased numbers of dominant lethal mutations expressed as both early and late deaths. See Table V–6. Non-lethal mutations expressed as birth abnormalities were also observed in live fetuses (3/312; 1 hydrocephaly and 2 runts).

The lower exposure (12.5 ppm) did not result in decreases in the total number of implants, nor in early deaths; however, the frequencies of late deaths and fetal abnormalities (7/282; 3 exencephalies in 1 litter and one in another, two runts and one with blood in the amniotic sac) were significantly increased.

The authors felt that their finding of increased late deaths and fetal abnormalities at a subchronic, low exposure of 12.5 ppm was the main new finding of the study. They noted that these adverse health effects were increased 2–3 fold over historical controls. In evaluating these latter two studies OSHA notes that while there was no demonstrable effect on dominant lethality as a result of a single exposure to 1250 ppm BD, subchronic exposure to 12.5 ppm, the lowest dose tested, resulted in the induction of dominant lethal mutations and perhaps non-lethal mutations. (Ex 117–1, p 171) OSHA has some reservations about whether or not the fetal abnormalities observed in the Anderson et al. ''subchronic'' study were actually caused by non-lethal mutations or by some other mechanism because they were observed in only a few of the litters produced by the mice. (Ex. 117–1, p. 171)

TABLE V–6.—EFFECT OF BD ON REPRODUCTIVE OUTCOMES IN CD–1 MICE

	Implantations		Early deaths		Late deaths		Late deaths including dead fetuses		Abnormal fetuses	
	No.	Mean	No.	Mean [a]	No.	Mean [a]	No.	Mean [a]	No.	Mean [a]
Control	278	12.09±1.276	13	0.050±0.0597	0		2	0.007±0.0222	0	
12.5	306	12.75±2.507	16	0.053±0.0581	7	0.23**±0.038	8	0.026±0.0424	[b]7	0.024*±0.062
1250 ppm ...	406	10.68**±3.103	87	0.204***±0161	6	0.014***±0.0324	7	0.016±0.339	[c]3	0.011**±0.043≤

* Significantly different from control at: *p≤0.05; **p≤0.01; ***p≤0.001 (by analysis of variance and least significance test on arc-sine transform data).

[a] Per implantation.

[b] Four exencephalies (three in one litter), two runts (≤70% and 60% of mean body weight of others in litter; total litter sizes 7 and 9, respectively one fetus with blood in amniotic sac but no obvious gross malformation (significance of difference not altered if this fetus is excluded).

[c] One hydrocephaly, two runts (71% and 75% of mean body weight of others in litter; total litter sizes; 2 and 11, respectively).

A dominant lethal test was also performed by Adler et al. (Ex. 126) Male(102/E1XC3H/E1)F_1 male mice were exposed to 0 and 1300 ppm BD. They were mated 4 hours after the end of exposure with untreated virgin females. Females were inspected for the presence of a vaginal plug every morning. Plugged females were replaced by new females. The mating continued for four consecutive weeks. At pregnancy day 14–16 the females were killed and uterus contents were evaluated for live and dead implants. Exposure of male mice to 1300 ppm BD caused an increase of dead implants during the first to the third mating week after 5 days of exposure. The dead implantation rate was significantly different from the concurrent controls only during the second mating week. Adler et al. concluded that dominant lethal mutations were induced by BD in spermatozoa and late stage spermatids and that these findings confirmed the results of the Battelle/NTP study which showed effects on the same stages of

sperm development. (Ex. 23–74) The authors were of the opinion that BD may induce heritable translocations in these germ cell stages.

The earliest reproductive study reported on BD was conducted by Carpenter et al. in 1944. (Ex. 23–64) In this study, male and female rats were exposed by inhalation to 600, 2,300 or 6,700 ppm BD, 7.5 hours per day, six days per week for an 8-month period. Although this study was not specifically designed as a reproductive study, the fertility and the number of progeny were recorded. No significant effects due to BD exposure were noted for either the number of litters per female animal or for the number of pups per litter.

In the Hazelton study, Sprague-Dawley (SD) rats were exposed by inhalation to 0, 200, 1,000 or 8,000 ppm BD on days 6 though 15 of gestation. (Ex. 2–32) There were dose-related effects on maternal body weight gain, fetal mean weight and crown-to-rump length. Post-implantation loss was slightly higher in all BD-exposed groups. In addition, there were significant increases in hematoma in pups in the 200 and 1,000 ppm exposure groups. In the 8,000 ppm exposure group, a significantly increased number of pups had lens opacities and there was an increased number of opacities per animal. According to the authors, the highest exposure groups also had a significantly increased number of fetuses with skeletal variants, a higher incidence of bipartite thoracic centra, elevated incidence of incomplete ossification of the sternum, higher incidence of irregular ossification of the ribs, and ''other abnormalities of the skull, spine, long bones, and ribs.'' The authors concluded that the fetal response was not indicative of a teratogenic effect, but was the result of maternal toxicity.

In the Battelle/NTP study, pregnant Sprague-Dawley (SD) rats and pregnant Swiss mice were exposed to 0, 40, 200, or 1,000 ppm BD for 6 hours per day from day 6 through day 15 of gestation. (Ex. 23–72) Animals were sacrificed and examined one day before expected delivery. In the rat, very little effect was noted; in the 1,000 ppm exposure group only there was evidence of maternal toxicity, i.e., depressed body weight gains during the first 5 days of exposure. No evidence of developmental toxicity was observed in the SD rats evaluated in the study, e.g., the number of live fetuses per litter and the number of intrauterine deaths were within normal limits.

In the mouse, exposure to the above mentioned concentrations did not result in significant maternal toxicity, with the exception of a reduction in extra-gestational weight gain for the 200 ppm and 1000 ppm BD exposed dams. In the female mice, there was a significant depression of fetal body weight only at the 200 and 1,000 ppm exposure levels. Fetal body weight for male pups was reduced at all exposure concentrations, including the 40 ppm exposure level, even though evidence of maternal toxicity was not observed at this exposure concentration. No significant differences were noted in incidence of malformations among the groups. However, the incidence of supernumerary ribs and reduced ossification of sternebrae was significantly increased in litters of mice exposed to 200 and 1,000 ppm BD.

In reviewing these data, Drs. Melnick and Huff noted that since maternal body weight gain was reduced at the 200 and 1000 ppm exposure levels and body weights of male fetuses were reduced at the 40, 200, and 1000 exposure levels ''[t]he male fetus is more susceptible than the dam to inhaled 1,3-butadiene.'' (Ex. 114, p. 116) They further stated that ''the results of the study in mice reveal that a toxic effect of 1,3-butadiene was manifested in the developing organism in the absence of maternal toxicity.'' On the basis of this study, the authors concluded that ''1,3-butadiene does not appear to be teratogenic in either the rat or the mouse, but there is some indication of fetotoxicity in the mouse.'' (Ex. 23–72)

On the other hand, Dr. Mildred Christian was of the opinion that the significant decrease in male mouse fetal weight gain in the 40 ppm exposure group was not a selective effect of BD on the conceptus, but rather was a result of the statistical analysis used which she considered inappropriate. (Ex. 118–13, Att. 3, p. 6) She was also of the opinion that the larger litter sizes in the 40 ppm exposure group as compared with the control group contributed to the statistical finding. Dr. Christian, however, did not present any specific information on the type of analysis used for statistical testing that she thought made the results inappropriate. In general, one would expect that the evaluation of data from larger litter sizes would give one more confidence in the statistical findings.

In reviewing the same study, the State of California, Department of Health Services was more cautious. It stated that ''The increased incidence of reduced ossifications and the fetal weight reductions in the absence of apparent maternal toxicity in the 40- and 200-ppm groups is evidence of fetotoxicity * * * in the Swiss (CD–1) mouse.'' After reviewing the study results and arguments about the study, OSHA concluded that the NTP study provides evidence of fetotoxicity in the mouse. (Ex. 23–72)

Mouse spot test

Adler et al. (1994) conducted a spot test in mice. (Ex. 126) The spot test is an *in vivo* method for detecting somatic cell mutations. A mutation in a melanoblast is detected as a coat color spot on the otherwise black fur of the offspring. Pregnant females were exposed to 0 or 500 ppm BD for 6 hours per day on pregnancy days 8, 9, 10, 11 and 12. They were allowed to come to term and to wean their litters. Offspring were inspected for coat color spots at ages 2 and 3 weeks. Gross abnormalities were also recorded. Exposure to a concentration of 500 ppm did not cause any embryotoxicity, nor were gross abnormalities observed. The BD exposure, however, significantly increased the frequency of coat color spots in the offspring. This study demonstrates that BD exposure is capable of causing transplacentally induced somatic cell mutations that can result in a teratogenic effect in mice.

Summary of Reproductive and Developmental Effect

OSHA has limited its discussion on reproductive and developmental hazards to a qualitative evaluation of the data. This approach was chosen because no generally accepted mathematical model for estimating reproductive/developmental risk on a quantitative basis was presented during the rulemaking. For example, the CMA Butadiene panel disagreed with OSHA's findings in the proposal regarding the potential reproductive and developmental risks presented by BD exposure using an uncertainty factor approach. (See Ex. 112) They cited Dr. Christian's conclusion that the mouse possessed a ''special sensitivity'' to BD and should not be used as a model on which to base risk estimates.

The agency has determined, however, that animal studies, taken as a whole, offer persuasive qualitative evidence that BD exposure can adversely effect reproduction in both male and female rodents. The Agency also notes that BD is mutagenic in both somatic and germ cells. (Ex. 23–71; Ex. 114; Ex. 126)

Some evidence of maternal and developmental toxicity was seen in rats exposed to BD, but the concentrations used were much higher than those that elicited a response in mice. (Ex. 118–13, Att. 3, p. 2) In mice, evidence of fetotoxicity was observed in either the presence or absence of maternal toxicity, the latter evidence being

provided by decreased fetal body weight in male mice whose dams were exposed to 40 ppm BD, the lowest dose tested in the study. In addition, a teratogenic effect was observed in mice (coat color spot test) as a result of transplacentally induced somatic cell mutation.

OSHA is also concerned about the observation of a significant excess of sperm head abnormalities as a result of BD exposure, even though this expression of toxicity is not necessarily correlated with the development of abnormal fetuses or of reduced fertility. The Anderson study, which did evaluate reduced fertility and fetal abnormality, demonstrated a significant excess of both early and late fetal mortality and perhaps fetal abnormality as a result of male mice exposure to BD. (Ex. 117–1, P. 171) This observation could only occur as a result of an adverse effect on the sperm. Two additional studies also provide evidence of dominant lethality as a result of male exposure to BD. (Ex. 23–74; Ex. 126) The observation of germ cell effects is supported by additional evidence of genotoxicity in somatic cells, as demonstrated by positive results in the micronucleus test and in the mouse spot test. (Ex. 126)

Some of the adverse effects related to reproductive and developmental toxicity in the mouse, e.g., ovarian atrophy, testicular atrophy, reduced testicular weight, abnormal sperm heads, dominant lethal effects, were acknowledged by Dr. Christian, but she urged the Agency not to rely on these findings because of negative study results in other species, or because positive findings in other species required much higher exposure levels. (Ex. 118–13, Att. 3, p. 1)

For example, a CMA witness has argued that the diepoxide is responsible for the ovarian atrophy observed in relation to low level BD exposure (6.25 ppm). (Ex. 118–13, Att. 3) However, the monoepoxide could also play a role in the ovarian atrophy and evidence indicates that humans can form the monoepoxide of BD and that humans have the enzymes present that could cause conversion to the diepoxide. Therefore on a qualitative basis, the observation of ovarian atrophy in the mouse is meaningful in OSHA's view. In addition, the metabolic factors related to testicular atrophy, malformed sperm and dominant lethal mutations in the mouse are not known. (See section on *in vitro* metabolic studies.) These observations further support the findings in mice as being meaningful for humans on a qualitative basis. The mouse spot test which demonstrates a somatic cell mutation leading to a teratogenic effect inconsistent with data showing the ability of BD to cause adverse effects on chromosomes and *hprt* mutations in humans exposed to BD.

OSHA also notes that studies of workers exposed to low concentrations of BD demonstrated a significant excess of chromosomal breakage and an inability to repair DNA damage. Thus, BD exposure seems capable of inducing genetic damage in humans as a result of low level exposure. Therefore, the mouse studies which demonstrate genetic damage (mutations) in both somatic and germinal cells seem to be a better model on a qualitative basis than the rat for predicting these adverse effects in humans.

D. Other Relevant Studies

1. Acute Hazards

At very high concentrations, BD produces narcosis with central nervous system depression and respiratory paralysis. (Ex. 2–11) LC_{50} values (the concentration that produces death in 50 percent of the animals exposed) were reported to be 122,170 ppm (12.2% v/v) in mice exposed for 2 hours and 129,000 ppm (12.9% v/v) in rats exposed for 4 hours. (Ex. 2–11, 23–91) These concentrations would present an explosion hazard, thus limiting the likelihood that humans would risk any such exposure except in extreme emergency situations. Oral LD_{50} values (oral dose that results in death of 50 percent of the animals) of 5.5 g/kg body weight for rats and 3.2 g/kg body weight for mice have been reported. (Ex. 23–31) These lethal effects occur at such high doses that BD would not be considered ''toxic'' for purposes of Appendix A of OSHA's Hazard Communication Standard (29 CFR 1910.1200), which describes a classification scheme for acute toxicity based on lethality data.

At concentrations somewhat above the previous permissible exposure level of 1,000 ppm, BD is a sensory irritant. Concentrations of several thousand ppm were reported to cause irritation to the skin, eyes, nose, and throat. (Ex. 23–64, 23–94) Two human subjects exposed to BD for 8 hours at 8000 ppm reported eye irritation, blurred vision, coughing, and drowsiness. (Ex. 23–64)

2. Systemic Effects

In the preamble to the proposal, OSHA reviewed the literature to discern the systemic effects of BD exposure. (55 FR 32736 at 32755) OSHA discussed an IARC review which briefly examined several studies from the former Soviet Union. In these, various adverse effects, such as hematologic disorders, liver enlargement and liver and bile-duct diseases, kidney malfunctions, laryngotracheitis, upper respiratory tract irritation, conjunctivitis, gastritis, various skin disorders and a variety of neurasthenic symptoms, were ascribed to occupational exposure to BD. (Ex. 23–31) OSHA and IARC have found these studies to be of limited use primarily due to their lack of exposure information. Except for sensory irritant effects and hematologic changes, evidence from studies of other exposed groups have failed to confirm these observations.

Melnick and Huff summarized the observed non-neoplastic effects of BD exposure in the NTP I and NTP II mouse bioassays. They listed the following effects associated with exposure of B6C3F [1] mice to BD for 6 hours per day 5 days per week for up to 65 weeks:

> * * * epithelial hyperplasia of the forestomach, endothelial hyperplasia of the heart, alveolar epithelial hyperplasia, hepatocellular necrosis, testicular atrophy, ovarian atrophy and toxic lesions in nasal tissues (chronic inflammation, fibrosis, osseous and cartilaginous metaplasia, and atrophy of the olfactory epithelium.) (Ex. 114, p. 114)

They noted that the nasal lesions were seen only in the group of male mice exposed to 1250 ppm BD and that no tumors were observed at this site. Further, Melnick and Huff suggested that some of the proliferative lesions observed in the bioassay might represent pre-neoplastic changes.

The findings of testicular and ovarian atrophy are discussed more fully in the Reproductive Effects section of this preamble,.

Nephropathy, or degeneration of the kidneys, was the most common non-carcinogenic effect reported for male rats in the Hazelton Laboratory Europe (HLE) study in which rats were exposed to 1000 or 8000 ppm BD for 6 hours per day, 5 days per week for up to 2 years. Nephropathy was one of the main causes of death for the high dose males. (Ex. 2–31, 23–84) The combined incidence of marked or severe nephropathy was significantly elevated in the high dose group over incidence in the low dose group and over incidence in the controls ($p<.001$). HLE's analysis of ''certainly fatal'' nephropathy shows a significant dose-related trend ($p<.05$), but when ''uncertainly fatal'' cases were included, the trend disappeared.

The HLE study authors concluded that the interpretation of the nephropathy incidence data was equivocal. They stated that ''an increase in the prevalence of the more severe grades of nephropathy, a common age-

related change in the kidney, was considered more likely to be a secondary effect associated with other unknown factors and not to represent a direct cytotoxic effect of the test article on the kidney.''

Upon reviewing the HLE rat study for the proposed rule, OSHA expressed concern that only 75% of the low-dose male rats in the HLE study exhibited nephropathy, while 87% of the control rats had some degree of nephropathy, suggesting low-dose male rats were less susceptible to kidney degeneration than control rats, thereby decreasing the comparability between rats in the low-dose and control groups. (55 FR 32736 at 32744) Dr. Robert K. Hinderer, in testifying for the CMA BD Panel, countered that the NTP I mouse study also had ''selected instances where the response in the test group (was) lower than that in the controls'' and that ''* * * (o)ne cannot look at single or a few individual site responses to evaluate the health status or overall effect of the chemical.'' (Ex. 51) OSHA agrees that there may be some variability in background response rates for specific outcomes. However, the Agency believes that it is important to assess the impact of the variability in background response rates when drawing conclusions about dose-related trends in the data. This was not done in the HLE study nephropathy analysis.

Other non-carcinogenic effects observed in the HLE rat study were elevated incidence of metaplasia in the lung of high dose male rats at terminal sacrifice as compared with incidence in male controls at terminal sacrifice, and a significant increase in high dose male rat kidney, heart, lung, and spleen weights over the organ weights in control male rats.

3. Bone Marrow Effects

There was a single study of BD-exposed humans discussed in the proposal—a study by Checkoway and Williams that examined 163 hourly production workers who were employed at the SBR facility studied by McMichael et al.. (described more fully in the Epidemiology Section of this Preamble.) (Ex. 23–4, 2–28).

Exposure to BD, styrene, benzene, and toluene was measured in all areas of the plant. BD and styrene concentrations, 20 (0.5–65) ppm and 13.7 (0.14–53) ppm, respectively, were considerably higher in the Tank Farm than in other departments. In contrast, benzene exposures, averaging 0.03 ppm, and toluene concentrations, averaging 0.53 ppm, were low in the Tank Farm. The authors compared the hematologic profiles of Tank Farm workers (n=8) with those of the other workers examined.

The investigation focused on two potential effects, bone marrow depression and cellular immaturity. Bone marrow depression was suspected if there were lower levels of erythrocytes, hemoglobin, neutrophils, and platelets. Cellular immaturity was suggested by increases in reticulocyte and neutrophil band form values.

Although the differences were small, adjusted for age and medical status, hematologic parameters in the Tank Farm workers differed from those of the other workers. Except for total leukocyte count, the hematologic profiles of the Tank Farm workers were consistent with an indication of bone marrow depression. The Tank Farm workers also had increases in band neutrophils, a possible sign of cellular immaturity, but no evidence that increased destruction of reticulocytes was the cause.

While acknowledging the limitations of the cross-sectional design of the study, the authors felt, nevertheless, that their results were ''suggestive of possible biological effects, the ultimate clinical consequences of which are not readily apparent.'' OSHA finds any evidence of hematological changes in workers exposed at BD levels well below the existing permissible limit (1000 ppm) to be of concern since such information suggests the inadequacy of the present exposure limit. However, this cross-sectional study involved only 8 workers with relatively high levels of exposure to BD and low levels of exposure to benzene, so it is quite insensitive to minor changes in hematologic parameters.

In a review of BD-related studies, published in 1986, an IARC Working Group felt the study of Checkoway and Williams could not be considered indicative of an effect of BD on the bone marrow (Ex. 2–28). In 1992, IARC concluded that the ''changes cannot be interpreted as an effect of 1,3-butadiene on the bone marrow particularly as alcohol intake was not evaluated.'' (Ex. 125, p. 262)

In light of the more recent animal studies that were not available to IARC, however, OSHA believes that the bone marrow is a target of BD toxicity. Furthermore, the fact that changes in hematologic parameters could be distinguished in workers exposed to BD at 20 ppm indicates that such measurements may prove a sensitive indicator of excessive exposure to BD.

In testimony for the CMA BD Panel, Dr. Michael Bird stated his conclusion that the hematological differences between the 8 tank farm workers and the lesser exposed group of workers was not ''statistically significant by the usual conventional statistics.'' (Tr. 1/18/1991, p. 1078) He believed that although the raw data were not available, the reported means were within the historical and expected range for these parameters. (Tr. 1/18/1991, p., 1078) In contrast, OSHA concludes from this study that the hematologic differences observed in BD-exposed workers, although small, are suggestive of an effect of BD on human bone marrow under occupational exposure conditions.

Thus OSHA considers the Checkoway and Williams study to be suggestive of hematologic effects in humans, but does not regard it as definitive. No other potential systemic effects of BD exposure on this population were addressed in the Checkoway and Williams study.

In 1992, Melnick and Huff reviewed the toxicologic studies of BD exposure in laboratory animals. (Ex. 114) Only slight to no systemic effects were observed in an early study of rats, guinea pigs, rabbits and a dog exposed to BD up to 6,700 ppm daily for 8 months. (Ex. 23–64) The study of Sprague Dawley rats exposed to doses of BD up to 8,000 ppm daily for 13 weeks also did not result in hematologic, biochemical, neuromuscular, nor urinary effects. However, there were marked effects seen in exposed mice.

Epidemiologic studies of the styrene-butadiene rubber (SBR) industry suggest that workers exposed to BD are at increased risk of developing leukemia or lymphoma, two forms of hematologic malignancy (see preamble section on epidemiology). Consequently, investigators have looked for evidence of hematopoietic toxicity resulting from BD exposure in animals and in workers. For example, Irons and co-workers at CIIT found that exposure of male $B6C3F_1$ mice to 1,250 ppm of BD for 6–24 weeks resulted in macrocytic-megaloblastic anemia, an increase in erythrocyte micronuclei and leukopenia, principally due to neutropenia. Bone marrow cell types overall were not altered, but there was an increase in the number of cells in the bone marrow of exposed mice due to an increase in DNA synthesis. (Ex. 23–12)

Melnick and Huff also reviewed the available information on bone marrow toxicity. (Ex. 114, p. 114) Table V–7 represents the reported findings of a study of 10 $B6C3F_1$ mice sacrificed after 6.25–625 ppm exposure to BD for 40 weeks. The authors concluded that these data demonstrated a concentration-dependent decrease in red blood cell number, hemoglobin concentration, and packed red cell

volume at BD exposure levels from 62.5 to 625 ppm. The effects were not observed at 6.25 and 20 ppm exposure levels. Melnick and Kohn also noted the increase in mean corpuscular volume in mice exposed at 625 ppm, and suggested that this and other observations (such as those of Tice (Ex. 32–38D)) who observed a decrease in the number of dividing cells in mice and decreased rate of their division), suggested that BD exposure led to a suppression of hematopoiesis in bone marrow. Melnick and Huff concluded that this, in turn, led to release of large immature cells from sites such as the spleen, which was considered indicative of macrocytic megaloblastic anemia by Irons. They concluded that these findings ''(establish) the bone marrow as a target of 1,3-butadiene toxicity in mice.'' (Ex. 114, p. 115)

TABLE I.—HEMATOLOGIC CHANGES IN MALE B6C3F$_1$ MICE EXPOSED FOR 6 HOURS/DAY, 5 DAYS/WEEK FOR 40 WEEKS

BD exposure (ppm)	Red blood cell count ($\times 10^6$/ul)	Hemoglobin conc. (g/dl)	Volume packed RBC (ml/dl)	Mean corpuscular vol
0	10.4±0.3	16.5±0.4	48.1±1.5	46.3±0.8
6.25	10.3±0.3	16.4±0.5	47.8±1.7	46.4±1.0
20	10.4±0.4	16.7±0.7	48.2±2.2	46.3±0.8
62.5	[a] 9.9±0.4	[a] 15.9±0.6	[a] 45.9±2.1	46.7±1.2
200	[a] 9.6±0.5	[a] 15.6±0.9	[a] 45.4±2.7	47.2±1.0
625	[a] 7.6±1.2	[a] 13.5±1.8	[a] 39.9±5.3	[a] 53.2±2.9

Adapted from Melnick and Huff, Exhibit 114.
[a] Different from chamber control (0 ppm), P<0.05. Results of treated groups were compared to those of control groups using Dunnett's t-test.

4. Mutagenicity and Other Genotoxic Effects

OSHA discussed the genotoxic effects of BD exposure in some detail in the proposal. (55 FR 32736 at 32760) Briefly, BD is mutagenic to *Salmonella typhimurium* strains TA 1530 and TA 1535 when activated with S9 liver fraction of Wistar rats treated with phenobarbital or Arochlor 1254. These bacterial strains are sensitive to base-pair substitution mutagens. Since the liver fraction is required to elicit the positive mutagenic response, BD is not a direct-acting mutagen and likely must be metabolized to an active form before becoming mutagenic in this test system. IARC published an extensive list of ''genetic and related effects of 1,3-butadiene.'' (Ex. 125) They noted in summarizing the data that BD was negative in tests for somatic mutation and recombination in *Drosophila,* and that neither mouse nor rat liver from animals exposed to 10,000 ppm BD showed evidence of unscheduled DNA synthesis.

As OSHA described in the proposed rule, and Tice et al. reported in 1987, BD is a potent *in vivo* genotoxic agent in mouse bone marrow cells that induced chromosomal aberrations and sister chromatid exchange in marrow cells and micronuclei in peripheral red blood cells. (55 FR 52736 at 52760) Some of these effects were evident at exposures as low as 6.25 ppm (6 hours/day, 10 days). However, similar effects were not observed in rat cells exposed to higher levels of BD (10,000 ppm for 2 days).

Sister chromatid exchange is a recombinational event in which nucleic acid is exchanged between the two sister chromatids in each chromosome. It is thought to result from breaks or nicks in the DNA. Irons et al. described micronuclei as ''* * * chromosome fragments or chromosomes remaining as the result of non-dysjunctional event. Their presence in the circulation is frequently associated with megaloblastic anemia.'' (Ex. 23–12).

In a subsequent study, Filser and Bolt exposed B6C3F$_1$ mice to the same 3 concentrations of BD, 6.25, 62.5 or 625 for 6 hours/day, 5 days/week, for 13 weeks. (Ex. 23–10) Peripheral blood samples were taken from 10 animals per group and scored for polychromatic erythrocytes (PCE) and micronucleated normochromatic erythrocytes (MN–NCE). The MN–NCE response, which reflects an accumulated response, was significantly increased in both sexes at all concentrations of BD, including 6.25 ppm.

Certain metabolites of BD also produce genotoxic effects. These are detailed in a number of reviews (see for example, Ex. 114, 125). Briefly, epoxybutene (the monoepoxide) is mutagenic in bacterial systems in the absence of exogenous metabolic activation. Epoxybutene also reacts with DNA, producing two structurally identical adducts and has been shown to induce sister chromatid exchanges in Chinese hamster ovary cells and in mouse bone marrow *in vivo.*

IARC in its review concluded that the diepoxide, 1,2,:3,4-diepoxybutane, induced DNA crosslinks in mouse hepatocytes and, like epoxybutene, is mutagenic without metabolic activation. As discussed below, BD diepoxide also induced SCE and chromosomal aberrations in cultured cells.

A human cross-sectional study involving a limited number of workers in a Texas BD plant indicated genotoxic effects. (Ex. 118–2D) Peripheral lymphocytes were cultured from 10 non-smoking workers and from age- and gender-matched controls who worked in an area of very low BD exposure (0.03 ppm). Production areas in the plant had a mean exposure of 3.5 ppm BD, with most exposed workers in this sample experiencing exposure of approximately 1 ppm BD.

Standard assays for chromosomal aberrations and a gamma irradiation challenge assay that was designed to detect DNA repair deficiencies were performed. The results of the standard assay indicated that the exposed group had a higher frequency of cells with chromosome aberrations and higher chromatid breaks compared with the control group. This difference was not statistically significant. In the challenge assay, the exposed group had a statistically significant increased frequency of aberrant cells, chromatid breaks, dicentrics (chromosomes having 2 centromeres) and a marginally significant higher frequency of chromosomal deletions than controls. Au and co-workers concluded that cells exposed to BD are likely to have more difficulty in repairing radiation induced damage. (Ex. 118–2D)

To determine the mutagenic potential of both BD and its three metabolite epoxides, Cochrane and Skopek studied effects in human lymphoblastoid cells (TK6) and in splenic T cells from exposed B6C3F$_1$ mice. (Ex. 117–2, p. 195) TK6 cells were exposed for 24 hours to epoxybutene (0–400 uM), 3,4-epoxy-1,2-butanediol (0–800 uM), or diepoxybutane (0–6 uM). All

metabolites were mutagenic at both the *hprt* (hypoxanthine-guanine phosphoribosyl transferase) and tk (thymidine kinase) loci, with diepoxybutane being active at concentrations 100 times lower than epoxybutane or epoxybutanediol.

They also studied mice exposed to 625 ppm BD for 2 weeks and found a 3-fold increase in *hprt* mutation frequency in splenic T cells compared with controls. They also intended to give daily IP doses of epoxybutene (60, 80 or 100 mg/kg) or diepoxybutane (7, 14, or 21 mg/kg) every other day for three days. However, only animals given the lowest dose of the diepoxide received three doses because of lethality. After two weeks of expression time, cells were isolated for determination of mutation frequency. Both exposure regimens resulted in increased mutation frequency. For example, at the highest exposure to epoxybutene, the average mutation frequency was 8.6×10^6, while the diepoxide exposed group had a frequency of 13×10^6, compared to a control mutation frequency of 1.2×10^6.

Cochrane and Skopek used denaturing gradient gel electrophoresis to study the nature of the splenic T cell *hprt* mutants in the DNA. They found about half were frameshift mutations. A potential ''hotspot'' was also described in which a plus one (+1) frameshift mutation in a run of six guanine bases was observed in four BD-exposed mice, in four expoxybutene-exposed mice and in two mice exposed to the diepoxide. They observed both G:C and A:T base pair substitutions in the epoxide treated group; however, similar to the findings of Recio, et al. (described below), A:T substitutions were observed only in the BD-treated group. The authors offered no hypothesis for this observation. These researchers also noted a significant correlation of dicentrics with the presence of a BD metabolite, (1,2-dihydroxy-4-(N-acetyl-cysteinyl-S)butane) in the urine of exposed workers. They further concluded that:

> This study indicates that the workers had exposure-induced mutagenic effects. Together with the observation of gene mutation in a subset of the population, this study indicates that the current occupational exposure to butadiene may not be safe to workers. (Ex. 118–2D)

An abstract by Hallberg submitted to the Environmental Mutagenesis Society describes a host-cell reaction assay in which lymphocytes transfected with a plasmid with an inactive chloramphenicol acetyl transferase (CAT) reporter gene were challenged to repair the damaged plasmid and reactivate the CAT gene. No effect was noted among cells of workers exposed to 0.3 ppm benzene; however, BD-exposed workers (mean exposure 3 ppm) had significantly reduced DNA repair capacity (p=0.001). The authors believed that this finding confirmed the DNA repair defect due to BD exposure observed in the Au et al. study's challenge assay. (Ex. 118–2D)

Ward and co-workers reported the results of a preliminary study to determine whether a biomarker for BD exposure and a biomarker for the genetic effect of BD exposure could be detected in BD-exposed workers. (Ex. 118–12A) The biomarker for exposure was excretion of a urinary metabolite of BD, (1,2-dihydroxy-4-(n-acetylcysteinyl-S)butane. The genetic biomarker was the frequency of lymphocytes containing mutations at the hypoxanthine-guanine phosphoribosyl transferase (*hprt*) locus. Study subjects included 20 subjects from a BD production plant and 9 from the authors' university; all were verified non-smokers. Seven workers were in areas or at jobs that were ''considered likely to expose them to higher levels of butadiene than in other parts of the plant.'' Ten worked in areas where the likelihood of BD exposure was low. Three ''variable'' employees worked in both types of jobs or areas. *hprt* assays of 6 of the 7 high exposure group and 5 of the 6 non-exposed groups were completed at the time of the report. Air sampling was used to estimate exposure. In the production area, the mean was approximately 3.5 ppm, with most samples below 1 ppm. In the central control area (lower exposure) the mean was 0.03 ppm. The frequency of mutant lymphocytes in the high-exposure group compared with either the low- or no-exposure group was significantly increased. The low- and non-exposed groups were not significantly different from each other in mutant frequencies.

Similarly, the concentration of the BD metabolite in urine was significantly greater in the high exposure group than in the lower- or non-exposed groups. There was a strong correlation among exposed subjects between the level of metabolite in urine and the frequency of the *hprt* mutants (r=0.85). (Ex. 118–2A)

Another study of humans for potential cytogenetic effects of BD exposure was reported recently by Sorsa et al. in which peripheral blood was drawn from 40 BD production facility workers and from 30 controls chosen from other departments of the same plants, roughly matched for age and smoking habits. (Ex. 124) Chromosome aberrations, micronuclei and sister-chromatid exchanges were analyzed. No exposure related effects were seen in any of the cytogenetic endpoints. The typical exposure was reported as less than 3 ppm. (Ex. 124)

Among the limited number of human studies involving BD exposed workers is that of Osterman-Golker who evaluated post-exposure adduct formation in the hemoglobin of mice, rats, and a small number of workers. (Ex. 117–2, p. 127) Mice and rats were exposed at 0, 2, 10, or 100 ppm for 6 hours per day, 5 days per week for 4 weeks and their blood tested for the presence and quantity of the BD metabolite, 1,2-epoxybutene, forming an adduct with the N-terminal valine of hemoglobin. The result was a linear response for mice at 2, 10 and 100 ppm; and, for rats at 2 and 10 ppm, with the 100 ppm dose group deviating from linearity. In addition, while the adduct level per gram of globin in the 100 ppm rats was about 4 times lower than the level observed in mice exposed to 100 ppm BD, at lower exposures, the adduct levels were similar.

In the portion of the study dealing with effects on humans, blood was taken from four workers in two areas of a chemical production plant with known BD exposure, and five workers from two non-production areas where BD concentrations were low. In the higher exposure area, the mean BD exposure was about 3.5 ppm, as determined by environmental sampling. The lower exposure areas had a mean BD level of about 0.03 ppm. On a mole of adduct per gram of hemoglobin level, the adduct levels in the higher BD exposed workers were 70 to 100 times lower than those of either the rat or mice exposed at the 2 ppm level discussed above. Production workers had adduct levels ranging from 1.1 to 2.6 pmol/g globin. Most controls in the study were below the level of detection of the assay (0.5 pmol adduct/ g globin). (Two heavy smokers reported from a previous study had higher adduct levels than non-smokers; their levels approached those observed in BD exposed workers and were consistent with the amount of BD in mainstream smoke.)

Similar results for mice and rats exposed to BD were reported by Albrecht et al. (Ex. 117–2, p. 135) In this study which exposed the rodents to 0, 50, 200, 500 or 1300 ppm for 6 hours/ day, for 5 consecutive days, BD monoepoxide adduct levels in the hemoglobin of mice were about five times that of the rat at most BD exposure concentrations. Humans were not studied in this report.

Another observation pertaining to human cytogenetics with potentially important implications for BD-induced

human disease is contained in a report by Wiencke and Kelsey. (Ex. 117–2, p. 265) These researchers studied the impact of the BD metabolite, diepoxybutane, exposure on sister chromatid exchange (SCE) frequencies in several groups of human blood cell cultures (n=173 healthy workers). They discovered that the study populations were bimodally distributed according to their sensitivity to induction of SCEs when cell cultures were exposed to 6 uM diepoxybutane. Wiencke and Kelsey reported that they had observed in earlier studies that ''genetic deficiency of glutathione S-transferase type u leads to bimodal induction of SCEs by epoxide substrates of the isozyme'' and that cells from individuals with the deficiency had SCE induction scores that were significantly higher than those observed in the general population. (Ex. 117–2, p. 271) Approximately 20% of the tested groups were sensitive to induction of SCE and the remaining 80% were relatively insensitive.[1] Subsequent testing indicated that the sensitive population was also sensitive to induction of chromosomal aberrations by diepoxybutane with significant increases in the frequencies of chromatid deletions, isochromatid deletions, chromatid exchanges and total aberrations. The relevance of these findings in not yet clear; however, they may indicate that certain subsets of the population are more highly susceptible to the effects of this mutagenic metabolite of BD.

Recio et al. used transgenic mice containing a shuttle vector with a recoverable lac 1 gene to study *in vivo* mutagenicity of BD and the spectrum of mutations produced in various tissues. (Ex. 118–7D) Mice were exposed to 62.5, 625 or 1250 ppm BD for 4 weeks (5 days/week, 6 hours/day). The investigators extracted DNA from bone marrow and determined mutagenicity at the lac 1 transgene.

The mutant DNA was sequenced. Dose-dependent mutagenicity—up to a 3-fold increase over air controls—was observed among mice exposed at 625 or 1250 ppm. Although a number of differences in patterns were noted, the most striking was that sequence analysis indicated an increased frequency of *in vivo* point mutations induced by BD exposure at adenine and thymine (A:T) base pairs following inhalation.

In further studies of BD-exposed transgenic mice, Sisk and co-workers exposed male $B6C3F_1$ mice to 0, 62.5, 625, or 1250 ppm, BD for 4 weeks (6 hour/day, 6 days/week). (Ex. 118–7Q) Bone marrow cells were isolated and mutation frequency and spectrum evaluated. Lac 1 mutation frequencies were significantly increased at all 3 exposure levels and were dose-responsive in the 62.5 and 625 ppm BD-exposed mice, compared to controls. A plateau in mutation frequencies was observed at 1250 ppm BD-exposed mice, perhaps indicating saturation or mutant loss due to the effects of high level exposure.

When the mutants were sequenced, several from the same animal were found to have identical mutations. Although they might have arisen independently, Sisk et al. felt that this was likely due to clonal expansion of a bone marrow cell with a mutated lac 1 gene.

As had Recio et al., Sisk et al. observed a higher frequency of mutations at A:T sites in the exposed mice DNA, compared with controls. A:T to G:C transitions comprised only 2% of the background mutations, but made up 15% of those in the exposed mice.

Sisk et al. concluded that their observation coupled with *in vitro* studies '' * * * suggest that BD may mutate hematopoietic stem cells.'' (Ex. 118–7Q, p. 476)

As discussed in the animal carcinogenicity section in this preamble, BD-induced mouse tumors have been found to have activated proto-oncogenes. Specifically, the K-ras oncogene is activated and is the most commonly detected oncogene in humans. (Ex. 129)

OSHA concludes that BD is mutagenic in a host of tests which show point and frameshift mutations, *hprt* mutations, chromosome breakage, and SCEs in both animals and humans. The data suggest that mice are more susceptible than rats to these alterations. In addition, certain subsets of the human population may be more susceptible to the effects of BD exposure than others (based on the Wiencke and Kelsey study of human blood cell cultures, Ex. 117–2, p. 265). OSHA further notes with concern the fact that the data suggest that BD exposure at relatively low levels adversely affects DNA repair mechanisms in humans and is associated with mutational effects.

5. Metabolism

In vitro genotoxicity studies have shown that BD is mutagenic only after it is metabolically activated. Biotransformation is probably also important to the carcinogenicity of this gas. It is thought that the formation of epoxides, specifically epoxybutene, also termed the ''monoepoxide'' and 1,2:3,4-diepoxybutane, termed the ''diepoxide,'' is required for activity and that the reaction is cytochrome P450 mediated[2]. Both the mono- and diepoxide are mutagenic in the Salmonella assay, with the diepoxide being more active. The reactive epoxides can bind to DNA, and formation of DNA adducts is hypothesized to initiate a series of events leading to malignancy.

As described earlier, for most cancer sites, mice are more sensitive than rats to the carcinogenic effects of BD exposure. Studies of the metabolism of BD have been undertaken in an attempt to elucidate the contributions of dose-metric factors for the observed differences in carcinogenicity between the species.

Much of the research in this area has been performed at the Chemical Industry Institute of Toxicology and in German laboratories. Work on metabolism of BD was described by OSHA in the 1990 proposal. (55 FR 32736 at 32756) OSHA reviewed the current literature in the record and concluded:

1. The rate of metabolism of BD in mice is approximately twice that in rats;
2. Mice accumulate more radiolabelled BD equivalents in a 6 hour exposure than do rats at the same concentration;
3. Mice have about twice the concentration of the metabolite (1,2-epoxy-3-butene) (BMO) in blood as rats exposed at similar concentrations;
4. Over a wide range of exposures, mice received a larger amount of inhaled BD per unit body weight than rats, and had a higher concentration of BMO in the blood than rats (As expected, because of body size differences and breathing rates, and some enzymology);
5. BD is readily absorbed and widely distributed in tissues of both mice and rats, with tissue concentrations per umole BD inhaled higher in mice than in rats, by factors of 15-fold or more;
6. While there are species differences in the amount of BD metabolism at various sites, both mice and rats metabolize BD to the same reactive metabolites suspected of being ultimate carcinogens.

In comments on OSHA's proposal, Dr. Michael Bird of Exxon testified on behalf of the CMA BD Task Group that the mouse ''will attain a significantly higher amount of the epoxides over a longer period of time than the rat. . . or primate when exposed to butadiene.''

[1] For example, in the 58 newspaper workers tested, 24% had greater than 95 SCE/cell, while the remaining 76% had fewer than 80 SCE/cell.

[2] Cytochrome is defined as any of a class of hemoproteins whose principal biologic function is electron transport by virtue of a reversible valency change of its heme iron. Cytochromes are widely distributed in animal and plant tissues.

(Ex. 52, p. 27) Dr. Bird concluded that the differences in metabolism of BD in the species help ''explain the greater sensitivity of the mouse to BD carcinogenic activity.'' He further concluded that the differences in rates of enzyme mediated processes indicate non-human primates have lower internal concentrations of BD or BMO, and ''man is more similar to the primate with respect to 1,2-epoxy-3-butene formation than the rat or mouse.'' (Ex. 52, p. 22) He argued that the mouse may be ''uniquely sensitive '' to BD carcinogenicity due to its greater uptake, faster BD metabolism and ''elimination of the epoxide 1,2-epoxy-3-butene is saturable in mice but not in rats.'' (Ex. 52, p. 21) He felt this observation correlated well with the observed cytogenetic and bone marrow response (seen in mouse, but not rats.)

Others hold an opposing view, e.g., Melnick and Kohn argued that ''[b]ecause the rat appears to be exceptionally insensitive to leukemia/lymphoma induction, the mouse must be considered as the more appropriate model for assessing human risk for lymphatic and hematopoietic cancers.'' (Ex. 130, p. 160)

Dr. Bird urged OSHA to use the monkey data of Dahl, et al. which indicated that the retention rate for BD in primates is over 6 times lower than that for the mouse, in ''drawing any firm conclusions about the cancer risk to humans.'' (Ex. 52, p. 36) During the public hearing, the work of Dahl was presented as a preliminary report. (Ex. 44) Dahl exposed 3 cynomolgus monkeys to BD and measured uptake and metabolism. Each animal was exposed to three concentrations of C^{14}-labeled BD, progressing from 10,300 to 8000 ppm with at least 3 months separating the re-exposure of each monkey. Post-exposure blood was taken. Each animal's breathing frequency and tidal volume was measured.

Dahl and co-workers found BD uptake to be lower in monkeys than in rats. The reported blood levels of the epoxides were also lower in the monkey than the levels reported by Bond et al. in rats and mice.

Dahl et al. attempted to quantitate total BD metabolites through collection of feces, urine and exhaled material though use of cryogenic traps. Measurement of residual labeled material retained in the animals at the end of the 96 hour post exposure period was not determined. HPLC (high-performance liquid chromatography) identification of the trapped material (at 95 C) indicated that only 5 to 15% of the radioactivity was present as monoepoxide.

Melnick and Huff, in reviewing this study, found its significance ''clouded'' because only three animals of unknown age were studied and there was uncertainty about the ability of vacuum line cryogenic distillation alone to identify and quantitate BD metabolites. (Ex. 114, p. 133) In testimony at the public hearing, Dr. James Bond of CIIT acknowledged the limitations of the use of vacuum-line cryogenic distillation as follows:

> * * * there will be some material no matter what kind of vacuum you apply to it * * * simply will not move into the traps. That's referred to as non-volatile material.
>
> We don't know what that material is and I think that's an important component of this study, because, in fact, in many cases it can represent 70 to 80 percent of the material that actually distills out. (Tr. 1/22/91, p. 1553)

Melnick and Huff were also concerned that only the monkeys, not the mice or rats, were anesthetized during exposure and question what impact that might have had on respiratory rates and cardiac output and what the influence might be on inhalation pharmacokinetics of BD. (Ex. 114, p. 133) In their 1992 review, Melnick and Huff concluded that studies to date have not revealed species pharmacokinetic differences of sufficient magnitude ''to account for the reported different toxic or carcinogenic responses in one strain of rats compared to two strains of mice.'' (Ex. 114, p. 134) In post hearing comments Dr. David A. Dankovic of NIOSH reviewed this topic and concluded ''* * * the most prudent course is to base 1,3-butadiene risk assessments on the external exposure concentration, unless substantial improvements are made in the methodology used for obtaining 'internal' dose estimates.'' (Ex. 101, Att. 2, p. 5)

Recent Studies

Recent studies have focused on the metabolism of BD to the epoxides, epoxybutene and diepoxybutane, and their detoxification by epoxide hydrolase and glutathione. Bond et al. recently reviewed BD toxicologic data. (Ex. 118–7G) Epoxybutene and diepoxybutane were reported to be carcinogenic to mice and rats via skin application and/or subcutaneous injection, with the diepoxide having more carcinogenic potency. Bond et al. also concluded that the diepoxide is more mutagenic than the monoepoxide by a factor of nearly 100 on a molar basis. The diepoxide also induces genetic damage *in vitro* mammalian cells (Chinese hamster ovary cells and human peripheral blood lymphocytes). These studies are summarized in this preamble discussion of reproductive effects.

In vitro metabolic studies

In 1992 Csanady et al. reported use of microsomal and cytosolic preparations from livers and lungs of Sprague-Dawley rats, $B6C3F_1$ mice and humans to examine cytochrome P450-dependent metabolism of BD. (Ex. 118–7AA) The preparations were placed in sealed vials and BD was injected by use of a gas-tight syringe. Air samples were taken from the head space at 5 minute intervals and analyzed by gas chromatography for epoxybutene.

Cytochrome P450-dependent metabolism of the monoepoxide to the diepoxide was examined. Enzyme mediated hydrolysis of BMO by epoxide hydrolase was measured. (Non-enzyme mediated hydrolysis was determined using heat-inactivated tissue and none was observed.) Second order rate constants were determined using 100 mM monoepoxide and 10 mM GSH. The human samples were quite variable, with rates ranging from 14 to 98 nmol/min/mg protein.

The maximum rates for BD oxidation to monoepoxide (Vmax) were determined to be highest for mouse liver microsomes[3] (2.6 nmol/mg protein/min); the Vmax values for humans were intermediate, at 1.2 nmol/mg protein/min; the Vmax values for rats was 0.6 nmol/mg protein/min. For lung microsomes, the Vmax in the mouse was found to be similar to the mouse liver rate, but over 10-fold greater than that of either humans or rats.

From these data Csanady et al. calculated a ratio of activation to detoxification for each species tested. These values, expressed as mg cytosolic protein/gm liver [glutathione-S-transferase is a cytosolic enzyme], resulted in the determination of an overall activation:detoxification ratio of 12.3 for the mouse, 1.3 for the rat, and 4.4 for the human samples.

If these *in vitro* liver microsomal studies can be extrapolated to the whole animal *in vivo*, then this implies, as pointed out by Kohn and Melnick, that the mouse produces 2.8 times as much BMO per mol of BD as the human and that the human activation:detoxification ratio is 3.4 times that of the rat. However, the Csanady et al. study demonstrated a wide variability in BD metabolic activity among the 3 human liver microsomes, and a 60-fold variation was found in 10 human liver

[3] A microsome is defined as one of the finely granular elements of protoplasm, resulting from fragmentation (homogenization) of the endoplasmic reticulum.

samples by Seaton et al. (Ex. 118–7N) Kohn and Melnick noted that this human variability in CYP2E1, the P450 enzyme primarily responsible for the activity, suggests that a ''* * * fraction of the human population may be as sensitive to butadiene as mice are.'' (Ex. 131, p. 620).

A study similar to that of Csanady et al., reported by Duescher and Elfarra in 1994, determined that the Vmax/Km ratios for BD metabolism in human and mouse liver microsome were similar and were nearly 3 to 3.5 fold higher than the ratio obtained with rat liver microsomes. (Ex. 128) Duescher and Elfarra suggest that differences between their results and those of Csanady et al. may have been due in part to experimental methodology differences, such as incubation and assay methods. Duescher and Elfarra found that two P450 isozymes, 2A6 and 2EI, were most active in forming BMO of the 7 isozymes tested. They concluded that since human liver microsomes oxidized BD at least as efficiently as mouse liver microsomes (and much more so than rat liver microsomes), this ''suggests that if [BMO] formation rate is the primary factor which leads to toxicity, humans may be at higher risk of expressing BD toxicity than mice or rats, and that the mouse may be the more appropriate animal model for assessing toxicity.'' Duescher and Elfarra felt that since P450/2A6 appears to play a major role in BD oxidation in human liver microsomes, and that it is more similar to that of mouse P450/2A5 than to rat P450/2A1, the mouse may be a better model to use in assessing human risk.

In 1994 Himmelstein et al. hypothesized that ''[S]pecies differences in metabolic activation and detoxification most likely contribute to the difference in carcinogenic potency of BD by modulating the circulating blood levels of the epoxides.'' (Ex. 118–13, Att 3) To address this, Himmelstein and colleagues looked at the levels of BD, BMO, and BDE in blood of rats and mice exposed at 62.5, 625, or 1250 ppm BD. Samples were collected at 2, 3, 4, and 6 hours of exposure for BD and BMO and at 3 and 6 h for the BDE. Blood was collected from mice by cardiac puncture and from rats through an in-dwelling jugular cannula. Melnick and Huff criticized earlier studies which failed to use in-dwelling cannulae.

Because steady state levels of [monoepoxide] are lower in rats than in mice and because the metabolic elimination rate for this compound is 5 times faster in rats than in mice, any delay in obtaining immediate blood samples would have a much greater effect on analyses in blood samples obtained from rats than those obtained from mice. (Ex. 114, p. 133)

Himmelstein et al. found that the concentration of BD in blood was not directly proportional to the inhaled concentration of BD, suggesting that the uptake of BD was saturable at the highest inhaled concentration. In both rats and mice BD and the BMO blood levels were at steady state at 2, 3, 4 and 6 hours of exposure and declined rapidly when exposure ceased. This is consistent with exhalation being the primary route of elimination of BD. (Ex. 118–7B)

Genter and Recio used Western blot and immunohistochemical analyses to detect P450/2E1 in bone marrow of $B6C3F_1$ mice. (Ex. 118–7T) Although both methods detected the presence of the protein in livers of both male and female mice, non was seen in the bone marrow. The limits of detection were not stated in the report. The author hypothesized the BD might be converted to the monoepoxide in the liver prior to uptake by the bone marrow or that another pathway (e.g., myeloperoxidase) is responsible for BD oxidation in the marrow. Recio and Genter suggest that the greater sensitivity of mice to BD-induced carcinogenicity can be explained in part by the higher levels of both epoxides in the blood of mice compared with that of rats.

Himmelstein et al. furthered this work in 1995 in a report in which they determined levels of the epoxides in livers and lungs of mice and rats exposed to BD. (Ex. 118–7/O) Animals were exposed at 625 or 1250 ppm of BD for 3 or 6 hours. Himmelstein et al. found that in mice exposed to this regimen, the monoepoxide levels were higher in lungs than in livers. Rats at 625 and 1250 ppm had lower concentrations of BMO in lungs and livers than mice. When rats were exposed to 8000 ppm BD, the maximum concentration of BMO in the lung and liver was nearly the same. The diepoxide levels in lungs of mice exposed at 625 and 1250 ppm were 0.71 and 1.5 nmol/g respectively. The diepoxide was not detected in livers or lungs of rats exposed at any tested level.

Himmelstein et al. also observed depletion of glutathione in liver and lung samples from both rodent species. Following 6 hours of exposure, the lungs of mice exhibited greater depletion of GSH than mouse liver, rat liver or rat lung at all concentrations of BD tested. The conclusion reached by the study authors was that their data indicate that GSH depletion is associated with tissue burden of the epoxides and that this target organ dosimetry might help explain some of the non-concordance of cancer sites observed between the species. OSHA notes, however, that while % GSH depletion was highest in the mouse lung, the major increase in depletion was at 1250 ppm BD, while lung tumor incidence was increased in the female mice at 6.25 ppm and in male mice at 62.5 ppm. Depletion of glutathione was dependent on concentration and duration of BD exposure.

Himmelstein et al. stressed the importance of the fact that the diepoxide was detected in the mouse lung but was not quantifiable in the mouse liver, and stated that if the diepoxide was formed in the liver, it is rapidly detoxified or otherwise moved out of the liver. They also found that depletion of glutathione was greater in mouse than rat tissues for similar inhaled concentrations of BD and concluded that conjugation of the monoepoxide with glutathione by glutathione S-transferase is an important detoxification step.

In contrast to rats and mice, lungs and livers from humans had much faster rates of microsomal monoepoxide hydrolysis by epoxide hydrolase compared to cytosolic conjugation with glutathione by the transferase. (Ex. 118–7AA)

Thornton-Manning et al. in 1995 examined the production and disposition of monoepoxide and diepoxide in tissues of rats and mice exposed at 62.5 ppm BD. (Ex. 118–13, Att. 3) They found monoepoxide was above background in blood, bone marrow, heart, lung, fat, spleen and thymus tissues of mice after 2 or 4 hours of exposures to BD. In rats, levels of monoepoxide were increased in blood, fat, spleen and thymus tissues. No increase in monoepoxide in rat lung was observed. The more mutagenic diepoxide was detected in all tissues of the mice examined immediately following 4 hours of exposure. It was detected in heart, lung, fat, spleen and thymus of rats, but at levels 40- to 160-fold lower than those seen in mice.

In mice, the level of diepoxide exceeded the monoepoxide levels immediately after exposure in such target organs as the heart and lungs. Thornton-Manning et al. concluded that the high concentrations of diepoxide in heart and lungs they observed suggested to them that this compound may be particularly important in BD-induced carcinogenesis.

The study authors noted that neither epoxide was detected in rats' liver and was present only in quite low concentrations in the livers of mice. Thornton-Manning et al. found this

surprising since epoxides present in blood in the liver should have yielded values greater than those observed in the liver samples. They hypothesized that it might be due to prior metabolism of the epoxides before reaching the liver or it might be an artifact due to post-exposure metabolism of the epoxides in the liver.

Thornton-Manning et al. did not detect the monoepoxide in rat lungs, and found the diepoxide level to be quite low. In contrast, in the mice they found both epoxides present in lung tissue, with the monoepoxide level present at a concentration less than expected using blood volume values, and the diepoxide level agreeing with that expected as a function of blood volume. Thornton-Manning et al. concluded that these results ''* * * suggest that the lung is capable of metabolizing BDO, but perhaps is less active in metabolizing BDO_2. (Ex. 118–13, Att. 3) Moreover, Thornton-Manning et al. believed that although BD is oxidatively metabolized by similar metabolic pathways in the rats and mice, the quantitative differences in tissue levels between species may be responsible for the increased carcinogenicity of BD in mice.

TABLE V–8.—TISSUE LEVELS [PMOL/GM TISSUE, MEAN±S.E.] OF EPOXYBUTENE AND DIEPOXYBUTANE IN RATS AND MICE FOLLOWING A 4-HOUR EXPOSURE TO 62.5 PPM BD BY INHALATION

Tissue	Epoxybutene		Diepoxybutane	
	Rats	Mice	Rats	Mice
Blood	36±7	295±27	5±1	204±15
Heart	40±16	120±15	3±0.4	144±16
Lung	ND	33±9	0.7±0.2	114±37
Liver	ND	8±4	ND	20±4
Fat	267±14	1302±213	2.6±0.4	98±15
Spleen	7±6	40±19	1.7±0.5	95±12
Thymus	12.5±3.2	104±55	2.7±0.7	109±19
Bone marrow [1]	0.2±0.1	2.3±1.5	ND	1.4±0.3

ND=Not Detected.
[1] Bone marrow data are presented as mean pmol/mg protein ±; n=3 or 4 for each determination. Adapted from Ex. 118–13, Att. 3.

These data are shown in Table V–8.

Seaton et al. examined the activities of cDNA-expressed human cytochrome P450 (CYP) isozymes for their ability to oxidize epoxybutene to diepoxybutane. (Ex. 118–7N) They also determined the rate of formation of the diepoxide by samples of human liver microsomes (n=10) and in mice and rat liver microsomes. Seaton et al. found that two of the cytochrome P450 isozymes, CYP2E1 and CYP3A4, catalyzed oxidation of 80 uM of monoepoxide to detectable levels of diepoxide, and that CYP2E1 catalyzed the reaction at higher levels of monoepoxide (5mM), suggesting the predominance of 2E1 activity at low substrate concentrations. Hepatic microsomes from all 3 species formed the diepoxide when incubated with the monoepoxide. Seaton et al. hypothesized that the difference between these results and those of Csanady et al. (who did not detect the diepoxide when the monoepoxide was substrate in a similar microsomal assay) was due to differences in experimental methodology.

Seaton et al. noted a 25-fold variability in Vmax/Km among the 4 human livers. They reported that Vmax/Km for oxidation of the monoepoxide to the diepoxide for the 4 human samples was 3.8, 1.2, 1.3 and 0.15, while that of the pooled rat samples was 2.8, and the mouse ratio was 9.2.

The authors, using available data, calculated an overall activation/detoxification ratio (Vmax/Km for oxidation of BD to the monoepoxide) taking into account hydrolysis of the monoepoxide by epoxide hydrolase and conjugation with glutathione. The activation/detoxification ratio was estimated at 1295 for the mouse, 157 for rats and 230 for humans. However, Melnick and Kohn point out that ''when yields of microsomal and cytosolic protein content and liver size were considered, the activation to detoxification ratio was only 2.8 times greater in mice than in humans and 3.4 times greater in humans than in rats. These ratios do not take into account inter-individual variability in the activities of the enzymes involved.'' (Ex. 131)

Recently, Seaton et al. studied production of the monoepoxide in whole airways isolated from mouse and rat lung. (Ex. 118–7C) They explained the impetus to use fresh intact tissue by stating that lung subcellular fractions, as employed in experiments by Csanady et al., described above, contained mixtures of cell type ''so that the metabolizing capacities of certain cell populations may have been masked.'' They anticipated that use of airway tissue would allow more precise quantitation of differences in lung metabolism of BD.

Whole airways or bronchioles isolated from both male $B6C3F_1$ mice and male Sprague-Dawley rats were incubated for 60 min with 34 um BD. Levels of 10.4±5.6 nmol epoxybutene/mg protein were detected in mouse lungs, while 2–3 nmol/mg protein was observed in rat lung airway regions. Seaton et al. noted that while the species differences ''are not dramatic,'' they may in part contribute to the differences in carcinogenicity observed in mice and rats.

To characterize conjugation of BD metabolites with glutathione (GSH), Boogard et al. prepared cytosol from lungs and livers of rats and mice and from 6 human donor livers and incubated them with 0.1 to 100 mM diepoxide and labeled glutathione (GSH). (Ex. 118–7J) NMR (nuclear mass resonance) and HPLC techniques were used to characterize and quantitate conjugate formation.

Non-enzymatic reaction was concluded to be negligible. The conjugation rates (Vmax) in mouse and rat livers were similar and 10-fold greater than those observed in the human samples. The initial rate of conjugation (Vmax) was much higher in mouse than rat lung. Both rodent species exhibited higher initial rates of conjugation than human. This led Boogard et al. to conclude that the higher diepoxide levels observed in BD-exposed mice compared with rats ''are not due to differences in hepatic or pulmonary GSH conjugation of BDE (the diepoxide),'' and further that since humans oxidize BD to the epoxides at a low rate, the low activity of GSH conjugation of the diepoxide in human liver cytosol demonstrated in this study ''will not necessarily lead to increased BDE (diepoxide) levels in humans

potentially exposed to BD.'' They also pointed out the need to determine the rate of BDE detoxification by other means, specifically by epoxide hydrolase in all three species.

Studies of Urinary Metabolites of BD

Two metabolites of BD have been identified in urine of exposed animals by Sabourin et al. (Ex. 118–13 Att. 3) These are 1,2-dihydroxy-4-N-acetylcysteinyl-S-)-butane, designated MI, and MII, which is 1-hydroxy-2-N-acetylcysteinyl-S-)-3-butene. (Ex. 118–13–Att. 3)

These mercapturic acids are formed by addition of glutathione (GSH) at either the double bond (MI) or the epoxide (MII). MI is thought to form by conjugation of GSH with butenediol, the hydrolysis product of the monoepoxide, while MII is thought to form from conjugation of the monoepoxide with GSH.

Sabourin et al. measured MI and MII in urine from rats, mice, hamster and monkeys. Mice were observed to excrete 3 to 4 times as much MII as MI, while the hamsters and rats produced about 1.5 times as much MII as MI. The monkeys produced primarily MI.

The ratio of formation of metabolite I to the total formation of the two mercapturic acids, MI and MII, correlated well with the known hepatic epoxide hydrolase activity in the different species, suggesting that the monoepoxide undergoes more rapid conjugation with glutathione in the mouse than in the hamster or rats, and that the least rapid conjugation occurs in the monkey. The epoxide availability is inversely related to the hepatic activity of epoxide hydrolase, which removed the epoxide by hydrolysis.

In 1994, Bechtold et al. published a paper describing a comparison of these metabolites between mice, rats, and humans.[4] In workers exposed to historical atmospheric concentrations of 3 to 4 ppm BD, Bechtold measured urine levels of MI and MII by use of isotope-dilution gas chromatography, and found MI, but not MII, to be readily detectable. Bechtold et al. found that employees who worked in production areas (having 3–4 ppm BD exposure) could be distinguished by this assay from outside controls and that low level human exposure to BD resulted in formation of epoxide.

Bechtold et al. stated in their abstract that since monkeys displayed a higher ratio of MI to MI + MII than mice did, and ''because humans are known to have epoxide hydrolase activities more similar to those of monkeys than mice, we postulated that after inhalation of butadiene, humans would excrete predominantly MI and little MII.'' (Ex. 118–13 Att. 3) Their observations suggested that the predominant pathway for clearance of the monoepoxide in humans is by hydrolysis rather than conjugation with glutathione.

Bechtold et al. found when mice and rats were exposed to 11.7 ppm BD for 4 hours and the ratio of the two metabolites was then measured, for mice, the ratio of MI to MI ± MII (or the % of total which is MI) was 20%, that of rats was 52%, while humans exhibited more than 97% MI. These data also indicate the predominance of clearance by hydrolysis pathways rather than GSH conjugation in the human.

Nauhaus et al. used NMR techniques to study urinary metabolites of rats and mice exposed to ([(1,2,3,4)-^{13}C]-butadiene). (Ex. 118–7I) They characterized metabolites in mouse and rat urine following exposure by inhalation to approximately 800 ppm BD for 5 hours. Urine was collected over 20 hours from exposed and control animals, centrifuged and frozen.

The findings of this study are quite extensive and are briefly summarized as follows. Nine metabolites were detected and chemically identified in mouse urine and 5 in that of rats. Five were similar in the 2 species, though differing markedly in concentration. One was unique to the rat and four to the mouse. Nauhaus et al. observed that ''when normalized to body weight (umol/kg body weight), the amount of diepoxide-derived metabolites was four times greater in mouse urine than in rat urine.'' They further hypothesized that ''the greater body burden of (diepoxide) in the mouse and the ability of rats to detoxify [it] though hydrolysis may be related to the greater toxicity of BD in the mouse.'' Nauhaus et al. found that both mice and rats conjugated the monoepoxide with glutathione, but the rat preferentially conjugated at the two carbon, while the mouse preferentially conjugated at the one carbon. Additionally, the finding of a metabolite of 3-butenal, a proposed intermediate in the oxidation of BD to crotonaldehyde, an animal carcinogen, is suggestive of an alternative carcinogenic pathway for BD. In general, this study supports the *in vitro* findings of Csanady et al. who reported similar rates for BMO conjugation with glutathione between rats and mice. (Ex. 118–7AA)

Interaction of Butadiene With Other Chemicals

Bond et al. described use of available data to simulate the potential interaction of BD with other workplace chemicals. (Ex. 118–7V) Specifically they modeled potential interaction assuming competitive inhibition of BD metabolism by styrene, benzene and ethanol. The model predicted that co-exposure to styrene would reduce the amount of BD metabolized, but that because of its relative insolubility, BD would not effectively inhibit styrene metabolism. Benzene, which, like BD, is metabolized by P450/2E1, was also predicted to be a highly effective inhibitor of BD metabolism because of its solubility in tissues. The models predicted that ethanol would have only a marginal effect on BD metabolism at concentrations of BD ''relevant to human exposure.''

BD and styrene co-exposures often occur in the SBR industry and both are metabolized by oxidation to active metabolites, in major part, by cytochrome P450/2E1. To determine the metabolic effect of joint exposure to BD and styrene, Levans and Bond developed and compared two PBPK models, one with one oxidative pathway and competition between BD and styrene and the other with two oxidation pathways for both BD and styrene. (Ex. 118–7E) For model validation, Levans and Bond exposed male mice to mixtures of BD and styrene of 100 or 1000 ppm BD and 50, 100 or 250 ppm styrene for 8 hours. They used chamber inlet and outlet concentrations to calculate uptake and, when steady-state was reached, calculated the rate of metabolism. They analyzed blood for styrene, styrene oxide, epoxybutene and diepoxybutane by GC–MS.

Leavens and Bond found BD metabolism was inhibited when mice were co-exposed to styrene. The inhibition approached maximum value at co-exposure concentrations of styrene above 100 ppm.

The report also described the preliminary development of pharmacokinetic models to simulate the observed rate of BD metabolism in co-exposed mice. Their results supported the hypothesis that ''more than one isozyme of P450 metabolized BD and styrene and competition does not occur between BD and styrene for all isozymes.'' They were unable to accurately predict blood concentrations of styrene following exposure, and felt that '' perhaps the diepoxide may inhibit metabolism of styrene by competing for the same P450 enzyme.''

[4] A preliminary study on the human population of this study is described in the section of this preamble dealing with the genetic toxicology of BD exposure.

Although preliminary in nature and reflecting effects of relatively high exposures, these observations of interactions between styrene and BD exposure may have implications for the observed pattern of BD-induced effects in human populations jointly exposed. Specifically, the cancer effects seen in SBR production workers may underestimate the effects of BD with no styrene or benzene exposure.

Pharmacokinetic Modeling of BD Metabolism

In a recent publication, Bond et al. reviewed the results of application of a number of physiologically-based pharmacokinetic (PBPK) dosimetry models. (Ex. 118–7M) They noted that three of the models which included monoepoxide disposition (Kohn and Melnick, Johanson and Filser, Medinsky) predicted that, for any BD exposure concentration, steady-state monoepoxide levels will be higher for mice than for rats. Bond et al. further observed that ''while the three models accurately predict BD uptake in rats and mice, they overestimate the circulating blood concentrations of (monoepoxide) in these species compared to those experimentally measured by Himmelstein.'' Their results also led Bond et al. to conclude that the disagreement between model predictions for the monoepoxide and experimental data suggests that the structure and/or parameter values employed in these models are not accurate for predicting blood levels of BD epoxides, and conclusions based on model predictions of BD epoxide levels in blood or tissue may be wrong.'' (Ex. 118–7M, p. 168) OSHA agrees with these authors that BD epoxide levels should not be used in assessing risk. In the discussion, the authors pointed to the need for inclusion of diepoxide toxicokinetics (as well as that of the monoepoxide) in future modeling exercises, since they believe the diepoxide to be the ultimate carcinogenic metabolite of BD.

Kohn and Melnick, in a recent publication, used available data and attempted to apply a PBPK model to see whether it was consistent with observed *in vivo* uptake and metabolism. (Ex. 131) The model included compartments for rapidly and for slowly perfused tissues. Rate equations for monoepoxide formation, its hydrolysis, and for conjugation with glutathione were included.

Kohn and Melnick acknowledged numerous sources of uncertainty in applying the model to the data (in which there are many gaps), necessitating various assumptions. Their calculations led them to conclude that the ''model reproduces whole-body observations for the mouse and rat'' and that it predicts that ''inhalation uptake of butadiene and formation and retention of epoxybutene are controlled to a much greater extent by physiological parameters than by biochemical parameters. . . '' (Ex. 131)

When Kohn and Melnick interchanged the biochemical parameters in the mouse and human models to see if ''the differences in calculated net uptake of butadiene among the three species were due to differences in metabolic activity,'' they found that use of human parameters in the mouse model decreased the level of absorption of BD, but not to a level as low as that of the human. Kohn and Melnick noted that the model predictions of epoxybutene levels in the heart and lung of mice and rats failed to account for the observation that mice, but not rats, develop tumors at these sites. Kohn and Melnick suggested that factors other than epoxybutene levels, not accounted for in the model, are probably crucial to induction of carcinogenesis.

Conclusions

Many metabolism studies have been conducted both *in vitro* and *in vivo*, mostly in mice and rats, to determine the BD metabolic, distribution, and elimination processes, and these studies have been extended in attempts to explain, at least in part, the greater carcinogenic potency of BD in the mouse, whether the mouse or the rat is a better surrogate for human cancer and reproductive risk assessment, and what is the proper dose-metric to use in dose-response assessments. The question of whether the mouse or the rat is a better model for the human on the basis of tumor response is partly addressed in the risk assessment section of this preamble. This section more specifically considers whether these metabolic studies in total can explain the different cancer responses and potencies observed in the mouse, rat, and human. What is clear throughout the record is that most scientists who study the topic consider not BD itself, but the major epoxide metabolites of BD, BMO and BDE and 1, 2-epoxybutane-3,4-diol, to be the putative carcinogenic agents. Most of this research has focused on the relative species production of BMO and BDE. Both BMO and BDO have been reported in early studies to be carcinogenic to mice and rats via skin application and/or subcutaneous injection, with BDO being somewhat more potent. (Ex. 23–88, Ex. 125).

Metabolism of BD to BMO in both the liver and lung of mice, rats and humans is by the P450 oxidation pathway, with CYP2E1 and CYP1A6 being the major enzymes. Based on the studies reviewed by OSHA, overall the mouse metabolizes BD to the monoepoxide and the diepoxide in these organs at a faster rate than do the rat and human. This is supported by the following evidence: (1) The mouse has higher BMO and BDE levels in blood, lung, and liver (i.e., see Ex. 118–7S, Ex. 118–7D, and Ex. 118–13), which are the target organs for cancer in the mouse but not the rat; (2) the mouse has higher *in vitro* lung and liver microsome Vmax/Km ratios for both BD and BMO metabolism than do rats or humans (Ex. 118–7AA); and (3) the mouse has higher hemoglobin-BMO adduct levels than rats and much higher levels than humans. (Ex. 118–7Y) A major exception to the findings of these studies is the study by Duescher and Elfarra, who found the *in vitro* BD Vmax/km ratios to be the same in mice and human liver microsomes and 3–4 times higher than they were in rats, suggesting that mice and humans have similar BD metabolic potential, at least in the liver. (Ex. 128) Large variations, about 60 fold, were found among 10 human liver microsome BD metabolic activities. (Ex. 118–7N) A recent BD *in vitro* metabolism study by Seaton et al. on whole rat and mouse lung airway isolates found that the mouse produced about twice the amount of BMO as the rat (this difference could not explain the difference between mouse and rat tumor incidence). (Ex. 118–7C)

BMO and BDE were also measured in heart, spleen, thymus, and bone marrow (target sites for mouse but not rat tumors) following 4 hour BD inhalation exposure (62.5 ppm) to mice and rats. (Ex. 118–13) In these tissues, mouse BMO and BDE levels were 3 to 55 fold higher than rat levels for the same metabolites, although the mice organ levels of these metabolites correlated poorly with the mouse target organ cancer response at this exposure level. Only high BDE levels in the mouse lung were consistent with the mortality adjusted cancer incidence (see hazard identification—animal studies section, Ex. 114). This suggests that BD metabolite tissue levels can, at best, only partly explain differences in carcinogenic response. Differences in both species and tissue sensitivity must also be accounted for.

The Thornton-Manning and other studies also provided information about BD elimination. (Ex. 118–7I) With higher experimental exposure levels, the major route of elimination of BD is via expiration. Elimination of BMO occurs

by different pathways in different species and different organs. At higher BD exposure concentrations, some BMO is expired. The mouse liver and lung appear to eliminate BMO predominantly by direct conjugation with GSH[5]. For the rat there is approximately equal elimination by the GSH and EH mediated pathways, while for the human and monkey hydrolysis to butanediol is the major pathway for excretion. (Ex. 118–13 Att. 3) This species elimination pathway difference is a partial explanation for the higher levels of both BMO and BDE seen in the mouse, assuming that most of the BD metabolism takes place in the liver. With respect to the bone marrow BD distribution and metabolism, mouse levels of the BD metabolites in the bone marrow were lower than at any of the other target organs studied. (Ex. 118–13) *In vitro* studies by Gentler and Recio have found no detectable P4502E1 in the bone marrow of $B6C3F_1$ mice. (Ex. 118–7T) These authors conclude that this ''suggests that BD is converted to BMO outside of bone marrow and is subsequently concentrated in bone marrow, or that the conversion of BD to BMO occurs by an alternate enzymatic pathway within the bone marrow.'' The latter appears to be the more likely since Maniglier-Poulet and co-workers showed that *in vitro* BD metabolism to BMO in both $B6C3F_1$ mouse and human bone marrow occur by a peroxidase-mediated process and not via the P450 cytochrome system. (Ex. L–133) Since in their system both human and mouse bone marrow generated about the same amount of BMO/cell, this suggests that both BD distribution to bone marrow and local metabolic reactions should be considered in species-to-species extrapolations and in PBPK modeling.

Inclusion of bone marrow local reactions becomes even more important when considering the animal species to use for modeling human cancer. BD is genotoxic in the bone marrow of mice, but not in rats. (Tice et al. 1987; Cunningham et al. 1986, reported in Ex. 131) BD and BMO have been implicated as affecting primitive hematopoietic bone marrow stem and progenitor cells related to both T-cell leukemia and anemia in the mouse. (Irons et al., 1993, in Ex. 117–2) BD causes lymphoma in mice, but no lymphoma or leukemia in rats even at 8,000 ppm. Furthermore, the body of epidemiologic evidence strongly indicates that BD exposure poses an increased risk of human leukemia (see the epidemiologic section and especially Ex. 117–1).

Fat storage of BD during exposure, and release following cessation of exposure, is also a major concern, both in estimating target organ levels and in determining species differences. There is little in the record on the effect of fat storage and release. In the Thornton-Manning study discussed above, both mouse and rat fat levels of both BMO and BDE declined rapidly following cessation of exposure, suggesting little lingering effect. However, Kohn and Melnick present a model in which post-exposure release of BD from the fat would result in extended epoxide production in humans in contrast with the mouse. (Ex. 131)

Bond et al. suggest that the more rapid metabolism of BD to BMO in the mouse, and the more rapid EH BMO elimination pathways in the rat and human may be an explanation for lower, if any, BDE levels seen in rat and human liver microsomes and why BD will not be carcinogenic to humans at exposure levels seen in the environment or the workplace. (Ex. 130) They also conclude that ''Since significant tumor induction in male rats occurs only at 8000 ppm BD, BMO levels are probably not predictive of a carcinogenic response.'' Thornton-Manning et al. characterize the peak levels of BDE in the mouse lung and heart as being either greater than or equivalent to peak levels of BMO, and suggest ''that the formation of BDE may be more important than the formation of BMO in the ultimate carcinogenicity of BD.'' (Ex. 118–13) However, BMO levels in these organs were also quite high, and were higher than BDE levels in blood and bone marrow, target organs for hematopoietic system cancers. OSHA believes that the evidence is not sufficient to dismiss the potential contribution of BMO to mouse, rat or human carcinogenicity; to conclude that BDE should be considered more actively carcinogenic than BMO; or to find that BDE levels are sufficiently characterized in either mouse or human tissue to be used as the dose metric for BD human risk assessment.

Thus, OSHA concludes, based on the body of metabolic and other evidence presented, and the above discussion, that the mouse is a suitable animal model for the human for BD cancer risk assessment purposes, and that metabolism of BD to active metabolites is probably necessary for carcinogenicity. However, while the uptake, distribution, and metabolism of BD to active carcinogenic agents are important, local BD metabolic reactions and specific species sensitivities appear to have at least as large an impact on BD potency in the various species. This is likely to be especially true in the human, whose metabolic processes appear to be much more variable with respect to BD. Thus, although the metabolism studies provide insight into BD's metabolic processes in various species and organs (with the possible exception of mouse lung tumorigenicity related to lung BDE levels and protein cross linking), OSHA finds that too many questions remain unanswered, both with PBPK modeling efforts and with actual *in vivo* measurements (and the lack of such measurements in humans) to base a quantitative risk assessment on BD metabolite level equivalence between mice and humans. (Ex. L–132)

VI. Quantitative Risk Assessment

A. Introduction

In 1980, the United States Supreme Court ruled on the necessity of a risk assessment in the case of *Industrial Union Department, AFL–CIO* v. *American Petroleum Institute,* 448 U.S. (607), the ''Benzene Decision.'' The United States Supreme Court concluded that the Occupational Safety and Health (OSH) Act requires, prior to issuance of a standard, that the new standard be based on substantial evidence in the record considered as a whole, that there is a significant risk of health impairment at existing permissible exposure limits (PELs) and that issuance of the standard will significantly reduce or eliminate that risk. The Court stated that, before the Secretary of Labor can promulgate any permanent health or safety standard, he is required to make a threshold finding that a place of employment is unsafe in the sense that significant risks are present and can be eliminated or lessened by a change in practices. (448 U.S. 642)

In 1981, the Court's ruling on the OSHA's Cotton Dust Standard (*American Textile Manufacturers Institute* v. *Donovan, 452 U.S. 490 (1981)*) reaffirmed its previous position in the Benzene Decision, that a risk assessment is not only appropriate, but that OSHA is required to identify significant health risk to workers and to determine if a proposed standard will achieve a reduction in that risk, and OSHA as a matter of policy agrees that assessments should be put into quantitative terms to the extent possible.

For this rulemaking, OSHA has conducted a quantitative risk assessment to estimate the excess risk for cancer and consequently for premature deaths associated with

[5] One exception: Seaton et al. found evidence ''that in mouse airways hydrolysis of BMO by epoxide hydrolase (EH) contributes to BMO detoxification to a greater extent than does glutathione conjugation.'' (Ex. 118–7C)

exposure to an 8-hour time-weighted-average (TWA), 5 days/week, 50 weeks/year, 45-year exposure to BD at concentrations ranging from 0.1 to 5 ppm, the range of permissible exposure limits (PELs) considered by OSHA in this rulemaking. The data used in the quantitative risk assessment were from a National Toxicology Program (NTP) chronic inhalation study in which $B_6C_3F_1$ mice of both sexes were exposed to either ambient air or BD exposure concentrations ranging from 6.25 to 200 ppm, known as NTP II. (Ex. 90) For seven gender-tumor site combinations, multistage Weibull time-to-tumor models were fit to these NTP II data. The best fitting models were chosen via a log-likelihood ratio test.

OSHA's maximum likelihood estimate (MLE) of the excess risk of developing cancer and subsequent premature death as a result of an 8-hour TWA occupational lifetime exposure to 2 ppm BD, the PEL proposed by OSHA in 1990, was 16.2 per 1,000 workers, based on the most sensitive gender-tumor site combination, female mouse lung tumors. If the occupational lifetime 8-hour time-weighted-average (TWA) exposure level is lowered to 1 ppm BD, based on female mouse lung tumors, the estimate of excess cancer and premature death drops to 8.1 per 1,000 workers. In other words, an 8-hour TWA lifetime occupational exposure reduction from 2 ppm to 1 ppm BD would be expected to prevent, on average, 8 additional cases of cancer and probable premature deaths per 1,000 exposed workers. Based on the individual tumor site dose-response data, which were best characterized by a 1-stage Weibull time-to-tumor model, (male-lymphoma, male-lung, female-lymphoma and ovarian), on average, one would expect there to be between 1 and 6 fewer excess cases of cancer per 1,000 workers based on a 8-hour TWA occupational lifetime exposure to BD at 1 ppm versus BD at 2 ppm. Estimates of leukemia deaths at the former 8-hour TWA PEL of 1,000 ppm of BD, for an occupational lifetime, are not presented because contemporary BD exposures are generally far lower than this level.

B. Assessment of Carcinogenic Risk

1. Choice of Data Base for Quantitative Risk Assessment

The choice of data provides the platform for a quantitative risk assessment (QRA). Either animal studies which evaluate the dose-response relationship between BD exposure and tumorigenesis or epidemiological dose-response data may be suitable sources of data.

Estimates of the quantitative risks to humans can be based on the experience of animals from a chronic lifetime exposure study. Chronic lifetime inhalation bioassays with rats and mice generally last 2 years or two-thirds of the lifespan of the animal. (Ex. 114) These types of studies provide insight into the nature of the relationship between exposure concentration, duration and resulting carcinogenic response under a controlled environment. Furthermore, some researchers have estimated a variety of measures of dose of BD, including inhaled and absorbed dose as well as BD metabolites, to estimate human risks based on the observed dose-response relationship of animals in a bioassay; the form of the dose used in a dose-response analyses is called the dose-metric.

The carcinogenicity of lifetime inhalation of BD was studied in Sprague-Dawley rats by the International Institute of Synthetic Rubber Producers (IISRP) and in $B_6C_3F_1$ mice by the National Toxicology Program. The IISRP sponsored a two-year inhalation bioassay of Sprague-Dawley rats performed at Hazelton Laboratories Europe (HLE). (Ex. 2–31) Groups of 110 male and female Sprague-Dawley rats were exposed for 6-hours per day, 5 days per week to 0, 1,000, or 8,000 parts per million (ppm) of BD. The males were exposed for 111 weeks and the females for 105 weeks. Statistically significant increased rates of tumors were found in both male and female rats. Among exposed male rats, there were increased occurrences of pancreatic and testicular tumors and among the exposed female rats there were higher incidence rates of uterine, zymbal gland, mammary and thyroid tumors than in the control groups.

The National Toxicology Program (NTP) has performed two chronic inhalation bioassays using $B_6C_3F_1$ mice. (Ex. 23–1; 90; 96) The first study, NTP I, was intended to be a two-year bioassay, exposing groups of 50 male and female mice to 0, 625, or 1,250 ppm of BD for a 6-hour day, 5 days/week. The study was prematurely curtailed at 60 weeks for the males 61 weeks for the females caused by an unusually high cancer mortality rate due to malignant neoplasms in multiple organs. Despite some weaknesses in the way the study was conducted, the results of this study show that BD is clearly carcinogenic in these mice, with statistically significant increases in malignant lymphomas, heart hemangiosarcomas, lung tumors, and forestomach tumors in comparison to the controls for exposed male and female mice. (Ex. 90)

The second NTP BD chronic inhalation bioassay, NTP II, had groups of 70 (except for the group exposed to the highest concentration, which contained 90) male and female mice exposed to concentrations of 0, 6.25, 20, 62.5, 200 and 625 ppm for 6 hours/day, 5 days/week for up to 104 weeks. The NTP II bioassay provided lower exposures, closer to prevailing occupational exposure levels, than the NTP I and HLE chronic inhalation studies. The NTP II supported the pattern of carcinogenic response found in NTP I. Both male and female mice exposed to BD developed tumors at multiple sites including: lymphomas, heart hemangiosarcomas, and tumors of the lung, liver, forestomach, and Harderian gland (an accessory lacrimal gland at the inner corner of the eye in animals; they are rudimentary in man). Reproductive tissues were also adversely affected. Among the exposed males there were significant increases in tumors of the preputial gland; among females there were significant increases in the incidence of ovarian and mammary tumors.

In 1996, a retrospective cohort study by Delzell and co-workers of about 18,000 men who worked in North American synthetic rubber plants was submitted to OSHA. (Ex. 117–1) In this study researchers derived estimates of occupational exposure to BD using a variety of resources, such as work histories, engineering data, production notes, and employees' institutional memories. In their October 2, 1995 report Dr. Delzell et al., characterized their effort as follows:

> Retrospective quantitative exposure estimation was done to increase the power of the study to detect associations and to assist with the assessment of the impact of specific exposure levels on mortality from leukemia and other lymphopoietic cancers. (Ex. 117–1)

In April 1996, Dr. Delzell expressed concern with possible discrepancies between estimated cumulative exposures and actual measurements. (Ex. 118–2) OSHA believes that in a well-conducted study, retrospective exposure estimates can be reasonable surrogates for true exposures; misclassifications or uncertainty can decrease the precision of the risk estimates derived from such a study, but the problem must be severe and widespread to invalidate the basic findings.

At the time of publication of the proposed standard on occupational exposure to BD (August 1990), only the NTP I mouse and HLE rat bioassays were available for quantitative risk assessments (QRA). Presented in Table

V–9 is an overview of authorship and data sets used in the various QRAs submitted to the OSHA docket. With one exception, the rest of the QRA's in the BD Docket have relied on animal chronic exposure lifetime bioassays. Each of the five risk assessments discussed in the proposal based its quantitative risk assessment on one or both of the higher-exposure chronic bioassays (exposure groups exposed to BD concentrations ranging between 625–8,000 ppm). (Exs. 17–5; 17–21; 23–19; 28–14; 29–3; 32–27) The three QRAs conducted using bioassay data subsequent to the publication of the NTP II study used NTP II data with exposures of 6.25–625 ppm BD, closer to actual occupational exposures, for calculating their best estimates of risk. (Exs. 90; 118–1b; 32–16)

A summary of each of the ten QRA's follows:

TABLE V–9.—SUMMARY TABLE OF QUANTITATIVE RISK ASSESSMENTS (QRAS) IN ORDER OF THEIR REVIEW IN THE OSHA BD STANDARD

Exhibit	Author	Data-set
90	National Institute for Occupational Safety and Health (NIOSH) (Preliminary).	NTP II [a] bioassay (preliminary).
118–1b	NIOSH	NTP II bioassay.
118–1	NIOSH	Delzell et al. epidemiological study.
17–21	United States EPA Carcinogen Assessment Group (CAG)	NTP I [b] and HLE [c] bioassays; Epidemiological based on Fajen Exposure Data.
32–27	California Occupational Health Program (COHP) of the California Department of Health services (CDHS).	NTP I; HLE bioassays Epidemiological based on Fajen Exposure Data
32–16	Shell Oil Corporation	NTP I, NTP II and HLE bioassays.
17–5	United States EPA Office of Toxic Substances (OTS)	NTP I bioassay.
23–19	ICF/Clement Inc	NTP I bioassay.
29–3	Center for Technology, Policy, and Industrial Development at the Massachusetts Institute of Technology.	NTP I and HLE bioassays.
28–14	Environ Inc	HLE bioassay.

[a] NTP II, The National Toxicology Program, Technical Report 434, 2-year bioassay of $B_6C_3F_1$ mice to 5 exposure groups receiving between 6.25 and 625 parts per million (ppm) of BD

[b] NTP I, The National Toxicology Program, prematurely terminated longtime bioassay of $B_6C_3F_1$ mice to 2 exposure groups receiving either 625 or 1,200 ppm of BD

[c] HLE, Hazelton Laboratories Europe's, lifetime bioassay of Sprague Dawley rats, exposed groups received 1,000 ppm of BD or 8,000 ppm of BD

NIOSH-Quantitative Risk Assessments based on NTP II

In the early 1990's, two QRAs were conducted sequentially by the National Institutes for Occupational Safety and Health (NIOSH). One was a preliminary and the other a final, with the latter using final pathology data for histiocytic sarcomas and one particular type of lymphoma from NTP II. In 1991, NIOSH submitted a preliminary QRA using the then preliminary NTP II tumor pathology data for various individual organ sites (8 from the female mice and 6 from the male mice) to estimate excess cancer risk at different BD exposures over an occupational lifetime. (Ex. 90) For all gender-tumor site analyses, NIOSH excluded the 625 ppm exposure group in its best estimate of risk since the plethora of competing tumors [6] in this high exposure group provide less information for a dose-response analysis of individual tumor sites than do data from some of the lower exposure groups. Another reason for the exclusion was that the dose-time-response relationship in mice is saturated for exposures above 500 ppm and the data would thus provide very little additional information for low dose extrapolation. NIOSH's QRA relied on an allometric conversion of body weight to the three-quarters power, (mg/kg)¾, and equated a 900-day-old mouse to a 74-year old human. To avoid duplication of risks, NIOSH presented only maximum likelihood estimates based on the aggregate of all types of lymphomas even though dose-response data were also available for the lymphocytic lymphoma subset.

Of the fourteen gender-tumor site data sets NIOSH modeled to extrapolate animal data to humans, 12 (86%) yielded excess risks greater than 2 cancer deaths per 1,000 workers, given an 8-hour TWA lifetime occupational exposure of 1 ppm BD. Estimates of excess risks to workers based on the best fitting models for each of the six dose-time-response relationships for male tumor sites were between 0.4 and 15.0 per 1,000 workers assuming an 8-hour TWA, 45 year occupational exposure to 1 ppm BD. Among estimates based on male mice's dose-response data, the lowest and highest excess risk estimates were from the heart hemangiosarcoma and Harderian gland dose-response relationships, respectively. For estimates of excess risk based on either gender's set of individual tumor dose-response relationships, only the heart hemangiosarcoma data predicted a risk of less than 1 per 1,000 workers with an occupational lifetime exposure of 1 ppm: these data predicted 0.4 and 3×10^{-3} excess cancer cases per 1,000 workers based on the best fitting models for male and female mice, respectively.

Based on tissue sites in females, the excess risk estimates for 8-hour TWA occupational lifetime exposure to 1 ppm BD range between 4 and 31 per 1,000 workers.

NIOSH presented its findings for lifetime exposure to 2 ppm as follows:

> Based on tumors at the most sensitive site, the female mouse lung [assuming (mg/kg)¾ conversion], our maximum likelihood estimates of the projected human increased risk of cancer due to a lifetime occupational exposure to BD at a TWA PEL of 2 ppm is approximately 60 in 1,000 (workers). (Ex. 90)

For the linear models, if scaling were on a (mg/kg) basis rather than the (mg/kg)¾ used by NIOSH for allometric conversion, the revised estimate of excess cancer risk for an 8-hour TWA occupational lifetime exposure to 2 ppm BD would decrease approximately 6 fold to 9.2 per 1,000 workers based on the same female mouse lung tumor data.

In 1993, NIOSH finalized its estimates of excess risk caused by occupational exposure based on the tumorigenesis

[6] Competing tumors refers to the lack of opportunity of a later developing tumor to express itself due to the occurrence of early developing lethal tumor; Among the 625 ppm exposure group lymphocytic lymphomas were mortal early developing tumors which prevented later developing disease such as heart hemangiosarcomas from possibly developing.

experience of mice in the NTP II study. (Ex. 118–1B) The rounded maximum likelihood estimates (MLE) from the final QRA are presented in Table V–10. NIOSH expanded the gender-tumor sites to include histiocytic sarcoma for both male and female mice. NIOSH chose to present only its risk estimate based on lymphocytic lymphoma, rather than an assessment based on the aggregate of lymphomas. In the preliminary and final NIOSH QRAs, 1-stage time-to-tumor models'' rounded estimates of risk associated with lifetime exposure to 1 ppm BD ranged from 1 to 30 excess cancer cases per 1,000 workers, with estimates based on the male-lymphocytic lymphoma and the female-lung dose-response data providing the lower and upper ends of the range of risk, respectively.

As part of its sensitivity analyses, NIOSH derived the estimates of risk based on (1) equating a human lifespan to a mouse equivalent age of 784 days, a figure OSHA has used, and (2) equating a human lifespan to a mouse lifespan of 900 days (a figure more often used by NIOSH.) The best estimates of risk equating human lifespan to a mouse lifespan of 784 days were lower, by about one-third, than those assuming a human lifespan equivalency to 900 days for the mouse, all else held constant.

TABLE V–10.—NIOSH'S [a] FINAL QUANTITATIVE RISK ASSESSMENT'S (QRA) MAXIMUM LIKELIHOOD ESTIMATES (M.L.E.S) [b] PER 1,000 WORKERS OF LIFETIME EXCESS RISK DUE TO AN OCCUPATIONAL [c] EXPOSURE TO 1 PPM OF BD USING BEST FITTING MODELS, AS DESIGNATED BY NUMBER OF STAGES OF THE WEIBULL TIME-TO-TUMOR MODEL

Gender-tumor site	MLE, Final QRA (Stages)
Male mouse:	.....
Forestomach	0.03 (2)
Harderian gland	10 (1)
Heart hemangiosarcoma	0.5 (2)
Histiocytic sarcoma	8 (1)
Liver	4 (1)
All Lymphoma	NA
Lymphocytic lymphoma	0.9 (1)
Lung	10 (1)
Female mouse:	.....
Forestomach	5 (1)
Harderian Gland	7 (1)
Heart hemangiosarcoma	3×10^{-3} (3)
Histiocytic sarcoma	10 (1)
Liver	7 (1)
All lymphoma	NA
Lymphocytic lymphoma	9 (1)
Lung	30 (1)
Mammary	4 (1)
Ovarian	9 (1)

[a] Based on NTP II, excluding the 625 ppm exposure category, equating a 900-day-old mouse to a 74-year old human and assuming an allometric conversion of $(mg/kg)^{3/4}$.
[b] Rounded to one significant figure.
[c] Occupational lifetime is an 8-hour time-weighted-average, 40-hours per week, 50-weeks per year, time-weighted-average (TWA) for 45-years.

The Carcinogen Assessment Group QRA

The Carcinogen Assessment Group (CAG) and the Reproductive Effects Assessment Group of the Office of Health and Environmental Assessment at the United States Environmental Protection Agency (EPA) also conducted an assessment of the mutagenicity and carcinogenicity of BD. (Ex. 17–21) In its quantitative risk assessment, CAG used both male and female response data from the two chronic bioassays available at the time, NTP I with $B_6C_3F_1$ mice and the HLE Sprague Dawley rat study. The CAG analysis is based on EPA's established procedures for quantitative risk analyses, which fit the total number of animals with significantly increased or highly unusual tumors with the linearized multistage model and use the upper 95% confidence interval. Mice dying before week 20 and rats dying during the first year of the study (before the observation of the first tumor) were eliminated from the analysis to adjust for non-tumor differential mortality.

The dose-metric was based on a preliminary report by the Lovelace Inhalation Toxicology Research Institute of its six-hour exposure study in $B_6C_3F_1$ mice and Sprague Dawley rats at different concentrations of BD, roughly corresponding to the concentrations used in NTP I and HLE, with total internal BD equivalent dose expressed as a function of inhalation exposure concentration. Then CAG estimated the amount and percent of BD retained for various exposure concentrations in these bioassays. These internal dose-estimates were then extrapolated to humans based on animal-to-human ppm air concentration equivalence.

CAG adjusted risk estimates from the mouse study by a factor of (study duration/lifetime)^3 to account for less-than-lifetime observations, since the NTP I study was prematurely terminated at 60 weeks for males and 61 weeks for females due to predominating cancer mortality. CAG extrapolated the short lifespan mouse data to an expected mouse lifetime, 104 weeks, in order to estimate lifetime risk to humans.

CAG estimated all risks based on continuous exposure to BD, 24 hours per day, 365 days per year, for a 70-year lifetime. The incremental unit risk estimates for the female mouse were about eight times as high as those for the female rat; for the males, the incremental unit risk estimate for mice was about 200 times as high as for rats. The CAG final incremental unit risk estimate of 0.64 $(ppm)^{-1}$ is based on the geometric mean of the upper-limit slope estimates for male and female mice and would predict an upper limit of 640 excess cancers per 1,000 people exposed to 1 ppm continuously throughout their lifetime, 70 years. Extrapolating this same estimate to an equivalent 45-year working lifetime of 240 work days per

year at an 8-hour TWA exposure to 1 ppm BD would yield an upper-limit risk estimate of 90 excess cancers per 1,000 workers. If the working day is assumed to require one-half ($10m^3$) the daily tidal volume, the total amount of air inhale, the excess would be 135 cancers per 1,000 workers.

California Occupational Health Program (COHP) QRA

In 1990, five years after the CAG conducted its quantitative risk assessment, the California Occupational Health Program (COHP) produced its estimates of risk with a similar assessment of the carcinogenicity of BD, using the same available bioassays, with more recent information on BD risk in humans, pharmacokinetic (PK) modeling, and animal low exposure absorption efficiency. (Ex. 32–16) Using three separate dose-metrics for each bioassay and multistage models to characterize the basic dose-response relationship, CAG presented several quantitative estimates of incremental lifetime unit risks. Quantal lifetime response multistage models were fit to the data. COHP, like NIOSH, used the individual data with a multistage Weibull time-to-tumor model to characterize the dose response relationship. COHP stated that it also fit Mantel-Bryan and log-normal models to the data, and that the multistage models gave a better fit; the results obtained with these other models were not reported.

COHP performed calculations on each primary tumor site separately, and also did calculations on the pool of primary tumors that showed significantly increased tumor incidences. For their main dose-metric, COHP refined the CAG approach, using a revised estimate of low-exposure absorption via inhalation. COHP also included an estimate of the PK model derived BD monoepoxide metabolites, but de-emphasized their use by stating that these were ''presented for comparative purposes only.'' The third dose-metric was straight ppm for animal-to-human species conversion (adjusting for duration of exposure). COHP stated:

> (COHP) followed standard EPA practice and assumed that a certain exposure concentration in ppm or mg/m^3 in experimental animals was equivalent to the same exposure concentration in humans. (Ex. 32–16)

Like CAG, COHP also adjusted for less than lifetime survival in the NTP I mouse study, by using a cubic power of time, $(\text{study duration/lifetime})^3$. COHP's potency estimate adjustment for the male mouse study with 60-week survival was 5.21; for the 61-week female mouse survival the adjustment was 4.96.

With all the combinations of sites, species, sexes, models, and dose-metrics, COHP presented over 60 potency estimates for the rat and over 100 for the mouse. As with the CAG and other analyses, the estimates based on NTP I were typically one to two orders of magnitude greater than those based on the rat for similar dose-metrics, models and total tumors. COHP chose the estimates based on the male mouse as final indicators of human risk based on the ''superior quality of the mouse study.'' From these estimates, using the quantal form of the multistage model, COHP chose ''the upper bound for plausible excess cancer risk to humans.'' COHP's final cancer potency estimate of $0.32\ (ppm)^{-1}$ presented in units of continuous lifetime exposure, is based on all significant tumors in the male mouse and uses the internal BD equivalent dose conversion factor of 0.54 mg/kg-d/ppm for the mouse and animal-to-human ppm equivalency. COHP's final potency estimate was one-half the value of $0.64\ (ppm)^{-1}$ calculated by the CAG; the difference is due mainly to a low exposure absorption modification by COHP. The continuous lifetime exposure potency factor converts to a working lifetime risk of 45 to 67 excess cancers per 1,000 workers, exposed to 1 ppm of BD at an 8-hour TWA over a 45 year working lifetime.

COHP, like CAG, attempted to determine whether its animal-based risk extrapolation could predict the leukemia mortality observed in epidemiology studies. Following the approach employed by CAG in its analyses of the Meinhardt (1982) study, the COHP compared its estimates of risk from bioassays to the then most recent epidemiological studies of Downs et al. (1987) and Matanoski and Schwartz (1987). Both COHP and CAG used MLEs based on mouse lymphoma for comparing the animal-derived potency estimates with the occupational response. In addition, neither COHP nor CAG used the upward adjustment factor of approximately 5 to correct for the less-than-lifetime duration of NTP I. Because neither of these epidemiology studies (Downs et al. (1987) or Matanoski and Schwartz (1987)) had recorded exposure estimates, the COHP relied on 8-hr TWA estimates of 1 and 10 ppm taken at different but similar plants reported by Fajen et al. (1986). For lifetime unit risk estimates, COHP used the initial MLE of $0.0168\ (ppm)^{-1}$ derived from the male mouse lymphoma analysis, unadjusted for less-than-lifetime survival. This part of the analysis also assumed that a lymphocytic outcome in the animals would equate to leukemia death in humans. These assumptions yielded a range of 6 to 21 predicted lymphocytic cancer deaths (for 1 and 10 ppm exposures) versus the 8 observed by Downs et al.

Office of Toxic Substances (OTS) QRA

The Office of Toxic Substances (OTS), U.S. Environmental Protection Agency (EPA) conducted a quantitative risk assessment using only the NTP I data. (Ex. 17–5) The reasons cited for this choice include: (1) The mouse is a more sensitive test species for BD than the rat; (2) a quality control review had been done for the mouse bioassay at the time OTS wrote its risk assessment whereas none was available for the rat bioassay; (3) greater amount of histopathological data was available for the NTP I study than for the HLE rat study; and (4) the type of BD feedstock used by NTP I had a much lower dimer concentration than the BD used by HLE (increased dimer concentration results in the lowering of availability of BD for metabolism to the mono- and di-epoxides, which are thought to be the carcinogenic agents). To compensate for early termination of the NTP I study, OTS adjusted dose by a factor of $(\text{study duration/lifetime})^3$. Butadiene ppm exposure concentration was used as the measure of dose and mouse-to-human species extrapolation was also on a ppm equivalence basis. OTS estimated cancer risks based on heart hemangiosarcoma and pooled tumors (grouping of sites showing statistically significant elevated incidence rates) tumors using a 1-stage quantal model. Workplace exposures to BD were converted to estimated lifetime average daily doses. Since the NTP I study was curtailed at 61 weeks, tumor incidence rates were adjusted for survival by life-table methods. Cancer risks were based on administered dose of BD and not delivered dose to various target organs. (Ex. 17–5) Estimated 95% upper confidence-limits for the excess risk of cancer from an occupational lifetime exposure to an 8-hour TWA of 1 ppm BD, for 240 days/year for 40 years, ranged between 10 and 30 per 1,000 workers, based on pooled tumor incidence for female and male animals, respectively.

ICF/Clement Estimates

In 1986, ICF/Clement (ICF) estimated the risk of cancer associated with occupational exposure to BD. (Ex. 23–19) ICF determined that only the NTP I data were suitable for a risk assessment based on animal data, (NTP II data were not available at that time) based on ICF/

Clement's concern over the discrepancies between HLE's summary statistics and individual counts. ICF chose to use individual tumor type data for some of its analyses. ICF fitted a linearized multistage quantal model to the NTP I data. Based on a preliminary study by Bond (a senior toxicologist at the Chemical Industry Institute of Toxicology), ICF adjusted the NTP I exposure concentrations for percent retention which varied inversely from 100% at 1 ppm to 5% at 1,000 ppm.

ICF assumed ppm as the proper dosemetric and ppm to ppm for the mouse-to-human species extrapolation factor. (Exs. 23–86; 23–19) The 95% upper confidence limit estimates of risk based on pooled female tumor data with a lifetime occupational exposure was 200 per 1,000 workers at 1 ppm BD, and 400 per 1,000 workers at 5 ppm BD; the non-proportionality reflects the assumption of lower percentage retentions at higher concentrations.

Massachusetts Institute of Technology (MIT) QRA

Hattis and Wasson at the Center for Technology, Policy, and Industrial Development at MIT conducted pharmacokinetic/mechanism-based analyses of the carcinogenic risk associated with BD. (Ex. 29–3) The analyses include both HLE and NTP I data. Key elements, such as partition coefficients for blood/air and tissue/blood, were not available to be measured and had to be estimated. The best estimate of excess risk of cancer given a lifetime occupational exposure of 1 ppm BD 8-hr TWA was 5 per 1,000 workers based on the NTP I female mouse data set, incorporating pharmacokinetic models which set the blood/air partition coefficient to 0.2552. Based on the HLE female rat data with a blood/air partition coefficient of 0.2552, an excess risk was estimated to be 0.4 additional cases of cancer for every 1,000 workers at an 8-hour TWA, occupational lifetime exposure to 1 ppm BD.

Environ QRA

Environ conducted a quantitative risk assessment based on the HLE rat bioassay data. (Ex. 28–14) Environ noted that the relatively high BD concentrations of the earlier bioassays (HLE with groups exposed to 8,000 and 1,000 ppm BD and NTP I with exposures of 1,250 and 625 ppm BD) made it difficult to extrapolate risks to the relevant, lower exposure levels of BD in occupational settings. Environ stated that among $B_6C_3F_1$ mice, metabolic saturation occurs with 8-hour TWA BD concentrations greater than 500 ppm; thus, the time-dose-response relationship is different at higher doses than at lower doses. Environ stated that the methodological problems and the high early mortality shown in the NTP I data contributed to the uncertainty of its relevance to human risks and therefore chose to use the HLE rat bioassay data instead. Environ believes that human metabolism of BD is more similar to that in the Sprague-Dawley rat than in the $B_6C_3F_1$ mouse. Extrapolated risks were based on estimates of absorbed dose, expressed in mg/kg, as defined in the Bond et al. (1986) absorption study. (Ex. 23–86)

Environ used the HLE female rats to estimate the extra lifetime risk of developing cancer given an occupational lifetime 8-hr TWA exposure to 1 ppm BD. Using MLEs from multistage, Weibull, and Mantel-Bryan models, based on the total number of female rats with significantly increased tumors, Environ's predicted occupational lifetime risks were 0.575 (Multistage), 0.576 (Weibull), and 0.277 (Mantel-Bryan) per 1,000 workers.

Shell Oil Company QRA

Shell Oil Company estimated excess cancer risks by the multistage quantal and the Weibull time-to-tumor models based on female heart hemangiosarcomas and pooled malignant tumors from the NTP II study. Shell estimated human risks based on various assumptions, correcting for BD retention and/or relative human epoxide dose. Shell stated that the Weibull time-to-tumor model better characterized risks since it was able to fully utilize available dose-response data, including time until onset of tumors and latency (time from initiation until detection of tumor). (Ex. 32–27) Shell used

> * * * crude time-to-tumor data consisting of early deaths to 40- weeks, 40-week interim sacrifices, deaths to 65- weeks, 65-week interim sacrifices, death to 104- weeks and terminal sacrifices * * * in-lieu of individual animal data [for NTP II data]. (Ex. 32–27)

OSHA believes that the true dose-response relationship is obscured by Shell's use of crude time-to-tumor data and its grouping of early deaths to 40 weeks, deaths to 65 weeks and deaths to 104 weeks; instead, dose-time-tumor response data for each individual mouse should have been used.

Shell did not explain why it chose one model over the other. For example, without explanation, Shell dropped the highest exposure group, 625 ppm, when estimating lifetime occupational risk for all of its Weibull time-to-tumor models and dropped additional dose groups when using some multistage quantal models. Moreover, estimates of excess risk were presented only for 5-stage Weibull time-to-tumor models, although there is no discussion of correct model specifications. For example, no reasons are given for choosing the 5-stage model rather than another. Also, Shell does not support its estimation that the latency between the induction of a tumor and its observation is for the pooled female mice malignant tumors and 40-weeks for the female mice heart hemangiosarcomas.

Based on the Shell analyses, extrapolating from pooled malignant female mice tumors, assuming 10% human BD retention efficiency at 2 ppm, and on a 5-stage Weibull time-to-tumor model, one would expect 18 excess cancers per 1,000 workers given an 8-hour TWA occupational lifetime exposure of 2 ppm BD. Based on the same data set, but assuming a mouse-to-human species conversion factor based on an epoxide ratio of 590 (mouse-to-monkey) in addition to a 10% BD retention efficiency factor, the estimate of excess risk of cancer drops to 0.3 cases per 1,000 workers with an 8-hour TWA occupational lifetime exposure of 2 ppm. Using the same pooled malignant female mice tumors, but assuming the blood epoxide estimates of the Dahl et al. study and an 8-hour TWA lifetime occupational BD exposure of 2 ppm, the estimate of excess risk of cancer is slightly lower, 0.24 per 1,000 workers. The excess risk estimates based on female hemangiosarcomas and a 5-stage Weibull time-to-tumor model and occupational lifetime exposure to 2 ppm of BD were: (a) 6.4×10^{-8} (assuming a 10% BD retention factor); (B) 6.2×10^{-15} (assuming a 10% BD retention factor and an epoxide ration of 590); and (c) 1.3×10^{-11} (assuming the blood epoxide estimates of the Dahl et al. study).

Shell also presented the Environ Inc. QRA based on the HLE Sprague-Dawley rat bioassay and made similar adjustments for BD retention and blood epoxide to those it made for the NTP II $B_6C_3F_1$ mice data. As had Environ, Shell stated that the dose- response of the rat is more relevant than that of the mice in predicting risk in humans. Shell concluded that the risk estimates derived from HLE Sprague Dawley rat data should be given greater weight than those based on the $B_6C_3F_1$ mouse data.

NIOSH's QRA Based on the Delzell et al. Study

NIOSH estimated the excess risk of workers developing leukemia based on the Delzell et al. preliminary estimates of occupational exposure categories of a retrospective cohort study. (Exs. 117–1; 118–1) NIOSH derived excess risks from

the best fitting relative risk (RR) model, the square root model, as fit by Delzell et al. who adjusted for age, years since hire, and calendar period. The preferred final model specified by Delzell et al. was:

$$\text{Relative Risk}=1+0.17\times(\text{BD ppm-years})^{0.5}$$

Under this model the age-cause specific leukemia death rates (ACSDR) are a function of cumulative occupational exposure up to that age. The occupational ACSDRs are a multiplicative function of background ACSDR times the BD-caused relative increase (0.17 * BD ppm-years) in leukemia. These total ACSDRs were then applied to an actuarial program which adjusted for competing risks to estimate lifetime excess risk of leukemia associated with 45-year 8-hour TWA occupational exposures for a number of PELs for BD. Estimates of background rates of leukemia and all causes of death were taken from the mortality rates for all males, 20 to 65 years of age, from the 1989 Vital Statistics of the United States. This model estimates the excess risk of leukemia death, given an occupational lifetime exposure of 2 ppm of BD, as 11 per 1,000 workers. Lowering the 8-hour TWA occupational lifetime BD PEL to 1 ppm, on average, one would expect there to be 8 excess leukemia deaths per 1,000 workers over a working lifetime.

In most animal bioassays, exposure to chemical carcinogens is usually associated with an elevated tumor incidence at only one or two target tissues. BD is of great concern because significantly increased incidences of tumors at multiple sites and doses were observed in both rats and mice.

OSHA's final risk assessment is based upon the NTP II bioassay. (Exs. 90; 96) In NTP II, the following tumor sites' incidence rates were elevated: Heart, lymph nodes, lung, forestomach, Harderian gland, preputial gland, liver, ovaries and mammary gland. The NTP II bioassay was preferred over the NTP I mouse and the HLE rat bioassay for several reasons. First, most of the exposure levels for NTP II (6.25, 20, 62.5 and 200 ppm) were closer to current occupational exposure levels than were those in the other bioassays (625; 1,000 and 8,000 ppm); studies with higher than typical occupational exposure concentrations may lead to difficulties in extrapolating the effects to the lower concentrations of BD which typically occur in current occupational settings. Furthermore, for doses (625 to 8,000 ppm) above the metabolic saturation level of 500 ppm, the biologically effective doses are not proportional to ppm exposure concentrations. Second, the NTP II mice were successfully randomized to exposure groups and their individual pathology reports were consistently coded. The randomization of the bioassay mouse population lends to the internal validity of the study through the similar composition of experimental and control groups. Third, Good Laboratory Practices were followed, as verified by audits. Fourth, there was a clear dose-response relationship for several cancer sites. Fifth, since the carcinogenic mechanism is still unknown, OSHA conservatively estimates excess risk to humans based on the experience of the more sensitive animal species unless there is specific evidence indicating that the choice of that species is inappropriate. Sixth, risk assessment results based on the preliminary findings from the most recent epidemiologic study suggest that the $B_6C_3F_1$ mouse is a reasonable species to use for quantitative risk assessment. (Ex. 118–1)

For its risk assessment, OSHA has focused exclusively on those tumor sites that are scientifically pertinent. From the NTP II study, the range of excess cancer risk associated with a lifetime occupational exposure to BD is estimated based on the dose-response relationships of four target tissues, three common to both genders: Heart (hemangiosarcoma), lung, and lymphoma, and one, ovarian tumors, observed in one gender only. OSHA's focus on these four individual target tissues is based not on an objection to the use of other tissue tumors and sites but rather on the judgment that the chosen animal sites are appropriate because they include both rare (e.g., heart hemangiosarcoma) and common tumors (e.g., lung) and those sites with the lowest (heart hemangiosarcoma) and highest incidence rates (lymphatic).

Three of the target organs chosen for the QRA demonstrated a significantly elevated tumor incidence in both male and female animals; ovarian tumor incidence was also significantly elevated in female animals. For both male and female mice, heart hemangiosarcomas were selected for modeling because there is virtually no background incidence of heart hemangiosarcoma among untreated mice in the NTP control population; only 0.04% of unexposed $B_6C_3F_1$ mice develop heart hemangiosarcoma, and thus any observed increase in the incidence of heart hemangiosarcoma could be attributed to BD exposure. (Ex. 114, p. 121) The earlier developing lymphocytic lymphoma caused a significant number of mice to die. Therefore, leaving mice are left at risk for the later developing tumor, heart hemangiosarcoma. (Ex. 114, p. 123) This situation is known as competing risk (the lack of opportunity for later developing tumors to express themselves because an earlier developing tumor has already caused the death of the animal. The occurrence of heart hemangiosarcomas in the NTP study is even more notable because of these competing risks.

In the absence of definitive, pharmacokinetic information, OSHA has estimated excess risks to humans based on the most sensitive species-sex-tumor site. Lung tumors are the most sensitive sites for both male and female $B_6C_3F_1$ mice and, as such, were included in OSHA's final risk assessment.

Ovarian tumors are an example of the group of reproductive tumors which also had significantly increased incidence rates among the animals in the NTP II bioassay. Other significantly increased incidence rates were seen in testicular, preputial and mammary tumors.

The increased risk of developing leukemia that has been observed in the epidemiological studies suggests that lymphomas might be the most relevant tumor site in animals for estimating the quantitative cancer risk to workers. Some have suggested that the high rate of lymphoma among $B_6C_3F_1$ mice might have been due to the presence of the murine retro virus (MuLV) and have asserted that the presence of this virus in $B_6C_3F_1$ mice may be partially responsible for the incidence of thymic lymphoma. For example, in 1990, Dr. Richard Irons reported,

> A major difference between NIH Swiss and $B_6C_3F_1$ mice is their respective exotropic retro viral background (MuLV) * * * Chronic exposure to BD (at 1250 ppm) for up to a year resulted in a fourfold difference in the incidence of thymic lymphoma between $B_6C_3F_1$ mice and NIH Swiss mice * * * The role of endogenous retro virus (MuLV) in the etiology of chemically induced murine leukemogenesis is presently not understood. (Ex. 23–104)

Dr. Melnick of the National Toxicology Program testified during his public hearing statement,

> In terms of the difference in response between the $B_6C_3F_1$ mouse or the NIH Swiss Mouse, you must be aware that the study is not a complete cancer study. It's a one-year exposure. We do not know the full response in the NIH Swiss mouse if it were conducted as a cancer study (about 2-years). (Tr. 1/16/91, p. 382)

Furthermore, NIOSH stated: ''It is not known whether the retro virus activation mechanism is operative at the lower exposure concentrations of 1,3-butadiene [below 1250 ppm].'' (Ex. 90)

There is no information in the record to show that retrovirus insertion into the $B_6C_3F_1$ mice of the NTP II study led to the induction of lymphoma. Nor is there information indicating that the murine retro virus may have led to an enhancement of butadiene-induced lymphomas in $B_6C_3F_1$ mice. The development of thymic lymphoma in BD-exposed NIH Swiss mice that do not have this endogenous virus argues against the virus alone inducing the lymphomas observed in the BD-exposed $B_6C_3F_1$ mice. (Ex. 23–104)

Tables V–11 and V–12 show the breakdown of microscopically examined tissues included in OSHA's QRA, by exposure concentration and death disposition of female and male mice. As illustrated in the tables, microscopic examination varied by tissue type, exposure group, means of death, and gender. Microscopic examinations of all tissues were made for all natural deaths, and moribund and terminal sacrifices, irrespective of exposure group.

For each gender-exposure-group, 10 animals were sacrificed at 40 and 65 weeks. Microscopic evaluations were not made for all tissue types among interim sacrifices (40 and 65 weeks). Among early sacrifices (40 weeks) for the 6.25 and 20 ppm exposure groups, there were no microscopic examinations of the relevant tissues. For the 65-week female sacrifices at the 6.25 and 20 ppm dose levels only lung and ovarian tissues were examined microscopically. No microscopic evaluations were made for male 65-week sacrifices at the 6.25 ppm exposure level, but at the 20 ppm exposure level, animals were microscopically examined for heart hemangiosarcoma and lung cancer. Male and female interim sacrifices exposed to 62.5 ppm of BD were not microscopically examined for heart hemangiosarcoma.

Only observations confirmed by microscopic examination were included in the analyses. Among natural deaths for some gender-tissue combinations, there were a few animals for which tissues were not available. Tissue unavailability was due to autolysis (cell destruction post death) and missing tissues due to the delay between accident and discovery.

TABLE V–11.—TYPES OF TISSUES MICROSCOPICALLY EXAMINED BY CONCENTRATION DOSE AND DISPOSITION GROUPS AMONG FEMALE MICE FROM NTP[a]

Concentration ppm	Natural death and moribund sacrifice	Week 40 sacrifice	Week 65 sacrifice	Terminal sacrifice
0	lymphoma, heart[b], lung, ovaries.	lymphoma, heart, lung, ovaries.	lymphoma, heart, lung, ovaries.	lymphoma, heart, lung, ovaries.
6.25	lymphoma, heart, lung, ovaries.	none[c]	lung, ovaries	lymphoma, heart, lung, ovaries.
20	lymphoma, heart, lung, ovaries.	none	lung, ovaries	lymphoma, heart, lung, ovaries.
62.5	lymphoma, heart, lung, ovaries.	lymphoma, lung, ovaries	lymphoma, heart, lung, ovaries.	lymphoma, heart, lung, ovaries.
200	lymphoma, heart, lung, ovaries.	lymphoma, heart, lung, ovaries.	lymphoma, heart, lung, ovaries.	lymphoma, heart, lung, ovaries.

[a] These organs and tissue types are those contained in the OSHA risk assessment and do not reflect all of the types of tissues which were microscopically examined.
[b] Heart, specifically Heart hemangiosarcoma.
[c] None of the four tissue types used in the OSHA quantitative risk assessment were microscopically examined.

TABLE V–12.—TYPES OF TISSUES MICROSCOPICALLY EXAMINED BY CONCENTRATION DOSE AND DISPOSITION GROUPS AMONG MALE MICE FROM NTP[a]

Concentration ppm	Natural death and moribund sacrifice	Week 40 sacrifice	Week 65 sacrifice	Terminal sacrifice
0	lymphoma, heart[b], lung,	lymphoma, heart, lung	lymphoma, heart, lung	lymphoma, heart, lung.
6.25	lymphoma, heart, lung,	none[c]	none	lymphoma, heart, lung.
20	lymphoma, heart, lung,	none	heart, lung	lymphoma, heart, lung.
62.5	lymphoma, heart, lung	lymphoma, lung,	lymphoma, heart, lung	lymphoma, heart, lung.
200	lymphoma, heart, lung	lymphoma, heart, lung	lymphoma, heart, lung	lymphoma, heart, lung.

[a] These organs and tissue types are those contained in the OSHA risk assessment and do not reflect all of the types of tissues which were microscopically examined.
[b] Heart, specifically heart, hemangiosarcoma
[c] None of the four tissue types used in the OSHA quantitative risk assessment were microscopically examined.

2. Measure of Dose

The mechanism of cancer induction by BD is unknown for both rodents and humans. One or more of the metabolites of BD, epoxybutene, diolepoxybutane and diepoxybutane, are suspected as being responsible for the carcinogenic response in at least some of the cancers. However, which of the metabolites may be responsible for how much of the carcinogenic response has yet to be determined. Bond suggests that epoxybutene and diepoxybutane may be responsible for carcinogenic responses. (Ex. 32–28) Dr. Bond wrote:

> If carcinogenic response is elicited by a metabolite, as has been suggested, mice because of their higher rate of metabolism, might be expected to yield a greater (carcinogenic) response than rats. (Ex. 17–21)

Because there are different theories about which metabolites of BD are responsible for the various carcinogenic responses, some risk assessments have characterized carcinogenic risk as a result of type of dose: External, absorbed, or retained. In the BD proposal (55 FR 32736), OSHA calculated the ^{14}C–BD equivalents that were retained in mice at the conclusion of a 6-hour exposure period and incorrectly labeled the level as ''absorbed dose.'' This does not necessarily represent all the BD absorbed through inhalation exposure. (Ex. 34–1)

The metabolic and pharmacokinetic properties of BD have not been fully characterized for either humans or animals. Despite the absence of a generally accepted pharmacokinetic model, some metabolic information can still be applied to OSHA's QRA. The overall rate of BD metabolism in $B_6C_3F_1$ mice is approximately linear at external concentrations up to 200 ppm; BD metabolism increases sublinearly as concentrations increase until it is saturated at 625 ppm. (Ex. 90) Bond reported that epoxybutene is one of the putative carcinogenic metabolites for which metabolism in the $B_6C_3F_1$ mouse becomes saturated at 500 ppm; thus, the $B_6C_3F_1$ mouse is unable to eliminate epoxybutene as quickly above 500 ppm. Bond suggests that above 500 ppm direct quantitative extrapolation of risk from mouse studies may not be justified. (Ex. 23–86) Therefore, the 625 ppm exposure group was excluded from OSHA's risk assessment. Similarly, NIOSH and Shell did not include the 625 ppm exposure group in their best estimates of risks using NTP II data. However, NIOSH did include the 625 ppm dose group in its sensitivity analyses to see how the inclusion of the data would affect the specification (the form and number of dose explanatory variables e.g., d, d^2, d^3, etc.) of the model and the estimates of risk. (Ex. 90)

3. Animal-to-Human Extrapolation

A QRA based on a mouse bioassay requires setting values for some mouse and human variables, including those used in animal-to-human extrapolations. The values of these variables were chosen before conducting the analyses. In OSHA's quantitative risk assessment, a mouse's life span was assumed to be 113 weeks. Mice were 8 weeks old at the beginning of the study and were exposed for up to 105 weeks. OSHA assumes workers will have an average lifespan of 74 years and an occupational lifetime, working 5 days/week, 50 weeks/year, of 45 years. In the NTP II study, the average male mouse weighed 40.8 grams and female mouse weighed 38.8 grams. (Ex. 90) Mice were assigned breathing rates of 0.0245 l/min. Breathing rates of workers (for an 8-hour workday) were set at 10 m^3/8-hr.

OSHA has chosen to use a straight mg/kg, body weight to the first power, $(BW)^1$, intake as the animal-to-human species extrapolation factor for dose equivalence. Other BD QRAs employed various extrapolation factors such as ppm equivalence, $(mg/kg)^{3/4}$ equivalence, BD mono-epoxide blood levels between mice and monkey equivalence, and BD total body equivalence in $(mg/kg)^{2/3}$. OSHA believes that the evidence for the use of any of the alternative extrapolation factors is persuasive, although the Agency believes that body weight extrapolation is appropriate in this case because of the systemic nature of the tumors observed in both animal bioassays. This conversion of body weight, $(BW)^1$, produces estimates of risk which are lower than those derived using $(BW)^{3/4}$, everything else held constant. For example, with a linear, 1-stage model, if OSHA used the $(BW)^{3/4}$ conversion, holding all other elements constant, one would expect the estimates of excess risk to humans to be about 6.5 times higher than if the (BW) extrapolation factor had been used because of the weight of the experimental species (between 38.8 and 40.8 grams), and their breathing rate. For the quadratic (2-stage) and cubic (3-stage) models, the effect of relying on the $(BW)^{3/4}$ conversion rather than the $(BW)^1$, holding all else constant, would be to increase the predicted excess human risk more than 6.5 fold. (Ex. 90)

4. Estimation of Occupational Dose

It is necessary to estimate the development of cancer at a variety of occupational doses. This requires occupational doses to be converted into units comparable to those used to measure the animal experimental dose. As discussed earlier, OSHA first converted animal experimental exposures measured in ppm into occupational intake dose measured in (mg/kg).

An exposure of 1 ppm BD is converted into an equivalent exposure measured in mg/m^3 using the equation:

$$1\text{ ppm BD} = \frac{\text{Molecular Weight BD}}{\text{Molecular Weight of Air}} \times \text{density of air}$$

$$1\text{ ppm BD} = \frac{54.1\text{ mg / mole}}{24.45\text{ mole / m}^3} = 2.21\text{ BD mg / m}^3$$

Given a worker weighing 70 kg, breathing 10 m^3 of air per 8-hour day, and exposed to air containing Y ppm BD, the inhaled dose of BD in mg/kg is given by:

$$\text{Y (mg / kg) BD inhaled} = \text{Y (ppm) BD} \times 2.21\,\frac{\text{mg / m}^3}{\text{ppm}} \times \frac{10\text{ m}^3}{70\text{ kg}}$$

Using the above formula, one can calculate the estimated equivalent inhaled BD exposure among workers based on the exposure concentrations for animals (See Table V–13).

TABLE V–13.—ESTIMATE OF TOTAL HUMAN INHALED DOSE OVER A WORKDAY FOR VARIOUS EXPOSURE LEVELS OF BD

Exposure concentrations (ppm)	Estimate of total human inhaled BD over a workday (mg/kg/8-hours)
200	63.2
62.5	19.8
20	6.3
5	1.6
2	0.6
1	0.3

5. Selection of Model for Quantitative Risk Assessment

In the proposal (55 FR 32736), OSHA estimated excess risk using a quantal form of the multistage model (in a reparameterized form as calculated by GLOBAL83), which based estimates of risk to humans on the experience of the group rather than the individual. Three of the later risk assessments, Shell, NIOSH, and COHP, used a Weibull time-to-tumor form of the multistage model to fit the mouse bioassays. (Exs. 32–27; 90; 32–16) Time-to-tumor

models use more of the available information than quantal multistage models to characterize time until the development of each observable tumor, and extrapolate risks, based on an occupational dosing pattern. Since significant increases in tumor incidence occurred at multiple sites in the NTP II bioassay and a time-to-tumor model takes these competing risks into account, a time-to-tumor method is preferred over a quantal model. (Ex. 118–1B)

Therefore OSHA used a Weibull time-to-tumor form of the multistage model to characterize the risks of development of observable tumors, using the software package, TOX__RISK Version 3.5 by ICF Kaiser. The model predicts the probability, P(t,d), of tumor onset with dose pattern d by time t. It adjusts for competing causes of death prior to time t.

The Weibull time-to-tumor model is a multistage model based on the theory of carcinogenesis developed by Armitage and Doll. This theory of carcinogenesis is based on the assumption that a single line of stem cells must pass through a certain number of stages sequentially for the development of a single tumor cell. In the reparameterized form of the model used here, a k stage model is described by a polynomial of degree k, with all dose parameters greater than or equal to zero. The number of stages necessary for a model to be correctly specified varies by type of tumor, animal, and exposure agent, or any combination of the three.

Both the MLE and the 95% upper limit of the risk of developing cancer in various tissues per 1,000 workers by time t are calculated. The 95% upper bound is the largest value of excess risk that is consistent with the observed data with two-sided 95% confidence intervals. The 95% upper bound is computed based on the Weibull time-to-tumor model for which the parameters satisfy:

$$-2\,(\text{Log likelihood} - \text{Log likelihood}_{max}) \leq 2.70554$$

Where: Log likelihood_{max} is the maximum value of the log-likelihood

A 1-stage model is linear in dose; a 2-stage model is quadratic in dose; a 3-stage Weibull model is cubic in dose. Below is a mathematical representation of a 3-stage Weibull time-to-tumor model:

$$P(t,d)=1-\exp\left[-(q_0 + q_1 d + q_2 d^2 + q_3 d^3)(t - t_0^z)\right]$$

where: t_0 designates the time of onset of the tumor, t is the variable for time the tumor was observed and is assumed to follow a Weibull distribution; d is the dose-metric and is multistage; z is a parameter to be estimated, constrained between 1 and 10; the background parameter q_o and the dose parameters, q_1, q_2, q_3, are constrained to be non-negative. Constraining the dose parameters to zero or greater is biologically based, since the dose parameters are proportional to the mutation rates of the successive stages in the development of a tumor cell. The Weibull time-to-tumor model provides reasonable fits for about 75% of the tissues in the NTP historical control data base, but the precision of the fit to the dose-response data depends on the specific agent. (Ex. 90)

Four forms of the model, one less than the number of exposure groups, for each gender-outcome were fit to the data. The correct specification of the model, the number of stages, is determined by the fit of the model to the data. The likelihood ratio test identifies which model is a better fit by determining if the log-likelihood of a model is significantly greater than another model's value. The 1-, 2-, 3- and 4-stage Weibull time-to-tumor models for each gender-outcome combination were ordered according to the value of their log-likelihood. If the log-likelihood of the higher stage model is significantly greater than that of the next lower stage model's log-likelihood, one would reject the null hypothesis (the additional stage does not create a model that better characterizes the data) and conclude that the higher stage model is a significantly better predictor of the estimates of risk in the observed range than is the lower stage model.

The steps of the likelihood ratio test are as follows:

For example, assuming an alpha of 0.05, and 1 degree of freedom (the difference in the number of parameters from 1-stage and 2-stage models), the critical value would be 3.84.

Fail to Reject H_0 if:

$$2\,(\log \text{likelihood}_{1\text{-stage}} - \log \text{likelihood}_{2\text{-stage}}) < 3.84$$

Reject H_0 if:

$$2\,(\log \text{likelihood}_{1\text{-stage}} - \log \text{likelihood}_{2\text{-stage}}) \geq 3.84$$

If two times the difference of the log likelihood values of the nth stage model and the nth + 1 stage model was less than 3.84, then the additional stage would be deemed unnecessary for goodness of fit; on the grounds of parsimony, the lower stage model would be used for the risk assessment. Otherwise, the higher stage model would be judged a better fit than the lower stage one and the process would continue.

While the likelihood ratio test is suitable for testing the significance of the next higher degree dose parameter, the biologically reasonable constraint on the background incidence parameter q_0 and dose parameters that they be non-negative q_1, q_2, q_3>=0,—may impair the log-likelihood ratio test's power to determine statistical significance.

The incidences of lymphoma, heart hemangiosarcoma, lung and ovarian tumors are shown in Tables V–14 and V–15 for males and females, respectively. The TOXRISK Weibull time-to-tumor model requires that the tumor context be described for each observation. Outcomes can be put into three context categories: (1) Censored, no tumor; (2) rapidly fatal tumor; and (3) observed, tumor incidental to the animal's survival. Since OSHA was predicting the time until onset of tumor, assuming no lag time between onset and detection of tumor, t_0 was set to zero. Therefore, estimates of risk to humans based on the contribution to the likelihood of either a rapidly fatal or incidental tumor are mathematically the same.

Tables V–16 and V–17 show the Weibull time-to-tumor model estimates of log-likelihoods, the shape parameters, intercept and dose coefficients for relevant target tissues for male and female mice, respectively. The relative performance of various staged models for a specific target tissue-gender are enumerated in the log-likelihood values. It should be noted that some of the tissue-gender combination's log-likelihood values do not vary even though there is a change in the number of the stages in the model. For example, the log-likelihood values for models of all lymphoma for males and lung tumors for males and females are −6.986 E+1, −1.763 E+2, −1.626 E+2, respectively, regardless of the specification, number of stages, in the model. OSHA concluded that the 1-stage models were preferred.

As identified in Tables V–16 and V–17, only heart hemangiosarcoma models are non-linear. This is consistent with NIOSH's results when fitting Weibull time-to-tumor models to these gender-tumor combinations. The quadratic (2-stage) model for males and the cubic (3-stage) model for females better characterized the dose-response relationship in modeling time to detection of heart hemangiosarcoma than did the linear models. The higher stage model necessary to fit the heart hemangiosarcoma data is driven by the absence of cases in the two lower exposure groups, shown in Tables V–14 and V–15. Unlike the other tissues studied, there were no cases of heart

hemangiosarcoma in the control and lowest exposure groups for both male and female mice. Both male and female mice had similar heart hemangiosarcoma tumor rates, almost 30%, among the 200 ppm exposure groups. The intercepts, q_0, were zero for models of both male and female mice based on the dose-response of heart hemangiosarcomas. This is consistent with what one would expect, given the absence of background incidence rates of heart hemangiosarcomas.

TABLE V–14.—UNIVARIATE ANALYSIS OF HEART, LUNG, AND ALL LYMPHOMA NEOPLASMS BY EXPOSURE LEVEL OF 1,3-BUTADIENE AMONG NTP II MALE MICE ANALYZED IN THE TIME-TO-TUMOR MODELS

Neoplasm	Outcome		
	Tumor n [a] (%N [b])	Censored [c] n (%N)	Total N
All lymphoma, 0 ppm	4 (5.7)	66 (94.3)	70
All lymphoma, 6.25 ppm	3 (6.0)	47 (94.0)	50
All lymphoma, 20 ppm	8 (16.0)	42 (84.0)	50
All lymphoma, 62.5 ppm	11 (15.9)	58 (84.1)	69
All lymphoma, 200 ppm	9 (12.9)	61 (87.1)	70
Heart hemangiosarcoma, 0 ppm	0 (0)	70 (100)	70
Heart hemangiosarcoma, 6.25 ppm	0 (0)	49 (100)	49
Heart hemangiosarcoma, 20 ppm	1 (1.7)	59 (98.3)	60
Heart hemangiosarcoma, 62.5 ppm	5 (8.6)	53 (91.4)	58
Heart hemangiosarcoma, 200 ppm	20 (29.4)	48 (70.6)	68
Lung tumor, 0 ppm	22 (31.4)	48 (68.6)	70
Lung tumor, 6.25 ppm	23 (46.9)	26 (53.1)	49
Lung tumor, 20 ppm	20 (33.3)	40 (66.7)	60
Lung tumor, 62.5 ppm	33 (47.8)	36 (52.2)	69
Lung tumor, 200 ppm	42 (60.0)	28 (40.0)	70

[a] n is number of microscopically determined outcomes per tumor-context, gender, exposure-group outcome site combination.
[b] N is the total number of gender, exposure-group, outcome site combination which were microscopically examined.
[c] Tumor's context is C (censored); animals were microscopically examined and no tumor was found at this site.

TABLE V–15.—UNIVARIATE ANALYSIS OF HEART, LUNG, ALL LYMPHOMA AND OVARIAN NEOPLASMS BY EXPOSURE LEVEL OF 1,3-BUTADIENE AMONG NTP II FEMALE MICE ANALYZED IN THE TIME-TO-TUMOR MODELS

Neoplasm	Outcome		
	Tumor n[a] (%N[b])	Censored [c] n (%N)	Total N
All lymphoma, 0 ppm	10 (14.3)	60 (85.7)	70
All lymphoma, 6.25 ppm	14 (28.0)	36 (72.0)	50
All lymphoma, 20 ppm	18 (36.0)	32 (64.0)	50
All lymphoma, 62.5 ppm	10 (14.3)	60 (85.7)	70
All lymphoma, 200 ppm	19 (27.1)	51 (72.9)	70
Heart hemangiosarcoma, 0 ppm	0 (0)	70 (100)	70
Heart hemangiosarcoma, 6.25 ppm	0 (0)	50 (100)	50
Heart hemangiosarcoma, 20 ppm	0 (0)	50 (100)	50
Heart hemangiosarcoma, 62.5 ppm	1 (1.7)	58 (98.3)	59
Heart hemangiosarcoma, 200 ppm	20 (28.6)	50 (71.4)	70
Lung tumor, 0 ppm	4 (5.7)	66 (94.3)	70
Lung tumor, 6.25 ppm	15 (25.0)	45 (75.0)	60
Lung tumor, 20 ppm	19 (31.7)	41 (68.3)	60
Lung tumor, 62.5 ppm	27 (38.6)	43 (61.4)	70
Lung tumor, 200 ppm	32 (45.7)	38 (54.3)	70
Ovarian tumor, 0 ppm	1 (1.4)	68 (98.6)	69
Ovarian tumor, 6.25 ppm	0 (0)	59 (100)	59
Ovarian tumor, 20 ppm	0 (0)	59 (100)	59
Ovarian tumor, 62.5 ppm	9 (12.9)	61 (87.1)	70
Ovarian tumor, 200 ppm	11 (15.7)	59 (84.3)	70

[a] n is number of microscopically determined outcomes per tumor-context, gender, exposure-group outcome site combination.
[b] N is the total number of gender, exposure-group, outcome site combination which were microscopically examined.
[c] Tumor's context is C (censored); animals were microscopically examined and no tumor was found at this site.

TABLE V–16.—MAXIMUM LIKELIHOOD ESTIMATES OF MODEL COEFFICIENTS FROM VARIOUS STAGES OF WEIBULL TIME-TO-TUMOR MODELS USING THREE TUMOR RESPONSES OF MALE MICE IN THE NTP II STUDY, EXCLUDING 625 PPM EXPOSURE GROUP; SELECTION OF SPECIFICATION OF MODEL IS BASED ON LIKELIHOOD RATIO TEST

Neoplasm	Stage [a]	Log-likelihood	Z [b]	q_0	q_1	q_2	q_3	q_4
Heart hemangiosarcoma	W1	−7.061	9.810	0.00	8.306 E–23			
Heart hemangiosarcoma	[c] W2	−2.783 E–1	10	0.00	0.00	3.071 E–25		
Heart hemangiosarcoma	W3	−2.712 E–1	10	0.00	1.058 E–24	2.636 E–25	2.057 E–28	
Heart hemangiosarcoma	W4	−2.659 E–1	10	0.00	1.119 E–24	2.664 E–25	0.00	9.626 E–31
All lymphoma	[c] W1	−6.986 E+1	4.743	2.709 E–11	6.136 E–13			
All lymphoma	W2	−6.986 E+1	4.743	2.709 E–11	6.136 E–13	0.00		
All lymphoma	W3	−6.986 E+1	4.743	2.709 E–11	6.136 E–13	0.00	6.540 E–33	
All lymphoma	W4	−6.986 E+1	4.743	2.709 E–11	6.136 E–13	0.00	0.00	0.00
Lung tumor	[c] W1	−1.763 E+2	3.318	1.132 E–7	2.636 E–9			
Lung tumor	W2	−1.760 E+2	3.413	7.674 E–8	1.253 E–9	3.134 E–12		
Lung tumor	W3	−1.760 E+2	3.143	7.674 E–8	1.253 E–9	3.134 E–12	0.00	
Lung tumor	W4	−1.760 E+2	3.413	7.674 E–8	1.253 E–9	3.139 E–12	0.00	0.00

[a] Stage of time-to-tumor model; W1, Weibull 1-stage time-to-tumor model; W2, Weibull 2-stage time-to-tumor model; W3, Weibull 3-stage time-to-tumor model; W4, Weibull 4-stage time-to-tumor model.
[b] Z is the shape parameter; it is bounded, (1<=z<=10).
[c] Selected Model.

TABLE V–17.—MAXIMUM LIKELIHOOD ESTIMATES OF MODEL COEFFICIENTS FROM VARIOUS STAGES OF WEIBULL TIME-TO-TUMOR MODELS USING FOUR TUMOR RESPONSES OF FEMALE MICE IN THE NTP II STUDY, EXCLUDING 625 PPM EXPOSURE GROUP; SELECTION OF SPECIFICATION OF MODEL IS BASED ON LIKELIHOOD RATIO TEST

Neoplasm	Stage[a]	Log-likelihood	Z[b]	q_0	q_1	q_2	q_3	q_4
Heart hemangiosarcoma	W1	−2.097 E+1	4.957	0.00	4.356 E–13			
Heart hemangiosarcoma	W2	–8.745	6.126	0.00	0.00	2.222 E–17		
Heart hemangiosarcoma	W3[c]	−4.866	6.770	0.00	0.00	0.00	8.088 E–21	
Heart hemangiosarcoma	W4	−4.267	7.011	0.00	0.00	0.00	2.637 E–22	1.368 E–3
Ovarian tumor	W1[c]	−6.140 E+1	2.857	1.407 E–8	.031 E–9			
Ovarian tumor	W2	−6.069 E+1	4.079	5.397 E–11	7.075 E–12	1.399 E–13		
Ovarian tumor	W3	−6.069 E+1	4.079	5.397 E–11	7.075 E–12	1.399 E–13	0.00	
Ovarian tumor	W4	−6.069 E+1	4.079	5.397 E–11	7.075 E–12	1.399 E–13	0.00	0.00
All lymphoma	W1[c]	−5.724 E+1	6.857	3.453 E–15	1.338 E–16			
All lymphoma	W2	−5.501 E+1	7.143	1.18 E–15	2.577 E–18	2.453 E–19		
All lymphoma	W3	−5.426 E+1	7.230	7.758 E–16	6.847 E–18	0.00	7.809 E–22	
All lymphoma	W4	−5.401 E+1	7.258	7.360 E–18	7.359 E–18	0.00	0.00	3.387 E–24
Lung tumor	W1[c]	−1.626 E+2	3.416	2.096 E–8	2.096 E–9			
Lung tumor	W2	−1.626 E+2	3.416	2.090 E–8	2.090 E—9	0.00		
Lung tumor	W3	−1.626 E+2	3.416	2.090 E–8	2.096 E–9	0.00	0.00	
Lung tumor	W4	−1.626 E+2	3.416	2.090 E–8	2.096 E–9	0.00	0.00	0.00

[a] Stage of time-to-tumor model; W1, Weibull 1-stage time-to-tumor model; W2, Weibull 2-stage time-to-tumor model; W3, Weibull 3-stage time-to-tumor model; W4, Weibull 4-stage time-to-tumor model.
[b] Z is the shape parameter; it is bounded, (1<=z<=10).
[c] Selected Model.

OSHA's Estimates of Risk

The estimates from OSHA's quantitative risk assessment based an 8-hour TWA, occupational lifetime, working 5 days/week, 50 weeks/year, for 45 years, at various BD PELS are shown in Table V–18. The MLEs of excess risk of material impairment of health per 1,000 workers for cancer, based on tumors of various tissue sites and the 95% upper bounds, are presented. Various 8-hour TWA PELS, ranging from 0.1 to 5 ppm, are presented to provide a context in which to evaluate the OSHA final rule PEL of 1 ppm and to explore the feasibility of other PELS, including the proposed PEL of 2 ppm. Risks at the former BD 8-hour TWA PEL, 1,000 ppm, are not presented in Table V–18. Although risks could be estimated for an occupational lifetime exposure to an 8-hour TWA of 1,000 ppm of BD from the linear models, there is little relevancy to estimating the true risk at an 8-hour PEL for BD at 1,000 ppm for an occupational lifetime, since

8-hour TWA BD exposures have been generally far lower than 1,000 ppm.

Although the estimates of carcinogenic outcomes differ, excess risks derived from tumor sites common to both male and female $B_6C_3F_1$ mice had the same relative ranking from lowest to highest risk estimates by target tissues (heart hemangiosarcomas < lymphomas < lungs) within each gender group. After a lifetime occupational exposure to BD at the proposed 8-hour TWA PEL of 2 ppm based on the above model fits to these three individual tumor sites, one would expect between 2.7×10^{-4} to 16.2 excess cancer cases per 1,000 workers, depending on which gender-tumor site dose-response relationship is used as the basis for the extrapolation to human occupational excess risks. Decreasing the BD 8-hour TWA PEL from 2 to 1 ppm, results in a reduction of the range of estimates of excess risk of cancer to between 3.4×10^{-5} to 8.1 cases per 1,000 workers.

The estimate of excess cancer risk based on male mouse lymphoma is 1.3 per 1,000 workers at an 8-hour TWA for an occupational lifetime exposure to 1 ppm BD. Extrapolating from female mouse lymphoma data results in an estimate of 6.0 extra cancer deaths per 1,000 workers at a BD 8-hour TWA PEL of 1 ppm for an occupational lifetime of exposure.

Extrapolating from the most sensitive site, the female mouse lung, based on the 1-stage Weibull time-to-tumor model, with an 8-hour TWA PEL of 2 ppm of BD for an occupational lifetime, one would expect 16 excess cancer cases per 1,000 workers. Lowering the PEL to 1 ppm would cut the expected number of excess cancers in half to 8 cases, based on the same gender-tumor site. Based on male lung tumors, the estimate of excess cancer deaths for an 8-hour TWA exposure to 2 ppm BD over an occupational lifetime was 12.8 per 1,000 workers; lowering the 8-hour TWA occupational lifetime exposure level to 1 ppm BD decreases the estimate of excess cancer risk to 6.4 per 1,000 workers, a reduction of 6 cancer cases per 1,000 workers.

OSHA's estimates of premature occupational leukemia deaths based on the 1-stage Weibull time-to-tumor models for the following outcome sites: All lymphoma, lung tumors, and ovarian tumors, ranged between 1.3 and 8.1 per 1,000 workers. Similarly, NIOSH's 14 estimates of the excess risk of death due to leukemia, based on 1-stage Weibull time-to-tumor models, as a consequence of exposure to an 8-hour TWA of 1 ppm BD over an occupational lifetime, ranged between 0.9 and 30 cases per 1,000 workers. The preliminary estimate of 8 per 1,000 from the Delzell et al. study is concordant with this range of animal-based estimates. OSHA acknowledges that there is uncertainty in the Delzell et al. estimate, perhaps due to the natural sampling variability present in any epidemiologic study plus the *possibility* of extra-binomial uncertainty stemming from exposure misclassification. While this uncertainty makes it difficult to say whether quantitative risk estimates would be adjusted up or down relative to animal-based estimates, this suggestion is far less important than the basic conclusion that the Delzell et al. study *reinforces* earlier estimates. Even if refinement of exposures caused the Delzell et al. estimate to move up or down by even as much as a factor of 5 or more, it would not change this qualitative, and roughly quantitative, agreement.

TABLE V–18.—MAXIMUM LIKELIHOOD ESTIMATES (MLE) AND NINETY-FIVE PERCENT UPPER BOUNDS OF LIFETIME EXTRA RISK TO DEVELOP AN OBSERVABLE TUMOR PER 1,000 WORKERS DUE TO AN 8-HOUR TWA FOR AN OCCUPATIONAL LIFETIME[a] OF EXPOSURE TO 1,3-BUTADIENE, USING NTP II BIOASSAY[b] AND THE BEST FITTING WEIBULL TIME-TO-TUMOR MODELS

Neoplasms	Stages	8-hour time-weighted average concentration[c]											
		0.1 ppm		0.2 ppm		0.5 ppm		1 ppm		2 ppm		5 ppm	
		MLE	95% U.B.[d]	MLE	95% U.B.	MLE	95% U.B.	MLE	95% U.B.	MLE	95% MLE	MLE	95% U.B.
Male mice:													
Heart Hemangiosarcoma	2	[e]<0.1	0.2	[e]<0.1	0.4	[e]<0.1	0.9	[e]<0.1	1.8	[e]< 0.1	3.6	0.4	9.1
All lymphoma	1	0.1	0.2	0.3	0.5	0.6	1.1	1.3	2.3	2.5	4.5	6.3	11.2
Lung tumor	1	0.7	0.1	1.3	2.0	3.2	4.9	6.4	9.8	12.8	19.4	31.7	47.9
Female mice:													
Heart Hemangiosarcoma	3	[f]<0.1	[f]<0.1	[f]<0.1	< 0.1	[f]<0.1	0.2	[f]< 0.1	0.5	[f]<0.1	1.0	[f]<0.1	2.4
Ovarian tumor	1	0.1	0.3	0.3	0.5	0.7	1.3	1.4	2.6	2.8	5.2	6.9	13.0
All lymphoma	1	0.6	0.9	1.2	1.8	3.0	4.6	6.0	9.2	12.0	18.3	29.7	45.0
Lung tumor	1	0.8	1.2	1.6	2.4	4.1	6.1	8.1	12.2	16.2	24.1	40.00	59.4

[a] Occupational lifetime, working 5 days/week, 50 weeks/year, for 45 years.
[b] Using data from NTP II for the following exposure groups: 0, 6.25, 20, 62.5 and 200 ppm; the 625 ppm exposure group was excluded.
[c] Estimated lifetime excess risk for cancer assuming: mouse life-span of 113 weeks, male mouse body weight of 40.8g; female mouse body weight of 38.8 g; worker's breathing rate is 1.25 m^3/hr; mouse to human risk extrapolated in mg/kg-day equivalent units.
[d] 95% U.B., 95% Upper Bounds is the largest value of excess risk that is compatible with the animal response data at a confidence level of 95%.
[e] MLEs ranged from $1.5\mu10^{-4}$ to $6.0\mu10^{-2}$
[f] MLEs ranged from $3.4\mu10^{-8}$ to $4.3\mu10^{-3}$

VII. Significance of Risk

A. Introduction

In the 1980 ''Benzene Decision,'' the Supreme Court, in its discussion of the level of risk that Congress authorized OSHA to regulate, indicated its view of the boundaries of acceptable and unacceptable risk. The Court stated:

It is the Agency's responsibility to determine in the first instance what it considers to be a ''significant'' risk. Some risks are plainly acceptable and others are plainly unacceptable. If for example, the odds are one in a billion that a person will die from cancer by taking a drink of chlorinated water, the risk clearly could not be considered significant. On the other hand, if the odds are one in a thousand that regular inhalation of gasoline vapors that are 2 percent benzene will be fatal, a reasonable person might well consider the risk significant and take the appropriate steps to decrease or eliminate it. (*I.U.D.* v. *A.P.I.,* 448 U.S. 607, 655).

So a risk of $1/1000$ (10^{-3}) is clearly significant. It represents the uppermost

end of the million-fold range suggested by the Court, somewhere below which the boundary of acceptable versus unacceptable risk must fall.

The Court further stated that ''while the Agency must support its findings that a certain level of risk exists with substantial evidence, we recognize that its determination that a particular level of risk is significant will be based largely on policy considerations.'' With regard to the methods used to determine the risk level present (as opposed to the policy choice of whether that level is ''significant'' or not), the Court added that assessment under the OSH Act is ''not a mathematical straitjacket,'' and that ''OSHA is not required to support its findings with anything approaching scientific certainty.'' The Court ruled that ''a reviewing court [is] to give OSHA some leeway where its findings must be made on the frontiers of scientific knowledge [and that] * * * the Agency is free to use conservative assumptions in interpreting the data with respect to carcinogens, risking error on the side of overprotection rather than underprotection'' (448 U.S. at 655, 656).

Nonetheless, OSHA has taken various steps that make it fairly confident its risk assessment methodology is not designed to be overly ''conservative'' (in the sense of erring on the side of overprotection). For example, there are several options for extrapolating human risks from animal data via interspecies scaling factors. The plausible factors range at least as widely as from body weight extrapolation at one extreme (risks equivalent at equivalent body weights, $(mg/kg)^1$) to $(\text{body weight})^{2/3}$ (risks equivalent at equivalent surface areas) at the other. Intermediate values have also been used, and the value of $(\text{body weight})^{3/4}$, which is supported by physiological theory and empirical evidence, is generally considered to be the midpoint of the plausible values. $(\text{Body weight})^{2/3}$ is the most conservative value in this series, while body weight extrapolation is the least conservative. OSHA has generally used body weight extrapolation in assessing risks from animal data, an approach that tends to be significantly less risk conservative than the other methodologies and is likely to be less conservative even than the central tendency of the plausible values.

Other steps in OSHA's risk assessment methodology where the Agency does not use the most conservative approach are selection of the maximum likelihood estimate (MLE) of the parameterized dose-response function rather than selection of the upper 95% confidence limit, and the use of site-specific tumor incidence, rather than pooled tumor response, in determining the dose-response function for a chemical agent.

Other aspects of OSHA's risk assessment methodology reflect more conservative choices, including: basing the risk estimate on the more sensitive species tested (the mouse); including lung tumors in the range of risks presented in the quantitative analysis, even though excess deaths from lung cancer have not been observed in any of the human studies; and, assuming workers will be exposed to butadiene at the maximum permissible level for 45 years. As discussed below, if workers are exposed to BD for fewer years, their estimated risks from BD will be less than indicated. This caveat, of course, does not address lifetime risks taking into account occupational exposure to other substances encountered at other jobs. For reasons already explained, OSHA believes these choices are appropriate for the BD risk assessment. OSHA also recognizes that use of the most conservative approach at every step of the risk assessment analysis could produce mathematical risk estimates which, because of the additive effect of multiple conservative assumptions, may overstate the likely risk. OSHA believes its quantitative risk assessment for BD strikes an appropriate balance.

Risk assessment is only one part of the process OSHA uses to regulate toxic substances in the workplace. OSHA's overall analytic approach to regulating occupational exposure to particular substances is a four-step process consistent with judicial interpretations of the OSH Act, such as the Benzene Decision, and rational policy formulation. In the first step, OSHA quantifies the pertinent health risks, to the extent possible, performing quantitative risk assessments. The Agency considers a number of factors to determine whether the substance to be regulated currently poses a significant risk to workers. These factors include the type of risk posed, the quality of the underlying data, the plausibility and precision of the risk assessment, the statistical significance of the findings and the magnitude of risk. (48 FR 1864, January 14, 1983) In the second step, OSHA considers which, if any, of the regulatory options being considered will substantially reduce the identified risks. In the third step, OSHA looks at the best available data to set permissible exposure limits that, to the extent possible, both protect employees from significant risks and are also technologically and economically feasible. In the fourth and final step, OSHA considers the most cost-effective way to fulfill its statutory mandate by crafting regulations that allow employers to reach the feasible PEL as efficiently as possible.

B. Review of Data Quality and Statistical Significance

As discussed in the Health Effects section, OSHA has concluded that butadiene is a probable human carcinogen. This conclusion is based on a body of evidence comprised of animal bioassays, human epidemiological investigations, and other experimental studies that together are both consistent in their findings and biologically plausible. First, OSHA has reviewed four rodent inhalation bioassays, two mouse bioassays conducted under the National Toxicology Program (designated NTP I and NTP II), a mouse study by Irons et al. in 1989, and a rat study sponsored by the IISRP. (Exs. 2–32, 23–1, 32–28D, 90, 96) All three mouse studies found a consistently high tumor response in BD-exposed mice, relative to control animals. Several target organs were identified, particularly by the NTP II study; however, all three studies found dose-related increases in the incidences of lymphocytic lymphoma and heart hemangiosarcomas associated with exposure to BD. Most significantly, the NTP II study reported statistically significant increases in tumor incidence among mice exposed to BD well below OSHA's current PEL of 1,000 ppm (exposure to as low as 6.25 ppm was associated with a statistically significant increase in tumors, e.g., lung tumors in female mice). There was also evidence for a dose-rate effect, meaning that the observed tumor incidence in mice exposed to high concentrations over short periods of time was higher than that observed in mice administered an equivalent cumulative concentration over a long period of time. The study employing BD-exposed rats also found increased incidences of several types of cancer, albeit at lower response rates than were observed in the mouse studies. The two major epoxide metabolites of BD have also been shown to be carcinogenic in rats and mice.

OSHA has also reviewed a number of human epidemiological studies that have examined the mortality experience of styrene-butadiene rubber (SBR) workers. These studies have consistently reported an elevated relative risk of leukemia-or lymphoma-related death among BD-exposed workers. The most recent of these, the study by Delzell et al., updated and expanded previous SBR worker mortality studies and found a positive

and statistically significant dose-response relationship between cumulative exposure to BD and increased leukemia mortality, which remained statistically significant even after controlling for the potential confounder of concurrent styrene exposure. (Ex. 117–1) The Delzell et al. study thus provides further and more directly relevant evidence that an increased risk of leukemia-related death is associated with exposure to BD. Furthermore, other epidemiologic studies have reported finding an unusually short latency period (as little as 3 to 4 years from time of initial exposure to death) for exposure-related hematologic malignancies among workers who experienced exposures to BD in the past that were higher than exposures that prevail today. (Ex. 2–26, 3–34 Vol III H–1)

Evidence for the carcinogenicity of BD is further strengthened by a collection of studies showing that the epoxide metabolites of BD are mutagenic in a wide variety of *in vitro* and *in vivo* test systems. Examination of cultured lymphocytes from BD-exposed workers has revealed the presence of chromosome aberrations, an elevated frequency of chromatid breaks, and various mutations, thereby providing direct evidence of genotoxicity in occupationally-exposed humans. (Exs. 118–2A, 118–2D) Furthermore, the finding of activated K-*ras* oncogenes in tumors of BD-exposed mice provides additional support for a mutagenic mode of action; this finding has particular relevance to human risk in that K-*ras* is the most commonly detected oncogene in human cancer. (Ex. 129)

The findings from the animal bioassays and human epidemiologic studies identify the hematopoietic system as a primary target organ for BD-related carcinogenesis. Target organs for toxicity are not necessarily those for carcinogenicity. Other experimental findings are consistent with these observations. Studies in BD-exposed rodents have found concentration-dependent decreases in red blood cell counts, hemoglobin concentration, and other indicators of hematopoietic suppression. (Exs. 114, 32–38D, 23–12) There is also some suggestive evidence that workers exposed to BD at levels well below the current 1,000 ppm PEL exhibit hematological changes indicative of bone marrow depression. (Exs. 23–4, 2–28) Finally, many of the tumor types found in BD-exposed mice, including lymphocytic/hematopoietic cancer, lung cancer, mammary gland tumors, and possibly hemangiosarcomas, are tumors that are often found in association with exposure to other industrial chemicals known to cause lymphocytic/hematopoietic cancer in humans. Thus, OSHA finds that the body of scientific studies contained in the BD record, which includes well-conducted animal bioassays, human epidemiologic studies, and other experimental investigations, provides convincing evidence that BD is a probable human carcinogen.

This view is also held by other scientific organizations that have examined some or all of the same evidence. EPA considers BD to be a probable human carcinogen, and NIOSH regards BD as a potential occupational carcinogen and recommends controlling exposures to the lowest feasible level. In 1983, based on the findings of the first NTP bioassay alone, ACGIH classified BD as an animal carcinogen and, in the following year, recommended a new TLV of 10 ppm. In 1992, before the Delzell et al. study was released, IARC classified BD as a probable human carcinogen (Group 2A).

As discussed in the Quantitative Risk Assessment section, OSHA has selected the NTP II mouse bioassay for quantitative assessment of cancer risks for several reasons. Chief among these is that the NTP II study was conducted at BD concentrations that are representative of current exposure conditions and that the results demonstrated a strong dose-response relationship for several cancer sites. In addition, the study is of very high quality and pathology results from individual animals were available to the Agency, enabling OSHA to use a time-to-tumor model that could account for the early cancer-related deaths that occurred among the test animals (competing risks). OSHA also chose to base its risk estimates on the dose-response relationships for three cancer types: lung, ovarian, and lymphoma. The incidence of each was significantly elevated. It should be noted that pooling the total number of animals having any of these tumor types would have yielded risk estimates higher than OSHA's final values.

Because data were available on individual animals, including time of death, OSHA chose to use a Weibull time-to tumor form of the multistage model based on the biological assumption that cancer is induced by carcinogens through a series of events. This model has the advantage of accounting for competing risks.

The multistage model is most frequently used by OSHA; it is also a mechanistic model based on the biological assumption that cancer is induced by carcinogens through a series of independent stages. The model may be conservative, because it assumes no threshold for carcinogenesis and because it is approximately linear at low doses, although there are other plausible models of carcinogenesis which are more conservative. The Agency believes that the multistage model conforms most closely to what we know about the etiology of cancer, including the fact that linear-at-low-dose behavior is expected for exogenous agents, which increases the risk of cancer already posed by similar ''background'' processes. There is no evidence that the multistage model is biologically incorrect and abundant evidence supports its use, especially for genotoxic carcinogens, a category that most likely includes BD. OSHA's preference is consistent with the position of the Office of Science and Technology Policy of the Executive Office of the President, which recommends that ''when data and information are limited, and when much uncertainty exists regarding the mechanisms of carcinogenic action, models or procedures that incorporate low-dose linearity are preferred when compatible with limited information.'' (OSTP, Chemical Carcinogens: A Review of the Science and Its Associated Principles. Federal Register, March 14, 1985, p. 10379)

The BD record contained a great deal of commentary on the possible role of the principal epoxide metabolites of BD on the development of cancer in test animals, and on whether differences in BD metabolism, distribution, and excretion can explain the observed differences in cancer responses between BD-exposed mice and rats. In evaluating this information, OSHA explored the possibility of using a physiologically-based pharmacokinetic (PBPK) approach to estimate cancer risk among BD-exposed workers. In considering the use of PBPK modeling for estimating equivalent human dose in its final risk assessment for BD, OSHA considered several preselected criteria for judging whether the available data was adequate to permit OSHA to rely on a PBPK analysis in place of administered exposure levels. These are the same criteria that OSHA has recently used to rely on a PBPK-based analysis in its risk assessment of methylene chloride. The criteria included the following:

1. The predominant and all relevant minor metabolic pathways must be well described in several species, including humans.

2. The metabolism must be adequately modeled.

3. There must be strong empirical support for the putative mechanism of carcinogenesis.

4. The kinetics for the putative carcinogenic metabolic pathway must have been measured in test animals *in vivo* and *in vitro* and in corresponding human tissues at least *in vitro*.

5. The putative carcinogenic metabolic pathway must contain metabolites that are plausible proximate carcinogens.

6. The contribution to carcinogenesis via other pathways must be adequately modeled or ruled out as a factor.

7. The dose surrogate in target tissues used in PBPK modeling must correlate with tumor responses experienced by test animals.

8. All biochemical parameters specific to the compound, such as blood:air partition coefficients, must have been experimentally and reproducibly measured. This must especially be true for those parameters to which the PBPK model is sensitive.

9. The model must adequately describe experimentally measured physiological and biochemical phenomena.

10. The PBPK models must have been validated with other data (including human data) that were not used to construct the models.

11. There must be sufficient data, especially data from a broadly representative sample of humans, to assess uncertainty and variability in the PBPK modeling.

For the BD risk assessment, OSHA has chosen to use for animal-to-human dose equivalency mg/kg-day uptake based on the ppm exposure levels in the NTP II mouse study as the dose-metric.[7] While the body of data in the record leads OSHA to conclude that metabolism of BD to active metabolites is probably necessary for carcinogenicity, OSHA has chosen total body uptake rather than organ metabolic levels because the Agency was unable to determine from the record (a) which of the active metabolites are responsible for which observed tumors in the mice, (b) what the mouse and human metabolic equivalent doses were, (c) whether any of the PBPK models can successfully correlate with the tumor responses observed in mice and rats, and (d) whether local reactions in the mouse and human bone marrow were more important than total body burden.

[7] A dose metric is the way in which dose is expressed in describing a dose-response relationship. A dose metric may be expressed as an applied dose, such as ppm concentration or mg of intake per kg body weight, or as an internal dose, such as mg per gram wet weight of an organ or mg of total metabolite formed per kg body weight.

OSHA would have considered using BD metabolite body burden based on total human BD metabolites if the human chamber concentration data had been available, which would support estimating total human BD metabolism. Data of this type were available and used in OSHA's PBPK modeling for methylene chloride. In the absence of human chamber data or some better estimate of human equivalent dose, OSHA has chosen to use mg/kg-day BD uptake from the ppm inhalation exposure levels in the NTP II mouse bioassay as suitable for animal-to-human equivalency.

C. Material Impairment of Health

The 1 ppm 8-hour TWA PEL is designed to reduce cancer risks among exposed workers. As mentioned above and in the Health Effects section, some epidemiological studies indicate that the increased risk of leukemia posed by BD exposure may occur within a short period after initial exposure. (This is supported by the NTP mouse bioassays, in which there was high early mortality resulting from the development of BD-induced cancers, especially lymphomas.) Therefore, OSHA believes these hematopoietic cancers are likely to be fatal, will result in substantially shortened worker lifespans, and clearly represent ''material impairment of health'' as defined in the OSH Act and case law.

OSHA has also concluded that exposure to BD is associated with a potential risk of adverse reproductive effects in both males and females. This conclusion is based on the two NTP animal bioassays, which found testicular atrophy in male mice exposed to 625 ppm BD and ovarian atrophy in female mice exposed to BD concentrations as low as 6.25 ppm, as well as other animal studies that have reported dominant lethal effects (indicating a genotoxic effect on germ cells) and abnormal sperm morphology in BD-exposed male mice. (Exs. 23–74, 23–75, 117–1) There is also evidence that BD exposure is associated with fetotoxicity in mice, and a teratogenic effect indicative of a transplacentally induced somatic cell mutation was observed in one mouse study. (Exs. 2–32, 23–72, 126) OSHA believes that teratogenic effects and gonadal atrophy would also unambiguously constitute ''material impairment of health.'' Furthermore, although OSHA did not quantify reproductive risks that may be associated with exposure to BD, OSHA believes that reducing the 8-hour TWA PEL from 1,000 ppm to 1 ppm is likely to substantially reduce this risk.

D. Risk Estimates

OSHA's final estimate of excess cancer risks associated with exposure to 5 ppm BD (8-hour TWA) ranges from 11.2 to 59.4 per 1000, based on lymphomas, lung tumors and ovarian tumors seen in the NTP II mouse study (OSHA did not estimate the risks associated with exposure to the current PEL of 1,000 ppm, since workers are rarely, if ever, exposed to BD levels of that magnitude). Based on linear models the estimated risks at the new PEL of 1 ppm range from 1.3 to 8.1 per 1000, which represents a substantial reduction in risk from those associated with exposures to 5 ppm or greater.

OSHA's risk estimates for the 1 ppm PEL are similar in magnitude to, or lower than, most of the estimates contained in several risk assessments submitted to the BD record, which utilized a variety of models and dose metrics. Furthermore, NIOSH's quantitative assessment based on the Delzell et al. epidemiologic study of SBR workers yielded an estimate of 8 cancer deaths per 1,000 workers exposed to 1 ppm BD, a figure that is in close agreement with the upper end of the range of risks predicted by OSHA.

Risks greater than or equal to 10^{-3} (1 per 1,000) are clearly significant and the Agency deems them unacceptably high. OSHA concludes that the new BD standard substantially lowers risk but does not reduce risk below the level of insignificance. The estimated levels of risk at 1 ppm are 1.3 to 8.1 per 1000. The ancillary provisions including the exposure goal program will further reduce risk from exposure to BD.

E. ''Significant Risk'' Policy Issues

Further guidance for the Agency in evaluating significant risk and narrowing the million-fold range described in the ''Benzene Decision'' is provided by an examination of occupational risk rates, legislative intent, and the academic literature on ''acceptable risk'' issues. For example, in the high risk occupations of mining and quarrying, the average risk of death from an occupational injury or an acute occupationally-related illness over a lifetime of employment (45 years) is 15.1 per 1,000 workers. The typical occupational risk of deaths for all manufacturing industries is 1.98 per 1,000. Typical lifetime occupational risk of death in an occupation of relatively low risk, like retail trade, is 0.82 per 1,000. (These rates are averages derived from 1984–1986 Bureau of Labor Statistics data for employers with 11 or more employees, adjusted to 45 years of employment, for 50 weeks per year).

Congress passed the Occupational Safety and Health Act of 1970 because of a determination that occupational safety and health risks were too high. Congress therefore gave OSHA authority to reduce significant risks when it is feasible to do so. Within this context, OSHA's final estimate of risk from occupational exposure to BD at levels of 2 ppm (2.5 to 16.2 deaths per 1,000 workers) or higher is substantially higher than other risks that OSHA has concluded are significant, is substantially higher than the risk of fatality in some high-risk occupations, and is substantially higher than the example presented by the Supreme Court in the benzene case. Moreover, a risk in the range of 1.3 to 8.1 per 1000 at 1 ppm is also clearly significant; therefore, the PEL must be set at least as low as the level of 1 ppm documented as feasible across all industries.

Because of technologic feasibility considerations, OSHA could not support promulgating a PEL below 1 ppm. However OSHA has integrated other protective provisions into the final standard to further reduce the risk of developing cancer among employees exposed to BD.

Based on OSHA's QRA, employees exposed to BD at the 8-hour TWA PEL limit, without the benefit of the supplementary provisions, would remain at significant risk of developing adverse health effects, so that inclusion of other protective provisions, such as medical surveillance and employee training, is both necessary and appropriate. The exposure goal program and action level trigger incorporated into the standard will encourage employers to lower exposures below 0.5 ppm to further reduce significant risk if it is feasible to do so in their workplaces. Consequently, the programs triggered by the action level will further decrease the incidence of disease beyond the predicted reductions attributable merely to a lower PEL.

As OSHA has explained, numerous issues arise in quantifying estimated risk to workers from BD. Such estimates are thus inherently uncertain; and, as more information becomes available, some of that uncertainty may be addressed and may substantially alter the risk estimate. Although OSHA believes the estimates fulfill its legal obligation to provide substantial evidence of significant risk the estimates should not be interpreted as a precise quantification of the cancer risk associated with the new PEL, or as demonstrated evidence of actual worker disease caused by BD.

OSHA's determination of significant risk is predicated, consistent with empirical evidence and the legal mandates of the OSHA Act, on determining the risk to a worker exposed to BD for a working lifetime (45 years) at the PEL. To the extent that future exposures to BD are (substantially) lower than 1 ppm, the estimated risks associated with those exposures will be (substantially) lower than the range presented in OSHA's QRA.

OSHA believes the final standard will reduce the risks of BD below those estimated using the mathematical model. The estimates of risk consider only exposures at the PEL, and do not take fully into account the other protective provisions of the standard such as medical surveillance, hazard communication, training, monitoring, and the exposure goal program. The decrease in risk to be achieved by additional provisions cannot be adequately quantified beyond a determination that they will add to the protection provided by the lower PEL alone. OSHA has determined that employers who fulfill the provisions of the standard as promulgated will provide protection for their employees from the hazards presented by occupational exposure to BD well beyond those which would be indicated solely by reduction of the PEL.

Furthermore, as discussed above and in the Health Effects section, there is evidence from the NTP bioassays that exposure to periodic high concentrations of BD may be associated with a higher cancer risk compared to an equivalent cumulative exposure administered over a longer time frame. OSHA has included a 5 ppm short-term exposure limit (STEL), averaged over 15 minutes, to provide protection to employees who are exposed to elevated BD concentrations during brief periods, such as in maintenance work.

As a result, OSHA concludes that its 8-hour TWA PEL of 1 ppm and associated action level (0.5 ppm) and STEL (5 ppm) will reduce significant risk and that employers who comply with the other provisions of the standard will be taking feasible, reasonable, and necessary steps to help protect their employees from the hazards of BD.

VIII. Summary of the Final Economic Analysis

As required by Executive Order 12866 and the Regulatory Flexibility Act of 1980 (as amended 1996), OSHA has prepared a Final Economic Analysis to accompany the final standard for occupational exposure to 1,3-butadiene (BD). (The entire analysis, with supporting appendix material, has been placed in the BD rulemaking docket. See Exhibit 137.) The purpose of the final economic analysis is to:

- Describe the need for a standard governing occupational exposure to 1,3-butadiene;
- Identify the establishments and industries potentially affected by the standard;
- Evaluate the costs, benefits, economic impacts and small business impacts of the standard on affected firms;
- Assess the technological and economic feasibility of the standard for affected establishments, industries, and small businesses; and
- Evaluate the availability of effective non-regulatory approaches to the problem of occupational exposure to 1,3-butadiene.

Need for the Standard

OSHA's final BD standard covers occupational exposures to this substance, a high-volume chemical used principally as a monomer in the manufacture of a wide range of synthetic rubber and plastic polymers and copolymers. In all, about 9,700 employees are estimated to be exposed to BD. However, for 2,100 of these employees in the petroleum refining industry, BD exposures are below the action level. The largest group of exposed workers is found in the BD end-product industry. Other BD operations in which workers are exposed are crude BD production, BD monomer production, and transportation terminals handling BD monomers (stand-alone terminals).

There is strong evidence that workplace exposure to BD poses an increased risk of cancer. Animal bioassays have shown BD to be a source of significant risk for tumors at multiple sites (i.e. lung tumors, heart hemangiosarcomas, lymphomas and ovarian tumors). BD may also potentially cause both male and female reproductive effects. To protect all BD-exposed workers from these adverse health effects, the final standard lowers the airborne concentration of BD to which workers may be exposed from the current permissible exposure limit (PEL) of 1,000 ppm as an 8-hour time-weighted average (8-hour TWA) to 1 ppm, and adds a short term exposure limit (STEL) of 5 ppm, measured over 15 minutes. (For a detailed discussion of the risks posed to workers from exposure to BD, see the Quantitative Risk Assessment and Significance of Risk sections of the preamble, above.)

OSHA's final BD standard is similar in format and content to other health standards issued under Section 6 (b)(5)

of the Act. In addition to PELs, the standard requires employers to monitor the exposures of workers; establish regulated areas when exposures may exceed one of these PELs; implement engineering and work practice controls to reduce employee exposures to BD; develop an exposure goal program; provide respiratory protection to supplement engineering controls where such controls are not feasible, are insufficient to meet the PELs, are necessary for short infrequent jobs, or in emergencies; provide medical screening; train workers about the hazards of BD (also required by OSHA's Hazard Communication Standard); and keep records relating to the BD standard. Recognizing that workers exposed to BD are at significant risk, an industry-labor working group joined together to develop joint recommendations for the final standard for BD. This group's recommendations form the basis for OSHA's final rule. The contents of the standard are explained briefly in Chapter I of the final economic analysis and in detail in the Summary and Explanation (Section X of the preamble, below).

Chapter II of the economic analysis describes the uses of BD and the industries in which such use occurs. Exposure to 1,3-butadiene occurs as a result of exposure to the monomer. Once BD is in polymer form, the exposure is minimal to non-existent. In all, OSHA analyzed 5 types of processes in which BD exposure occurs: crude BD production, where the feedstock for BD monomer is produced; BD monomer production, in which BD is refined from crude BD to a 99 percent pure monomer; BD product manufacture, where BD monomer is converted to various polymer products; stand-alone terminals, which receive, store and distribute BD monomer; and petroleum refineries, where BD may occur as an unwanted byproduct in some types of refining units. Table VIII–1 shows these industry operations and the number of workers affected by the final rule. A total of 255 facilities are estimated to be potentially affected by the standard. These establishments employ 9,700 workers who are estimated to be exposed to BD in the course of their work. The industry operation with the largest number of directly exposed employees is BD product manufacture, which has 6,500 exposed employees (over two-thirds of the total).

TABLE VIII–1.—INDUSTRY OPERATIONS AND NUMBER OF WORKERS AFFECTED BY THE FINAL RULE FOR 1,3-BUTADIENE

	Number of affected workers	Number of facilities in industry [a]
Crude 1,3-Butadiene Production	540	27
1,3-Butadiene Monomer Production	552	12
1,3-Butadiene Polymer Product Manufacture	6,461	[c] 71
Standard-Alone Terminals	50	5
Subtotal	7,603	115
Petroleum Refining Sector	[b] 2,100	140
Total	9,703	255

Source: U.S. Department of Labor, OSHA, Office of Regulatory Analysis, 1996.

[a] Some facilities may fall under several industry sectors. For example, 9 monomer facilities are also crude producing facilities.

[b] Potential exposures to 1,3-butadiene are low and of extremely short duration in refining.

[c] Represents number of processes and not necessarily plants.

Chapter III of the analysis assesses the technological feasibility of the final standard's requirements, and particularly its PELs, for firms in the 5 industry operations with employee exposure identified in the Industry Profile. OSHA finds, based on an analysis of exposure data taken on workers performing the BD-related tasks identified for each operation, that compliance with the standard is technologically feasible for establishments in the industries studied. With few exceptions, employers will be able to achieve compliance with both PELs through the use of engineering controls and work practices. The few exceptions are maintenance activities, such as vessel cleaning, which have traditionally often involved the use of respiratory protection.

The exposure data relied on by OSHA in making its technological feasibility determinations were gathered by NIOSH in a series of site visits to plants in the affected industries. These data show that many facilities in the affected industries have already achieved the reductions in employee exposures required by the final rule. At least some workers in every job category work in facilities that have already achieved the PEL requirements. OSHA's analysis of technological feasibility evaluates employee exposures at the operation or task level to the extent that such data are available. In other words, the analysis identifies relevant exposure data on a job category-by-job category basis to permit the Agency to pinpoint those BD-exposed workers and job operations that are not yet under good process control and will thus need additional controls (including improved housekeeping, maintenance procedures, and employee work practices) to achieve compliance. Costs are then developed (in Chapter V of the economic analysis) for the improved controls needed to reach the new levels.

The benefits that will accrue to BD-exposed employees and their employers, and thus to society at large, are substantial and take a number of forms. Chapter IV of the analysis describes these benefits, both in quantitative and qualitative form. At the current baseline exposure levels to BD, the risk model estimates that 76 cancer deaths will be averted over a 45-year period. By reducing the total number of BD-related cancer deaths from 76 deaths to 17 deaths over 45 years, the standard is projected to save an average of 1.3 cancer deaths per year. Table VIII–2 shows these risk estimates. In addition to cancer deaths, the standard may prevent male and female reproductive effects.

TABLE VIII–2.—WORKER EXPOSURE TO BD AND LUNG CANCER RISK OVER 45 YEARS AT CURRENT EXPOSURE LEVELS AND LEVELS EXPECTED UNDER THE STANDARD

	8-hour time weighted average (ppm)							
	0–0.5	0.5–1.0	1	1.0–2.0	2.0–5.0	5.0–10.0	10+[c]	Total
Lifetime Excess Cancer Risk (per thousand workers)[a]	2.05	6.1	8.1	12.15	28.1	60	480	.....
Baseline Number of Workers Exposed	5697	354	156	598	320	440	38	7603
Estimated Excess Deaths in Baseline (Existing PEL)[b]	12	2	1	7	9	27	18	76
Predicted Number of Workers Exposed at New PEL	7177	426	0	0	0	0	0	7603

TABLE VIII–2.—WORKER EXPOSURE TO BD AND LUNG CANCER RISK OVER 45 YEARS AT CURRENT EXPOSURE LEVELS AND LEVELS EXPECTED UNDER THE STANDARD—Continued

	8-hour time weighted average (ppm)							
	0–0.5	0.5–1.0	1	1.0–2.0	2.0–5.0	5.0–10.0	10+[c]	Total
Predicted Excess Deaths at New PEL[b]	14	3	0	0	0	0	0	17

[a] Based on OSHA 1-stage Weibull time-to-tumor model for lung tumors.
[b] Computed as level of lifetime risk times the number of exposed workers.
[c] Based on a median exposure for these workers of 60 ppm.
Source: Office of Regulatory Analysis, OSHA; Department of Labor.

The costs employers in the affected industries are estimated to incur to comply with the standard total $2.9 million in 1996 dollars. These costs, which are presented in Chapter V, the full economic analysis, are annualized over a 10-year horizon at a discount rate of 7 percent. Table VIII–3 shows annualized costs by provision of the standard; the most costly provisions are those requiring engineering controls ($1.6 million per year) and respiratory protection ($0.7 million per year). Table VIII–4 analyzes compliance costs by operation and shows that BD products manufacture will incur over two-thirds of the standard's costs of compliance.

TABLE VIII–3.—ANNUAL COSTS OF THE FINAL BUTADIENE STANDARD, BY PROVISION

Provision	Annualized costs
Engineering Controls	$1,551,000
Exposure Goal Program	104,000
Respirators	685,000
Exposure Monitoring	364,000
Objective Data	3,000
Medical Surveillance	72,000
Leak and Spill Detection	27,000
Regulated Areas	4,000
Information and Training	12,000
Recordkeeping	29,000
Total	2,851,000

TABLE VIII–4.—ANNUAL COSTS OF THE FINAL BUTADIENE STANDARD, BY INDUSTRY SECTOR

Industry sector	Annualized costs
Crude Production	$333,000
Monomer	210,000
BD Products	2,252,000
Stand-Alone Terminals	53,000
Petroleum Refining	3,000
Total	2,851,000

Chapter VI of the economic analysis analyzes the impacts of compliance costs on firms in affected operations. The final rule is clearly economically feasible: annualized compliance costs are less than 0.5 percent of estimated sales in every industry and are less than 4 percent of profits in every industry (see Table VIII–5). Costs of this magnitude will not affect the viability even of marginal firms.

TABLE VIII–5.— ESTIMATED SALES AND PROFITS OF ESTABLISHMENTS AFFECTED BY THE 1,3–BUTADIENE RULE

	SIC	Sales per average establishment ($000)	Pre-tax profit per average establishment in SIC	Annualized cost per establishment	Cost as percentage of sales	Cost as percetage of profit
Crude 1,3–Butadiene Production	2869	$53,998	$5,645,237	$12,341	0.02	0.22
1,3–Butadiene Monomer Production	2869	53,998	5,645,237	17,502	0.03	0.31
1,3–Butadiene Product Production:						
—ABS Resins, Butadiene Copolymers (<50% butadiene)	2821	38,000	2,015,155	31,724	0.08	1.57
—Butadiene Copolymers (.50% butadiene), Neoprene, Nitrile Rubber, Chloroprene Rubbers, EPDM Polymers, Styrene-Butadiene Rubber (SBR Latex), Polybutadiene	2822	16,243	1,328,956	31,724	0.20	2.39
—Adipontrile/Hexamethylene	2869	53,998	5,645,237	31,724	0.06	0.56
—Fungicides	2879	42,694	1,681,885	31,724	0.07	1.89
Petroleum Refining	2911	525,273	19,100,851	22	Negligible	Negligible
Stand-Alone Terminals	4226	2,400	287,273	10,556	0.44	3.67

Source: US Department of Labor, OSHA, Office of Regulatory Analysis, 1996.
Negligible denotes less than 0.005 percent.

Under the Regulatory Flexibility Act, OSHA is required to determine whether its regulations have a significant impact on a substantial number of small entities. The small firm standards established by the U.S. Small Business Administration (SBA) for industries using 1,3-butadiene are as follows: 1,500 employees for firms in SIC 2911 (petroleum refining); 1,000 employees for firms in SICs 2869 (industrial organic chemicals, which includes BD crude and monomer producers) and 2822 (synthetic rubber); 750 employees for firms in SIC 2821 (plastic Table VIII–5 materials and resins); 500 employees for firms in SIC 2879 (agricultural chemicals, which includes some producers of BD products); and annual receipts of $18.5 million for firms in SIC 4226 (special warehousing and storage, which includes stand-alone terminals). Using these definitions, OSHA identified two small firms among crude

BD producers, one small firm among monomer producers, 10 small firms among BD product manufacturers, and no small firms among stand-alone terminals. Because the ownership of one stand-alone terminal could not be identified, OSHA assumed that there would be one small stand-alone terminal. For each of these industries, OSHA estimated revenues and costs for small firms based on the average size of the small firms using BD. The typical petroleum refining establishment has fewer than 1,500 employees. However, because OSHA did not have data on the number of firms with fewer than 1,500 employees, the Agency relied on establishment data to examine possible impacts on small petroleum refineries.

Table VIII–6 presents the results of the regulatory flexibility screening analysis and shows estimated compliance costs and economic impacts relative to revenues and pre-tax income for affected small businesses at the four-digit SIC code level. This approach reflects extreme case impacts because the impacts on small firms are analyzed using average per-establishment compliance costs. As shown in the table, compliance costs as a percentage of industry revenues never reach one percent; they range from less than 0.005 percent to 0.44 percent for establishments in all affected industries. Estimates of compliance costs as a percentage of profits range from less than 0.005 percent to 3.67 percent. Such impacts are not large enough to be significant. In addition, the impacts reflected in the table are likely to be overestimated because Table VIII–6 they are based on extreme-case costs.

TABLE VIII–6.—ESTIMATED SALES AND PROFITS OF ESTABLISHMENTS AFFECTED BY THE 1,3-BUTADIENE RULE

	SIC	Definition of small entity per the SBA	Average sales per small establishment ($million)	Pre-tax profit per small establishment in SIC	Annualized cost per establishment	Cost as percentage of sales	Cost as percentage of profit
Crude 1,3-Butadiene production	2869	1,000 employees	51.30	$5,363,182	$12,341	0.02	0.23
1,3-Butadiene Monomer production	2869	1,000 employees	10.60	1,108,182	17,502	0.17	1.58
1,3-Butadiene product production:							
ABS Resins, Butadiene Copolymers (<50% butadiene).	2821	750 employees	50.00	2,651,515	31,724	0.06	1.20
Butadiene Copolymers (.50% butadiene), Neoprene, Nitrile Rubber, Chloroprene Rubbers, EPDM Polymers Styrene-Butadiene Rubber (SBR Latex), Polybutadiene.	2822	1,000 employees	24.00	1,963,636	31,724	0.13	1.62
Adiponitrile/Hexamethylenediamine	2869	1,000 employees	10.60	1,108,182	31,724	0.30	2.86
Fungicides	2879	500 employees	30.40	1,197,578	31,724	0.10	2.65
Petroleum refining	2911	1,500 employees	45.80	1,655,455	22	Negligible	Negligible
Stand-alone terminals	4226	$18.5 million (receipts).	2.40	287,273	10,556	0.44	3.67

Source: US Department of Labor, OSHA, Office of Regulatory Analysis, 1996.
Negligible denotes less than 0.005 percent.

Thus, because this standard will not have a significant impact either on the smallest establishments (as defined by the SBA) or on the typical establishment in this industry, OSHA certifies that this final standard will not have a significant economic impact on a substantial number of small entities.

OSHA also examined the impact of this standard on increased expenditures by State, local or tribal governments. OSHA found that none of the affected employers were State, local, or tribal governments. Further, since the total costs of the standard are $2.8 million, the stand will not increase expenditures for the private sector by more than $100 million. As a result, OSHA certifies that, for the purposes of the Unfunded Mandates Reform Act of 1995, as well as E.O. 12875, this rule does not include any federal mandate that may result in increased expenditures by State, local and tribal governments, or increased expenditures by the private sector of more than $100 million.

IX. Environmental Impacts

In accordance with the National Environmental Policy Act (NEPA), OSHA has reviewed this standard for occupational exposure to BD and determined that this action will have no significant impact on the external environment. The new standard can be achieved through a combination of engineering controls, work practices, and respirator use in maintenance situations. OSHA reviewed the extent to which any of the engineering controls or work practices might have an environmental impact. OSHA found that these controls will have no significant adverse impact on the eternal environment because no additional solid waste would be contaminated with BD and that any new releases to the external atmosphere would constitute an insignificant increase in emissions. Indeed, most of the recommended controls would prove advantageous from an environmental viewpoint. For example, such controls as replacing slip-tube gauges with magnetic gauges, use of closed loop sampling systems, and the use of dual mechanical seals all serve to reduce both worker exposures and emissions to the environment. Other controls, such as exhaust ventilation in laboratories, leave environmental emissions unchanged.

Based on its review, OSHA concludes that there will be no significant impact on the environment external to the work place as a result of the promulgation of this standard.

X. Summary and Explanation of the Final Standard

OSHA has determined that the requirements set forth in this final standard are those which, based on currently available data, are necessary and appropriate to provide adequate protection to employees exposed to BD. In the development of this standard, OSHA carefully considered the comments received in the docket in response to the proposed rule as well as information received in the BD docket by OSHA since initiation of this

rulemaking. OSHA believes that these provisions are, in large part, similar to the requirements recommended by the labor/industry group in the recent reopening of the BD rulemaking record. (Ex. 118–12A)

A. Scope and Application

The final rule covers all occupational exposure to 1,3-butadiene, with certain exceptions which are described below. OSHA does not believe there are any impacts in construction or maritime employment, but, consistent with OSHA's policy, the standard is being made applicable to these sectors to avoid gaps in coverage and to protect workers in unusual circumstances. Coverage in longshoring and marine terminals would only be triggered if BD is present outside sealed intact containers.

The final rule contains three exemptions from the scope and application; all three exemptions are typically included in OSHA chemical-specific health standards. These exemptions address situations in which the Agency has concluded that the likelihood of significant exposure is quite low. The final rule's exemptions are as follows:

(a)(2)(i) Except for the recordkeeping provisions in paragraph (m)(1), this section does not apply to processing, use, or handling of products containing BD or to other work operations and streams in which BD is present where objective data are reasonably relied upon that demonstrate that the work operation or the product or the group of products or operations to which it belongs may not reasonably be foreseen to release BD in airborne concentrations at or above the action level or in excess of the STEL under either the expected conditions of processing, use, or handling that will cause the greatest possible release or in any plausible accident.

(a)(2)(ii) This section also does not apply to work operations, products or streams where the only exposure to BD is from liquid mixtures containing 0.1% or less of BD by volume or the vapors released from such liquids, unless objective data become available that show that airborne concentrations can exceed the action level or STEL under reasonably predictable conditions of processing, use or handling that will cause the greatest possible release.

(a)(2)(iii) Except for labeling requirements and requirements for emergency response, this section also does not apply to storage, transportation, distribution or sale of BD or liquid mixtures in intact containers or in transportation pipelines sealed in such a manner as to fully contain BD vapors or liquid.

The language of this section, with a single exception, reflects the joint recommendations of the labor-industry group. The exception relates to the suggested language in the labor/industry agreement ''or in any credible accident'' at the end of paragraph (a)(2)(i).[8] (Ex. 118–12A) OSHA believes that this phrase lacks clarity and has chosen to use the word ''plausible'' instead of ''credible'' to better convey the Agency's intent. Dow Chemical Company, which reviewed a draft of the Agreement, objected to the use of the phrase ''credible accident'' because Dow personnel were unsure of its meaning. (Ex. 118–16, p. 3) Additionally, OSHA has modified the definition of objective data to more clearly delineate its intended source and use.

Although the agreement itself offered little explanation for each of the recommended exemptions, the submission of CMA, a participant in the joint discussions, sheds some light on the issue of why the term ''credible accident'' was included. They felt that the ''focus in applying the (objective data) exemption should be on reasonably predictable conditions of processing, use or handling associated with each product, stream or work operation.'' (Ex. 118–13, p. 3) CMA said that the addition of the phrase ''credible accident'' was meant to trigger only the emergency response requirements of the standard when objective data demonstrate that exposures may reasonably be foreseen to exceed the action level or STEL during a ''credible accident.''

OSHA believes that the phrase ''credible accident'' is unnecessary because paragraph (a)(2)(i) already states that objective data may be used to address situations that can reasonably be foreseen. However, OSHA has decided to include the phrase ''any plausible accident'' to stress the point that the objective data criteria are not intended to be so circumscribed that it is impossible to meet them. OSHA acknowledges that a constellation of unforeseen circumstances can occur that might lead to exposure above the action level or STEL even when the objective data demonstration has been correctly made, but believes that such occurrences will be rare. OSHA further believes that compliance with other regulations, such as the Process Safety Management standard (29 CFR 1910.119), will provide additional assurance that such accidents will not occur.

OSHA proposed to exempt ''processing, use, or handling of products containing BD where objective data are reasonably relied upon that demonstrate that the product is not capable of releasing BD in airborne concentrations at or above the action level or in excess of the STEL under the expected conditions of processing, use, or handling that will cause the greatest possible release * * *'' (55 FR 32736 at 32803) The proposed regulation also included a requirement that the employer keep the data supporting the exemption as long as such data were relied upon.

Roger Daniel of the CMA BD panel objected to the requirement that in order to be relied upon as objective data, the data must reflect include the ''greatest possible release.'' He argued that ''* * * to verify the greatest possible release and thereby obtain an exemption, employers could be forced to conduct extensive worst case analyses for every product.'' (Ex. 112, p. 133)

OSHA agrees that a worst-case demonstration for each product is not necessary to qualify for this exemption under the ''objective data'' provision of the scope and application paragraph of the standard. Due to concern that the proposed language might be overly difficult to interpret, OSHA has modified the language in the standard to reflect this and added a definition of the term ''objective data.'' The definition now states that ''objective data means monitoring data, or mathematical modelling or calculations based on composition, chemical and physical properties of a material, stream or product.'' The exemption allows use of objective data, and states that when objective data are used to exempt employers from the BD standard, the data must demonstrate that the work may not ''reasonably be foreseen'' to release BD above the action level or the STEL.

The objective data may be, at least partially, comprised of monitoring results. For example, data collected by a trade association from its members that meet the definition of objective data may be used. However, a single employer's initial monitoring results would not be sufficient to meet the criteria for objective data under this standard (see discussion of objective data in Definitions section of this preamble). A showing by initial monitoring that the level of BD is below the action level does greatly reduce the responsibilities of the employer; however, it would not support an

[8] This section does not apply to processing, use, or handling of products containing BD or to other work operations and streams in which BD is present where objective data are reasonably relied upon that demonstrate that the work operation or the product or the group of products or operations to which it belongs may no reasonably be foreseen to release BD in airborne concentrations at or above the action level or in excess of the STEL under either the expected conditions of processing, use, or handling that will cause the greatest possible release or in *any credible accident.*

exemption from the standard. Instead, to qualify as objective data, OSHA means employers' reliance on manufacturers' worst case studies, laboratory studies, and other research that demonstrate, usually by means of exposure data, that meaningful exposures cannot occur. Paragraph (a)(3) requires that all such data be maintained by the employer as long as they are relied upon to support the exemption.

In comments received during the recent re-opening of the record, Total Petroleum suggested that objective data be kept as long as they are relied upon and for 5 years thereafter. (Ex. 118–5) However, OSHA believes that keeping these data for as long as they are used is a better use of resources, and this requirement is included in the final rule.

OSHA has allowed the use of objective data in past standards to exempt employers from initial monitoring requirements and hence, from most of the provisions of these standards, e.g., formaldehyde 29 CFR 1910.1048, asbestos 29 CFR 1926.1101. The American Petroleum Institute (API) and others voiced support for this approach. (Ex. 108; 112)

The objective data definition is discussed more extensively in the definition section of this preamble.

The following paragraphs deal with the comments and testimony received during the rulemaking on topics related to the scope and application of the standard. Some of these comments would appear to address both the objective data exemption and an exemption for materials containing less than 0.1% BD. This is due, in part, to the fact that the proposal did not contain an exemption for the latter materials, and commenters objected to having to make a demonstration using objective data that materials containing less than 0.1% BD would not release BD at levels in excess of the action level or STEL in order to be exempted. OSHA has reexamined the issue and has included the 0.1% BD cutoff in the final rule paragraph (a)(2)(ii).

Crude Oil and Refinery Products

Oil refiners indicated that BD is absent from crude oil, and requested that OSHA explicitly exempt oil and gas well drilling, production and servicing operations, and transportation of crude oil from the standard. (Ex. 108; 109; 91) They also indicated that, although BD may be an undesirable intermediate by-product with trace quantities in enclosed streams in modern petroleum refinery processes, BD is normally destroyed, so it would not be present in refined products, such as gasoline, motor fuel, or other fuels. They asked for an exemption for those refined products.

A site visit report was submitted to the rulemaking record by OSHA's contractor, Kearney/Centaur, which described the processes at a refinery. (Ex. 23–119) The site visit report contained the following conclusions:

> The concentrations of 1,3-butadiene in the process streams studied rarely if ever exceed 2500 ppm. * * * The contents of the streams are released to the atmosphere only in extremely small quantities through sampling, or by significant spills, leaks or accidents. * * * Employees are rarely in close proximity to the sampling points or any other potential release point. * * * Monitoring data show that exposures are well below the proposed limits, below the actions levels and even below measurable levels in most cases. (Ex. 23–119)

Based on these comments and data in the docket, OSHA has included the exemption for ''streams'' containing less than 0.1% BD, such as those found in refineries, and in the final rule has included streams among the items for which an objective data exemption can be claimed.

Polymers

Duke Power asked OSHA to exempt finished BD polymer from the BD standard to be consistent with the vinyl chloride and acrylonitrile standards, so that the utility would not need to maintain records of objective data. (Ex. 32–12) The Rubber Manufacturers Association (RMA) said that ''synthetic rubbers made from polymerized BD are used extensively by (their 200 companies) members in manufacturing a wide range of these rubber products.'' (Ex. 32–13). In the preamble to the proposal, OSHA acknowledged that ''[i]t is likely that in a number of products made from, containing or treated with BD, there may be insignificant residual BD present to the extent that minimal exposure would be expected.'' (55 FR 32736 at 32787) RMA indicated that four studies indicated the levels of BD in the samples from their plants range from 4 ppb to 0.2 ppm. These values are clearly well below the 0.1% cutoff in the final rule and the percentage exemption would therefore apply.

Intact Containers

Exxon Chemical Company, a producer of BD, which ships it by several modes of transportation (ship, barge, tankcar, tanktruck and pipeline) indicated that there is no potential for BD exposure since BD-containing streams are totally contained in pressurized equipment during transportation. (Ex. 32–17) Exxon said: ''The developing and maintaining the 'objective' data would be very cumbersome (for many carriers and shipment points and various kinds of BD-containing streams) * * * time-consuming and would not contribute to reduced exposure.'' Exxon asked OSHA to provide a general exemption for intact transportation containers. The Independent Liquid Terminals Association (ILTA), whose members own or lease facilities in which BD is stored, asked OSHA to establish a concentration cutoff and to grant reasonable exemptions from the standard. (Ex. 32–18) Roger Daniel of the CMA panel made a similar request. (Tr. 1/18/91, p. 1174) The labor-industry agreement also recommended exemption of intact containers and pipelines from the standard except for labeling and emergency provisions. (Ex. 119)

OSHA is allowing the exemption of ''storage, transportation, distribution or sale of BD or liquid mixtures in intact containers or in transportation pipelines sealed in such a manner as to fully contain BD vapors or liquid,'' OSHA is not excluding by this exemption, the situation where BD-containing material is being transferred to or from containers, pipelines, or vehicles. Data have shown that there is a potential for significant exposure to BD during these operations. For example, exposure data indicate high potential exposure during unloading of railcars and tank trucks in both monomer and polymer production facilities. (Ex. 30) Such operations are not exempt from the standard-they are not considered ''sealed'' for purposes of this standard and do not ''fully contain BD vapors or liquid.''

Mixtures of Less Than 0.1% BD

The final rule contains a specific, though qualified, exemption for instances where materials containing less than 0.1% BD are present.

In the proposal, OSHA discussed the application of the Hazard Communication Standard (29 CFR 1910.1200) to materials containing less than 0.1% of BD, a carcinogen, but did not specifically include an exemption for these materials.

Jack Hinton of Texaco, representative of API, which represents over 250 companies involved in all aspects of the petroleum industry, indicated that

> * * * many petroleum streams and products will have little or no BD present (and that) much of the petroleum industry, such as production, transportation and marketing operations would qualify for these case-by-case exemptions. (Ex. 74; Tr.2/20/91, p.1842–44).

Since the ''objective data'' obligation could impose a burden on their

industry, Mr. Hinton urged OSHA to expand the exemption to include the processing, use and handling of streams containing BD, as well as products. (Tr. 2/20/91, pp. 1842–44)

Similarly, CMA stated, ''* * * facilities that manufacture, process or use BD often have very extensive, integrated operations.'' (Ex. 32–28, p. 108; Ex. 112, p. 134) At these facilities, BD is found at quantities below 0.1% not just in the immediate area of BD production, but in many other streams and products as well. Under these circumstances, the burden of generating ''objective data'' which would qualify for the exemption would be ''so enormous as to largely eliminate its value.'' (Ex. 112, p. 134).

Exxon Chemical Company also indicated that ''BD is present in a large number of product and intermediate streams throughout chemical plants and refineries.'' (Ex. 32–17) According to Exxon, there is very little exposure potential at low levels, since precautions are taken to contain these flammable materials and its rapid dispersion as a gas at ambient condition. Exxon suggested an exemption for product and intermediate streams containing less than 0.1 percent BD ''as is used in the Hazard Communication Standard and in the Benzene Standard.'' They claimed that their resources to develop ''objective data'' could be devoted to ''more productive activities aimed at exposure reduction.'' Arco Products Company stated that ''potential exposures are of extremely short duration in the refining business'' and asked for the exemption of ''streams with less than 0.1% as in the benzene final standard.'' (Ex. 32–20)

OSHA has found that, on the basis of the record and comments of participants in the rulemaking, as well as the recommendations of the labor/industry group, the exemptions as stated above are justified. The criteria for each exemption are helpful in assuring that only very low exposure to BD is possible when the exemptions apply.

The exemptions from the scope of the standard closely resemble those in the benzene standard. The exclusion of products containing less than 0.1 percent BD is consistent with the Hazard Communication Standard, which has this as a cutoff for application of certain requirements to carcinogens (paragraph (a)(2)(ii)).

The basis for the exemptions for sealed containers and pipelines containing mixtures with more than 0.1 percent BD is that it is unlikely for such containers and pipelines to leak sufficient BD to expose employees over the action level on a regular basis. Further, sealed containers and pipelines with liquids containing more than 0.1 percent BD are covered by the emergency provisions of the standard (e.g., personal protective equipment, medical screening). Sealed containers and pipelines are also covered by the Hazard Communication Standard, 29 CFR 1910.1200. If the containers or pipelines contain more than 0.1 percent BD, employers are required to: label the containers and pipelines to indicate that they contain BD, a carcinogen; to have employee training specifying what to do if the container was opened or broken; and to supply employees with material safety data sheets. Labeling and training provisions of the Hazard Communication Standard provide protection in normal situations where a container or pipeline breaks so that employees will know how to handle and clean up the material safely. The emergency provisions of the Hazardous Waste and Emergency Response Standard would cover emergency situations caused by major releases.

Further, operations where the containers and pipelines are opened or the chemicals contained in them are used are covered because of the possibility of exposure above the action level or PELs. It should be noted that while the Hazard Communication Standard generally exempts materials containing less than 0.1 percent of a carcinogen, any material containing BD (defined as a potential carcinogen in this standard) that is capable of causing exposure above the action level is covered even if the 0.1 percent exemption applies. Specifically this provision states:

> If the chemical manufacturer, importer or employer has evidence to indicate that a component present in the mixture in concentrations of less than one per cent (or in the case of carcinogens, less than 0.1 percent) could be released in concentrations which would exceed an established OSHA permissible exposure limit or ACGIH Threshold Limit Value, or could present a health risk to employees in those concentrations, the mixture shall be assumed to present the same hazard. (29 CFR 1910.1200(d)(5)(iv))

OSHA also notes that a similar provision is included in the standard for DBCP (1,2-dibromo-3-chloropropane). (29 CFR 1910.1044).

B. Definitions

Action level means airborne concentration of BD of 0.5 ppm calculated as an eight (8)-hour time-weighted average (TWA). OSHA has determined that the final PEL for BD is 1 ppm and the final action level for BD is one half that level, 0.5 ppm. OSHA notes that this is the action level recommended in the Labor-Industry Joint Recommendations. (Ex. 119)

Due to the variable nature of employee exposures to airborne concentrations of BD, an action level provides a means by which the employer may have greater assurance that employees will not be exposed to BD over the PEL on days when measurements are not taken.

The action level also increases the cost-effectiveness and performance orientation of the standard while improving employee protection. Employers who can, in a cost-effective manner, develop innovative methodology to reduce exposures below the action level will be encouraged to do so in order to save on the expenses for the monitoring and medical surveillance provisions of the standard. Their employees will be further protected because their exposures will be less than half of the permissible exposure limit. They will also avoid the need to implement controls specified under paragraph (g) of this section, Exposure Goal Program.

The statistical basis for using an ''action level'' has been discussed in connection with several other OSHA health standards (see, for example, acrylonitrile (29 CFR § 1910.1045; 43 FR 45809 (1978)). In brief, the standard does not require the employer to monitor employee exposure on a daily basis. This would be prohibitively expensive. Use of the action level is a method that gives the employer confidence that if employees are exposed to less than the action level on days when measurements are taken, they are most likely not exposed over the PEL on days when no measurements are taken—all other factors being equal. Where exposure measurements are above the action level, the employer cannot reasonably be confident that the employee may not be overexposed. Therefore, requiring periodic employee exposure measurements to be made where exposures are at or above the action level provides the employer with a reasonable degree of confidence that employee exposures have been adequately characterized. (Ex. 23–59)

Use of the action level concept will result in the necessary inclusion of employees under this standard whose exposures are above the action level and for whom further protection is warranted. The action level mechanism will also greatly limit the percentage of workplaces covered under the standard because employers whose employees are under the action level will be exempt from most provisions of the standard. The action level concept,

therefore, provides an objective means of tailoring different sections of the standard to those employees who are at the greatest risk of developing adverse health effects from exposure to BD.

Unique to the BD standard is paragraph (g), Exposure Goal Program, which is also triggered at the action level. This program, which OSHA included at the recommendation of the Labor/Industry group, is described further in the Summary and Explanation of paragraph (g).

Assistant Secretary means the Assistant Secretary of Labor for Occupational Safety and Health, U.S. Department of Labor, or designee.

Authorized person means any person specifically authorized by the employer whose duties require the person to enter a regulated area, or any person entering such an area as a designated representative of employees for the purpose of exercising the right to observe monitoring and measuring procedures, or any other person authorized by the Act or regulations issued under the Act. Due to the highly hazardous nature of BD exposure, the number of persons designated as authorized should be limited, insofar as possible.

Business day is newly defined in the final rule as any Monday through Friday, except those days designated as federal, state, local or company holidays. (Ex. 18–12A) This term is used in the paragraph dealing with employee notification of monitoring results, (d)(7), in which OSHA had proposed that notification occur within 15 working days after the receipt of monitoring results. The joint labor/industry group recommended 5 business days instead. In addition, they recommended that the notification of the corrective action being taken when monitoring results indicate exposures in excess of the PELs be required within 15 business days, (paragraph (d)(7)(ii)). OSHA has accepted the recommendations because it is protective of workers. As a general rule, OSHA health standards require notification within 15 days of receipt of results. Quicker notification is, of course, desirable, but feasibility considerations usually make the 15-day period the shortest practical. However, in this case, the parties agreed that 5-day notification is feasible and desirable and OSHA wholeheartedly endorses the concept.

OSHA has also allowed 15 business days between medical evaluations and notification of employees of their results. This change was recommended by the labor/industry agreement and was not proposed by OSHA in 1990. OSHA believes that the requirement of paragraph (j)(7) requiring that written notification of the medical opinion be provided by the employer within 15 business days of the examination or other medical evaluation is reasonable and adequately protective of worker health.

1,3–Butadiene means an organic compound with chemical formula $CH_2{=}CH-CH{=}CH_2$ which has a molecular weight of 54.15 gm/mole. Its Chemical Abstracts Registry Number is 106–99–0. The definition was needlessly lengthy in the proposal and has been shortened.

OSHA has added a definition for the *complete blood count* required in the medical screening and surveillance section. Because the definition may vary, OSHA believes that a definition which includes each component of what the Agency requires to be included in a *complete* blood count is needed. These components (which are laboratory tests performed on whole blood specimens) are: White blood cell count (WBC), hematocrit (Hct), red blood cell count (RBC), hemoglobin (Hgb), differential count of white blood cells, red blood cell morphology, red blood cell indices, and platelet count.

Day means any part of a calendar day. Therefore, if a requirement is applicable to an employer whose employee is exposed to BD on 10 days in a calendar year, that requirement is applicable if the employee is exposed to BD for any part of each of 10 calendar days in a year.

Director means the Director of the National Institute for Occupational Safety and Health (NIOSH), U.S. Department of Health and Human Services, or designee. This definition remains unchanged from that in the proposal.

OSHA proposed that *Emergency situation* would mean an occurrence such as, but not limited to, equipment failure, rupture of containers, or failure of control equipment that may or does result in a substantial release of BD that could cause employee exposures that greatly exceed the PELs.

The provisions that the employer must comply with in case of an emergency situation include Respiratory Protection, Medical Screening and Surveillance, and Employee Information and Training. As is also the case in the benzene standard, OSHA does not intend that every leak will automatically constitute an emergency situation. The exposure must be high and unexpected. Thus, the nature of the emergency provisions is performance-oriented and relies upon judgement, for it is not possible to specify detailed circumstances which constitute an emergency.

In objecting to the proposed definition of emergency, Shell noted that ''a release does not necessarily equate to high employee exposure.'' (Ex. 32–27) OSHA also sought additional guidance in its definition of ''emergency;'' when the record was re-opened for comment on the labor/industry draft agreement, OSHA raised the issue by presenting a revised definition for comment. This was:

> * * * any occurrence such as, but not limited to, equipment failure, rupture of containers, or failure of control equipment that may or does result in an uncontrolled significant release of BD.

The revised definition changed the conditions of release to qualify as an emergency from ''unexpected'' to ''uncontrolled'' to more clearly define what the agency considered to be an emergency situation which would trigger specific provisions of the standard (e.g., respirator use, limited medical screening and surveillance). OSHA asked whether the change provided adequate guidance to the public. Relatively few commenters dealt specifically with this issue. However, Bridgestone/Firestone, Inc. stated that ''* * * a controlled release, even in significant quantities, is not an emergency precisely because it can be controlled.'' (Ex. 118–14, p. 5) They recommended that OSHA define what constitutes a significant release as an ''uncontrolled release of BD that presents serious danger to employees in the workplace,'' noting that OSHA defined catastrophic release in 29 CFR 1910.119 as one posing a ''serious danger to employees.'' Bridgestone/Firestone feared that defining emergency as proposed might result in application of it to situations which are ''lawful, safe and managed by the standard through respirator use.'' (Ex. 118–14, p. 6)

Dow Chemical Company also submitted comments in support of defining emergency in terms of ''uncontrolled significant release of BD'' because of its consistency with other standards. (Ex. 118–16, p. 3)

Akzo Nobel Chemicals, Inc. suggested that the definition of an emergency should be:

> An uncontrolled dangerous event due to a combination of unforeseen circumstances, such as the spill of significant quantities of hazardous substances, fire or explosion, massive failure of equipment/personnel or other occurrences which require an immediate response by persons not working in the immediate area, except maintenance activities and which could result in harmful

exposures during hazardous activities, fires or explosions. (Ex. 118–3)

They also expressed the belief that use of the term ''uncontrolled'' is essential to the definition of an emergency, and that ''daily, foreseeable events are not emergencies.'' Azko Nobel gave, as an example, the rupture of a container, which they felt would constitute an emergency ''only when a dangerous amount of material escaped.'' Akzo Nobel felt that the definition of emergency should also depend on the type of responder needed to deal with the situation—that ''if the responders are persons outside the work area (other than maintenance type personnel) that fact suggests that an emergency is occurring.'' Akzo Nobel believes the definition of emergency must be tied to the amount of hazardous material released and the exposure resulting from it.

All these comments in general support OSHA's revised definition. Therefore, OSHA is adopting the revised definition for the reasons stated in the comments.

Employee exposure means exposure to airborne BD which would occur if the employee were not using respiratory protection. This definition is intended to apply to all variations of the term ''employee exposure'' that have essentially the same meaning, such as ''exposed employee'' and ''exposure.'' The definition is consistent with OSHA's previous use of the term ''employee exposure'' in other health standards (Asbestos, 29 CFR 1910.1001; Benzene, 29 CFR 1910.1028; Ethylene Oxide, 29 CFR 1910.1047; Cadmium, 29 CFR 1910.1027).

Objective data are redefined in the final rule to clarify and better define what OSHA believes they entail. Objective data are defined as:

monitoring data, or mathematical modelling or calculations based on composition, chemical and physical properties of a material, stream or product.

In the proposed rule, the term ''objective data'' was used to provide an exemption from the scope and application of the rule and was not specifically defined in the definition section.[9]

There appeared to be some confusion as to what was meant by objective data as presented in the proposal. OSHA has determined that a specific definition of objective data is necessary, and it has included it in the definition section.

OSHA believes that objective data may include such data as: (1) Information provided by the manufacturer or a determination that air concentrations will not exceed the action level or STEL, under foreseeable conditions of use, based on the information provided by the manufacturer; (2) representative data or collective industry data which are relevant to the materials, process streams, and products for which the exemption is being documented, under foreseeable conditions of use.

Charles Adkins, then Director of OSHA's Health Standards Programs Directorate, explained at the hearing that ''. . . you are allowed to make a calculation to determine whether or not you need to do monitoring or not. . . . If you're below the action level, you do not need to do anything.'' (Tr. 1/15/91, pp. 29–31) Indeed, to qualify for an exemption does not necessarily ''. . . have to be actual data collected or experimental data. . . . (The employer) . . . can make . . . appropriate calculations, and if he can support his calculation, that would be considered part of his objective data.'' (Tr. 1/15/91, p. 30)

The definition of objective data contained in the final rule adopts the one contained in the Labor-Industry Joint Recommendations. (Ex. 119) OSHA believes that such a definition meets the intent of the proposal. While OSHA does not require employers to perform complex modeling to avail themselves of the objective data exemption, it should be noted that there may be times when it would be difficult or inappropriate to attempt to use objective data. This issue was discussed in the formaldehyde standard, wherein the Agency stated that complex modeling exercises may not be a substitute for employee exposure monitoring

. . . in workplaces where many complex factors must be considered to use objective data, a high degree of uncertainty will be associated with trying to assess employee exposure from objective data. In these instances employers should conduct exposure monitoring instead of relying on objective data so that they can have confidence that they are in compliance with the standard's provisions. (52 FR 46100, 46255–46256, 12/4/87)

However, if carefully used in appropriate circumstances, OSHA believes that objective data may be useful in minimizing needless exposure monitoring.

Permissible Exposure Limits, PELs means either the 8 hour Time Weighted Average (8-hr TWA) exposure or the Short-Term Exposure Limit (STEL). The two limits are often referred to as PELs in various documents and this definition clarifies what is meant by ''PELs.''

Physician or Other Licensed Health Care Professional has been incorporated into the standard's medical screening and surveillance provisions to include persons certified, registered, or licensed to perform various activities required by the standard. OSHA's authority does not supersede a state's right to license, register, or certify individuals to perform these tasks. Therefore, in the final rule, OSHA has replaced the word ''physician'' with the phrase ''physician or other licensed health care professional'' to allow individuals to perform duties under the provisions of the standard which they are permitted to perform in their jurisdiction through their licensure, registration, or certification.

Regulated area means an area where airborne concentrations of BD exceed or can reasonably be expected to exceed the permissible exposure limits. The definition of regulated areas in the final rule is the same as the proposed definition. Texaco was concerned that the phrase ''can reasonably be expected'' is open to varied interpretations or could be misunderstood, and recommended that regulated areas be required only where exposure monitoring indicates that air concentrations of BD are above the PELs. (Ex. 32–26) OSHA believes workers will be better protected where a regulated area is required even if one of the PELs is not exceeded at all times. The specific requirements for a regulated area are discussed in the summary and explanation for paragraph (e) below.

This section is newly defined in the final rule to clarify that this term is synonymous with the 1,3-Butadiene Final Rule.

C. Permissible Exposure Limits

Since 1970, the PEL for 1,3-butadiene has been 1,000 parts per million (ppm) as an 8-hour TWA. The final rule reduces the permissible exposure limits to 1 ppm as an 8-hour time-weighted average (TWA) and to 5 ppm as a 15-minute short-term exposure limit (STEL). As part of this rulemaking, OSHA is deleting from Table Z–2 of 29 CFR 1910.1000 the exposure limit of 1000 ppm as an 8-hour TWA for BD. OSHA has determined that the former PEL presented a significant risk of cancer to employees exposed to BD and

[9] This section does not apply to the processing, use or handling of products containing BD where objective data are reasonably relied upon that demonstrate that the product is not capable of releasing BD in airborne concentrations at or above the action level or in excess of the STEL under the expected conditions of processing, use, or handling that will cause the greatest possible release. (55 FR 32803)

that compliance with the new standard will substantially reduce that risk. The basis for the 8-hour TWA–PEL and STEL is discussed in the sections of this preamble dealing with health effects, risk assessment, significance of risk, and in the economic analysis. This section briefly summarizes some of that discussion.

As discussed earlier in the Health Effects section, in the NTP bioassays, mice exposed to BD via inhalation developed cancer at multiple sites. When these data were used to estimate risk via a quantitative risk assessment, the data indicated that risk at the former PEL was quite high and should be lowered. In addition, epidemiologic studies of BD-exposed worker groups have suggested that BD induced leukemia in a dose responsive manner. In the proposal, OSHA's preliminary risk assessment found its ''best'' estimate of risk, derived from the female mouse heart hemangiosarcoma data using the multistage model, predicted 147 excess deaths per 1,000 workers at the former PEL of 1,000 ppm.

In 1990 OSHA proposed a PEL of 2 ppm as an 8-hour TWA and 10 ppm as a short-term limit, based in part on its preliminary risk assessment, which estimated an excess cancer risk of 5.1 per 1,000 workers at the proposed PEL of 2 ppm. As discussed earlier in this preamble, economic and technologic feasibility considerations led OSHA to propose a PEL of 2 ppm, although the preliminary risk assessment estimated that there was still significant remaining risk at that level of BD. As discussed in the Quantitative Risk Assessment section, OSHA used a more recent lower dose NTP mouse study to estimate risk. That estimate using lung cancer in female mice, the most sensitive cancer site in the most sensitive species, was 8.1 excess cancers per 1,000 workers exposed to 1 ppm BD over a 45-year working lifetime (the estimate at 2 ppm for this site was 16.2 lung cancers per 1,000 workers).

In light of the need to reduce the significant residual risk remaining at a PEL of 2 ppm, OSHA determined that it must reevaluate the record evidence to assure that significant risk is reduced to the extent feasible. This review, discussed at length earlier in this preamble, has led OSHA to conclude that an 8-hour time-weighted average permissible exposure limit of 1 ppm is both feasible and is needed to further protect worker health.

Throughout this rulemaking there was consensus that the existing PEL adopted by OSHA in 1971, 1,000 ppm, which ACGIH had developed as a TLV for BD to prevent irritation and narcosis, was inadequate to protect workers from the hazard presented by this chemical (e.g., IISRP, Ex. 34–4, CMA Ex. 32–28, American Lung Association, Ex. 32–10). However, there was *not* unanimity as to the appropriate level. OSHA's expert witness, Dr. Philip Landrigan, stated the following:

> * * * I was distressed to see that in setting the PEL at two parts per million that you decided to accept the occurrence of five excess deaths per thousand exposed workers which translates to 5,000 excess deaths per million exposed workers. It seems to me that this is not consistent with optimal practice and if the agency has a chance to reconsider that risk assessment and possibly lower the standard from the proposed PEL of two parts per million, I certainly would like to ask you to reconsider. * * * Five thousand cancer deaths seems like a lot to me. (Tr. 1/15/91, p. 204)

In testimony and submissions to the rulemaking record, NIOSH recommended that the permissible exposure level be set at the lowest feasible levels and recommended 6 parts per billion on the basis of its assessment of risk. (Ex. 32–25, Tr. 1/17/91, p. 681) NIOSH's quantitative risk assessment was based on NTP's lower dose mouse study and application of a time-to-tumor model (see Quantitative Risk Assessment and Ex. 90). Although some of the underlying assumptions made by NIOSH in its analysis differ from those OSHA has used in a subsequent time-to-tumor analysis, the level of risk estimated by NIOSH further contributed to OSHA's concern regarding the level of risk estimated to remain at the proposed PEL of 2 ppm.

Other risk assessments were submitted which yielded lower estimates of risk. (Shell Oil Company, Ex. 32–27; CMA, 28–14) Each of the risk assessments in the record is discussed in the section of this preamble dealing with the quantitative risk assessment.

At the time of the public hearings, industry representatives opposed lowering the PEL below 2 ppm. For example, participants from Shell stated that they had already ''set an internal standard at 2 ppm,'' and felt a lower level would not increase employee protection. (Shell, Ex. 32–27, 34–7) This was echoed in the comments of styrene-butadiene latex manufacturers. (Ex. 34–5) In fact, IISRP felt that a 10 ppm PEL was low enough to eliminate significant risk. They described the difficulties the polymer industry anticipated at lower PELS. (Ex. 34–4, 32–33)

Labor representatives, particularly the United Rubber Workers, and supporters, among them: Irving Selikoff, Cesare Maltoni, Sheldon Samuels, Myron Mehlman, and Louis Beliczky, urged OSHA to adopt a PEL of 0.2 ppm. (Ex 32–1, 34–6) Diane Factor, representing the AFL–CIO, said that ''OSHA must conduct an analysis that attempts to show feasibility below 2 ppm and not stop at the industry acceptable level.'' (Tr. 1/17/91, p. 839)

Dr. Myron Mehlman, Professor of Environmental and Community Medicine at UMDNJ, Robert Wood Johnson Medical School, New Jersey, testifying on behalf of the United Rubber, Cork, Linoleum and Plastic Workers of America, AFL–CIO, and the Sierra Club, stated his opinion that a PEL of 2 ppm was ''dangerously high.'' (Ex. 79) He urged OSHA to ''adopt a 0.05 to 2 ppm PEL and 0.2 to 1 ppm STEL to protect the health of workers and the environment. (Tr. 2/20/91, p. 1776) The Department of Health Services, State of California, performed a quantitative risk assessment using the NTP–I mouse study data and urged OSHA to ''* * * consider the feasibility of adopting 1 ppm or a lower level.'' (Ex. 32–16)

The issues raised by participants and OSHA's concern about the level of risk remaining at the 2 ppm PEL led OSHA to conclude that further scrutiny and re-analysis of the record data were necessary and prudent to assure that the limit set by the Agency is that which is reasonably necessary and appropriate and that reduces significant risk to the extent feasible, particularly in view of the high degree of carcinogenicity of BD.

Joint Recommendations of Labor/Industry Group Regarding PELs

The March 1996 industry/labor agreement recommended that OSHA adopt a PEL of 1 ppm and a STEL of 5 ppm (also an action level of 0.5 ppm). OSHA is pleased that this group of interested parties have reached the same conclusion as the Agency in this regard. The joint recommendations suggest a STEL of 5 ppm, but questioned whether the record would support this STEL. IISRP nonetheless agreed that the PELs included in the recommendation are feasible in view of the fact that the final rule allows the use of respirators in intermittent, short-duration work. OSHA's own analysis also shows that a 1 ppm TWA and 5 ppm STEL are technologically and economically feasible and necessary to substantially reduce significant risk of material impairment of health. (See the extensive discussions in the health effects, risk assessment, significant risk and feasibility sections.) Therefore, OSHA is promulgating these limits in its final rule for BD.

Short-Term Exposure Limit (STEL)

The proposed STEL was five times the proposed PEL, 10 ppm. The final rule includes a STEL which is five times the new 8-hour TWA limit, or 5 ppm.

The choice of the level of the STEL was a concern to a number of rulemaking participants. The CMA Butadiene Panel did not feel a STEL was needed at all and strongly objected to its being lower than 10 ppm. (Ex. 32–28) The SB latex manufacturers expressed a similar view. (Ex. 34–5) CMA alleged that the STEL provision lacked a legal basis and that the analyses on which OSHA based its proposed STEL were flawed. (Ex. 32–28) Others objected to the STEL on the basis that BD lacked acute health effects. (Ex. 32–19; 32–26; 32–27; 32–33; 60)

A major labor participant in the rulemaking, URW, urged OSHA to adopt a lower STEL of 1 ppm. (Ex. 34–6) As Kenneth Cross stated in his testimony for URW,

''Based on more recent toxicological, medical and epidemiological data, some of which was unavailable to OSHA when it sent its proposed standard to OMB about two years ago, the URW feels more secure with a 0.2 part per million PEL and one part per million STEL.'' (Tr. 2/20/91, p. 1750)

OSHA's expert witness, Dr. Ronald L. Melnick of NTP, presented data suggesting that a STEL will reduce risk. He performed a ''stop-exposure'' study that he described as follows:

Groups of 50 male mice were exposed to one of the following regimens: (a) 625 ppm for 13 weeks; (b) 200 ppm for 40 weeks; (c) 625 for 26 weeks; or (d) 312 ppm for 52 weeks. After the exposures were terminated, these groups of animals were placed in control chambers for the remainder of the 104 week studies * * * Survival was markedly reduced in all of the stop-exposure groups due to the development of related malignant tumors. The tumor incidence profiles in the * * * groups show that lymphocytic lymphomas, hemangiosarcomas of the heart, alveolar-bronchiolar neoplasms, forestomach squamous cell neoplasms, Harderian gland neoplasms, and preputial gland neoplasms were increased compared with controls even after only 13 weeks of exposure to 625 ppm * * * at comparable total exposures, the incidence of lymphocytic lymphoma was greater with exposure to a higher concentration of 1,3-butadiene for a short time compared with exposure to a lower concentration for an extended duration. (Ex. 42)

Dr. Melnick concluded as follows:

The stop-exposure studies show that multiple organ site neoplasia occurs in mice after only 13 weeks of exposure to 1,3-butadiene. It is likely that shorter exposure durations would also produce a positive carcinogenic response * * * the stop-exposure studies show that *the concentration of 1,3-butadiene is a much greater contributing factor than is the duration of exposure* [emphasis added]. (Ex. 42, p. 17)

Industry representatives objected in particular to using the thymic lymphomas induced in the mouse due to the potential role of an endogenous retrovirus in eliciting this response, and more generally, to the use of this study as the basis for imposing a STEL. (e.g., Exs. 112, 113) In its post-hearing comments, the CMA 1,3–Butadiene Panel stated:

The relevance of these studies to an assessment of the human cancer risks from 15-minute exposures to butadiene at levels up to 64 ppm (the highest exposure that would be consistent with an 8-hour TWA of 2 ppm) is highly doubtful. This is particularly the case where: (1) A dose-rate effect is evident in mice only for lymphomas and only at high exposure concentrations; (2) the MuLV retrovirus is known to be a significant factor in BD-induced lymphomas in the $B_6C_3F_1$ mouse; (3) the lymphomas do not appear to play a significant role in BD-induced carcinogenicity in the * * * mouse at the lower levels of exposure of interest to OSHA * * * (4) there is no evidence that concentration is more important than duration of exposure for any other tumor type.

NIOSH disagreed, and objected to OSHA's omission of the lymphomas from the quantitative risk assessment provided in the proposal. NIOSH stated:

OSHA's justification for eliminating these tumors was that lymphomas may be related to the presence of an endogenous leukemia virus in the $B_6C_3F_1$ mouse used in the NTP bioassay. The endogenous leukemia virus should have increased the background rate of lymphoma in both the control and exposed animals, and thus the potential confounding effect of this virus was controlled for in OSHA's risk assessment. It is still possible that the increased lymphoma incidence observed in the * * * mouse was related to an interaction between the virus and 1,3-butadiene. However, OSHA also cites evidence that a similar lymphoma response was observed in a study of NIH-Swiss mice exposed to BD, and indicated that this strain of mice is not known to carry the leukemia virus * * * (Ex. 32–25, p. 4)

NIOSH also cited evidence that retroviruses may be associated with certain leukemias and lymphomas in humans and pointed out that ''even if 1,3-butadiene interacts with a leukemia virus, a similar mechanism might conceivably be involved in producing tumors'' in exposed workers. (Ex. 32–25, p. 5) OSHA agrees with the opinion expressed by NIOSH and rejects industry's arguments that the observations in the ''stop-exposure'' study are irrelevant.

Some further support for a STEL comes from a recent report describing analysis of an epidemiologic study of BD-exposed workers entitled ''A Follow-up Study of Synthetic Rubber Workers'' by Delzell et al. (Ex.117–1) One part of this study pertains to the risk of leukemia in workers exposed to BD in what the authors termed ''peak-years.'' Peak years are estimates of the number of times per year a worker was exposed above 100 ppm (a peak) during 15 minute periods. This estimate was then multiplied by 225, the number of workdays in a year. This value was used as a variable in Poisson regression analysis. There was an association between peak-years and leukemia risk, even after controlling for BD ppm-years (cumulative BD exposure) as well as other covariates. The relationship was said to be ''irregular'' since the risk ratios were 1.0, 2.6 and 0.8 for BD peak-years categories of 0, >0–199 and 200+, respectively. The underlying reason for the lack of a dose-response is unclear; however, the finding of a statistically significant elevation in relative risk for peak exposure, even when total cumulative exposure is accounted for, is of concern and appears to support the need to control peak exposures.

OSHA further notes that the basis for adopting a STEL does not rest solely on the points raised above; in 1986, the US Court of Appeals for DC reviewed OSHA's ethylene oxide standard, which did not contain a STEL. (*Public Citizen Health Research Group* v. *Tyson,* 796 F2d, D.C. Cir., 1986). The reason given by OSHA for not including a short-term limit in the ethylene oxide standard was that a dose-rate effect had not been demonstrated by record data. The Court held that the OSH Act compels the Agency to adopt a short term limit if the rulemaking record shows that it would further reduce a significant health risk and is feasible to implement regardless of whether the record supports a ''dose-rate'' effect (796 F. 2nd at 1505). This decision states that

If in fact a STEL would further reduce a significant health risk and is feasible to implement, then the OSH Act *compels* the agency to adopt it (barring alternative avenues to the same result). OSHA *shall* set the standard which most adequately assures, to the extent feasible, on the basis of best available evidence, that no employee will suffer material impairment of health.'' (29 U.S.C. 655(b)(5) (1982)) Since OSHA has found that a significant health hazard remains even with the 1 ppm PEL, the agency must find either that a STEL would have no effect on that risk or that a STEL is not feasible. (796 F.2d 1479 (D.C. Cir. 1986))

Without a STEL, employees could have exposures to BD as high as 32 ppm, albeit for short periods (15 minutes). Since many workers experience intermittent exposure to BD,

for example, during sampling, transport and laboratory work, imposing an 8-hour limit alone would not control these higher peak exposures. The STEL by controlling such peak exposures, will reduce total cumulative dose, thereby reducing significant risk further, as stated by the Court. In addition, properly installed and maintained engineering controls should prevent high variability in exposures generally. As a general rule, it is good industrial hygiene policy to control excessive variabilities as a STEL will do.

OSHA has concluded that the adoption of a 5 ppm STEL for BD is appropriate to further reduce the significant residual risk of cancer that remains from exposure to BD at the revised TWA PEL of 1 ppm. In addition, there is some evidence of a dose-rate effect as described above. Specifically: (a) The ''stop-exposure'' study of Melnick which demonstrated that ''at comparable total exposures, the incidence of lymphoma was greater with exposure to a higher concentration of BD for a short time compared with exposure to a lower concentration for an extended duration'' (Ex. 114, p. 125); (b) although a retrovirus in $B6C3F_1$ mice likely played a role in the induction of thymic lymphoma, the fact that BD exposure in another strain of mouse that did not express the virus also developed the same type of cancer, strongly suggests that BD induced this tumor very early after exposure; and, (c) the suggestive data from the cohort study of Delzell et al., indicating the importance of ''peak-year'' exposure to risk of leukemia.

D. Exposure Monitoring

Section 6(b)(7) of the OSH Act (29 U.S.C. 655) mandates that any standard promulgated under section 6(b) shall, where appropriate, ''provide for monitoring or measuring of employee exposure at such locations and intervals, and in such manner as may be necessary for the protection of employees.'' The purposes of requiring air sampling for employee exposure to BD include the prevention of overexposure of employees; the determination of the extent of exposure at the worksite; the identification of the source of exposure to BD; and collection of exposure data by which the employer can select the proper control methods to be used to reduce exposure and to evaluate the effectiveness of the control methods selected. Monitoring helps employers to meet the legal obligation of the standard to assure that their employees are not exposed to BD in excess of the permissible exposure levels, and to be able to notify employees of their exposure levels. In addition, collection of exposure monitoring data enables the examining physician to be informed of employee exposure levels, which may be useful in forming the physician's medical opinion (see paragraph (k)).

Many provisions of the final rule are quite similar to those proposed. However, some felt that clearer or more concise language should be used. Thus, the specific language of the exposure monitoring provisions varies somewhat from that of the proposal. Moreover, additional modifications have been made, as appropriate, in response to record information and recommendations contained in the record.

The final rule does not require that exposure monitoring be performed wherever BD is present. Under certain circumstances, outlined in the scope and application (paragraph (a) of this section), objective data may be used in lieu of the monitoring required by paragraph (d) of the final rule.

In the final rule, as in other standards, various provisions of the standard are triggered if an employee is exposed above the action level, and are not required if the employee is exposed below the action level. Thus the importance of correctly determining employee exposure cannot be over emphasized.

Paragraph (d)(1) requires the employer to determine the exposure for each employee exposed to BD. This does not mean that separate measurements for each employee must be taken but rather that the rule allows this obligation to be fulfilled by determining ''representative employee exposure.'' Paragraph (d)(1)(I) requires that samples collected to fulfill this requirement be taken within the employee's breathing zone (also known as ''personal breathing zone samples'' or ''personal samples''). (Area sampling is required under the standard only following emergencies.) The samples used to determine whether an employee is exposed above the action level must represent the employee's exposure to airborne concentrations of BD over an eight-hour period without regard to the use of respirators (See ''Employee exposure'', as defined in the definitions section).

In certain circumstances sampling each employee's exposure to BD may be required for initial monitoring. However, in many cases, the employer under paragraph (d)(1) may monitor selected employees to determine ''representative employee exposures.'' Representative exposure sampling is permitted when there are a number of employees performing essentially the same job, with BD exposures of similar durations and magnitude, under essentially the same conditions. Where there are groups of employees whose job functions are similar, OSHA permits the use of representative monitoring to characterize employee exposures to enable the employer to design a cost-effective monitoring program. In designing a representative monitoring plan, OSHA intends that employers select a sufficient number of employees within a group of employees who are engaged in similar work for sampling such that their exposures adequately characterize the exposures of all employees within the group. In addition, the employees who are judged as likely to have the highest exposures to BD within the group should be selected for monitoring to ensure that exposures of the remaining employees in the group are not underestimated. Although the employer is free to use formal statistical approaches for characterizing the exposures of a group of similarly exposed employees, OSHA does not require such approaches be used, and allows the employer to use professional judgement to select employees for monitoring and for attributing exposure results to employees whose exposures were not measured. The rationale for designing the representative monitoring plan and for selecting employees whose exposures were monitored can be retained as part of the exposure monitoring records required to be maintained by the employer under paragraph (l)(2) of the final rule.

To measure representative 8-hour TWA exposures, at least full-shift sampling must be conducted for each job function in each job classification, in each work area, and for each shift (paragraph (d)(1)(ii)). At least one sample covering the entire shift, or consecutive representative samples taken over the duration of the shift, must be taken. Representative 15-minute short-term employee exposures are to be determined on the basis of one or more samples representing 15-minute exposures associated with operations that are most likely to produce exposures above the short term exposure limit for each shift for each job classification in each work area (paragraph (d)(1)(iii)).

To eliminate unnecessary monitoring and improve the cost-effectiveness of the standard, paragraph (d)(1)(iv) also allows employers who can document that exposure levels are the same for similar operations during different work shifts to sample only the shift for which the highest exposures are expected to

occur. The employer must be able to demonstrate that employees on the shifts who are not monitored are not likely to have exposures higher than those of employees on the shifts monitored.

Paragraph (d)(2) requires all employers who have a place of employment covered under the scope of this standard to perform initial monitoring for their employees. In addition, the final standard requires that the initial monitoring be conducted within 60 days of the effective date of the final standard or the introduction of BD into the work place. This effective date provision (proposed paragraph (d)(2)(ii)) has been moved to the paragraph containing the other start-up dates, paragraph (m)(2)(I). Although Dow in a recent submission expressed concerns that additional time might be needed to set up an exposure monitoring program, OSHA believes that initial monitoring can be completed within the allowed period of time. (Ex. 118–16) The parties to the labor/industry agreement also recommended a start-up date for the initial monitoring under the standard of 60 days from the effective date. (Ex. 118–12A) Additional flexibility is provided in paragraph (d)(2)(ii), in that monitoring data collected up to two years prior to the effective date may be relied upon as initial monitoring data, provided that it has been collected in accordance with the requirements of this paragraph.

The employer is required to perform initial monitoring of employee exposures to BD where objective data are not available to satisfy the condition for exemption. If the results of initial monitoring indicate employee exposures are below the action level, the employer may discontinue monitoring for those employees and is relieved of some other obligations under the final rule (e.g., medical surveillance, use of personal protective equipment, development of an exposure goal program, establishment of regulated areas). Thus, the employer can focus attention and resources on employees whose exposures are more significant. Therefore, even if operations are not specifically exempted from the proposal, keeping exposure levels below the 0.5 ppm ''action level'' will relieve employers from some duties under the standard. A similar approach is used in a number of OSHA standards (acrylonitrile, 29 CFR 1910.1045; arsenic, 29 CFR 1910.1018; ethylene oxide, 29 CFR 1910.1047).

Paragraph (d)(2)(ii) of the proposal has been modified as shown in paragraph (d)(1)(ii) in the final rule to allow monitoring data produced within 2 years prior to the effective date of the standard to be relied upon to satisfy the initial monitoring requirement. OSHA had proposed a one year limit on the use of this grand-fathered monitoring data, but at the suggestion of a number of participants in the rulemaking and the labor/industry agreement, OSHA has agreed that allowing a two year period is reasonable for this standard. (Ex. 112; 113; 118–12) Dow Chemical Company in comments on a draft of the labor/industry joint recommendations asked that OSHA allow the use of data which are over two years old to serve as initial monitoring data. (Ex. 118–16) Dow said that such data ''that are consistent with current data reflecting no process changes that might have increased exposure over the time period of interest'' should be included as initial monitoring data. OSHA believes that expanding the period to two years allows adequate latitude to the employer in determining the need for initial monitoring.

In addition, the final rule now more clearly states what OSHA means by conditions under which historical monitoring data may not be used and initial monitoring is required. Rather than stating that historical data may be used only if the conditions under which the monitoring was conducted ''remain unchanged,'' it now states that the conditions ''* * * have not changed in a manner that may result in new or additional exposures.'' This language was recommended by the labor/industry group and has been found acceptable and OSHA believes that it more clearly articulates its intent than the corresponding provision in the proposal; therefore it is included in the final rule. (Ex. 118–12A) However, OSHA notes that employers will likely wish to monitor following installation of controls to determine their effectiveness.

Paragraph (d)(3) describes the requirement for periodic monitoring and its frequency. CMA suggested that the OSHA BD standard should have the same monitoring frequency as OSHA's benzene standard. (Ex. 112) The initial submission of the labor/industry group recommended that OSHA require more extensive sampling than the Agency had proposed to qualify as initial monitoring and establish a baseline. Specifically the group recommendation stated:

> Establish a baseline of at least 8 samples. The samples may be taken in a single year, so long as at least one sample is taken in each quarter, and no two are taken within 30 days of each other. The employer may utilize monitoring data from the previous two years to satisfy the initial monitoring requirement as long as process has been consistent. (Ex. 119)

The labor/industry group also recommended less frequent periodic monitoring than the quarterly monitoring OSHA proposed when exposures exceeded the PELs. The labor/industry group recommended:

> After the baseline has been established, monitoring is * * * every 6 months if exposure exceeds PEL or STEL * * * Annually if exposure is at or above the AL [action level] but below the PEL. (Ex. 119)

In the Federal Register notice re-opening the record, OSHA raised its concerns as follows:

> OSHA is concerned that the taking of 8 samples to establish a baseline may not be an effective use of scarce industrial hygiene resources in that the number of samples taken may be far less important than the quality of the samples used to characterize the exposure of BD employees. Are there other ways to improve OSHA's traditional approach of monitoring at least the one most exposed employee in each job classification on each shift? (61 FR 9381, 9383, 3/8/960)

In its submission, Texas Petro Chemicals objected to the 8 sample baseline because they said that they do not have BD exposure for four quarters of the year and do not monitor in winter due to ''high mobility'' of their employees during the winter and the ''strong potential for samples to be invalid'' due to problems with the sampling devices during bad weather. (Ex. 118–6) Dow Chemical Company objected to specification of the number of sampling events and the schedule suggested by the agreement. Dow felt this did not allow the employer adequate flexibility in evaluating employee exposures. (Ex. 118–16, p. 4) Hampshire Chemical Corporation felt that it was unclear what was meant by the 8 baseline samples described in the notice. (Ex. 118–8) The American Petroleum Institute expressed its preference for a more performance-oriented approach to exposure monitoring strategies. (Ex. 118–11)

In comments of the Chemical Manufacturers Association, who participated in the labor/industry discussion resulting in the agreement, the following view was expressed:

> The parties to the negotiations have revisited the exposure monitoring provisions. The agreement's monitoring scheme now would follow OSHA's traditional requirement for initial representative monitoring to detect job classifications where the action level is exceeded * * * It is only the periodic monitoring that is required where there are exceedances that could involve the taking of eight samples * * * After this periodic monitoring had been completed, additional periodic monitoring would occur at the

frequency proposed * * * sampling could be terminated when there are two consecutive low measurements. (Ex. 118–13, p. 4–5)

Similar comments were received from the International Institute of Synthetic Rubber Producers, Inc. (Ex. 118–12, p. 4)

The labor/industry agreement was more fully discussed by the group in a submission received during the period when the record was re-opened for comment. (Ex. 118–12) Numerous modifications to OSHA's proposed provisions for an exposure monitoring program for BD were endorsed by the group. (Ex. 119) Primarily these dealt with the sampling strategy. OSHA has carefully evaluated the suggested changes and has, for the most part, included them in the final rule.

The periodic monitoring paragraphs have been modified upon the basis of the record and the recommendations of the labor/industry group. Paragraph (d)(3) states that ''If the monitoring required by (d)(2) of this section reveals exposure at or above the action level but at or below both the 8-hr TWA and the STEL, the employer shall repeat the representative monitoring required by paragraph (d)(1) every twelve months.'' OSHA proposed that such monitoring be repeated at least every six months. However, OSHA believes that the additional monitoring[10] required in the final rule for those whose BD levels remain above the PELs will compensate for less frequent periodic monitoring in situations where the level is likely to remain lower. It must be noted here that additional monitoring requirements are triggered whenever there is a change in process or personnel which may result in new or additional exposures to BD. A similar schedule for periodic monitoring is required in the benzene standard. (29 CFR 1910.1028)

The results of initial monitoring represent the data which will be used to determine when further periodic monitoring will be required. If the initial monitoring of employees reveals exposures that are between the action level and the 8-hour TWA, then the employer must repeat monitoring annually (paragraph (d)(3)(I)). While these employees have been shown to be exposed to levels of BD below the 8-hour TWA, their levels of exposures are not so far below the PELs that monitoring could safely be discontinued. Even minor changes in engineering controls or work practices could result in exposures increasing to levels above the PEL. Remonitoring on an annual basis will enable the employer to be confident that the controls are working or, in the event exposures are shown to exceed the 8-hour TWA, will alert the employer as to the need for additional controls, and for changes to a more frequent monitoring program.

The draft regulatory text submitted by the labor/industry group recommended marked changes to paragraph (d)(3) (ii) and (iii) which OSHA believes will provide even greater protection to workers than that proposed by the Agency in 1990. (Ex. 118–12A)

The requirements in paragraphs (d)(3) (ii) and (iii) of the final rule provide for periodic monitoring in situations in which either the 8-hr TWA or STEL is exceeded to be carried out quarterly ''until the employer has collected two samples per quarter (each at least 7 days apart) within a two-year period * * * after which such monitoring must occur at least every 6 months.'' However, if the monitoring result indicates that exposure is below the action level as indicated by 2 consecutive samples taken at least 7 days apart, monitoring may cease unless the conditions change, (see (d)(5)). A single low sampling result is inadequate to allow monitoring to terminate; for various reasons, it may be artifactually low perhaps due to process changes during the time of sampling. OSHA believes that such differences are unlikely to persist for more than a week and has determined that this period is minimal to assure that exposures are truly low enough for the employer to stop monitoring.

Paragraph (d)(3)(iv) has also been modified to allow less frequent monitoring when the initial monitoring results exceed either PEL, but two consecutive subsequent samples taken at least 7 days apart indicate that BD levels no longer exceed either PEL but remain above the action level. In this situation, monitoring is required annually. OSHA proposed that such monitoring take place every six months.

OSHA believes that although this approach differs from the Agency's usual approach to monitoring, it will meet the need for determining the level of BD exposure in the workplace and will focus on situations having higher exposure potential. The conditions of use of BD in production and manufacturing present exposure patterns that are more likely to be predicted by initial monitoring than is the case for some of the other substances OSHA has regulated, such as asbestos, where exposures primarily occur during disturbing or removing the material in various forms. OSHA agrees that monitoring carried out as scheduled in the agreement is more likely to reflect the ''true'' exposure level in a workplace than monitoring at a single point in time. OSHA notes, however, as is the case in other standards, the sampling must be performed according to provisions of the standard—i.e., they must be personal samples, representative of each shift and job, etc.

If exposures are above the 8-hour TWA limit, then the employer must remonitor every six months. If the employee's exposure is above the STEL, the employee shall repeat such monitoring at least every six months until the employee's exposure falls to or below the STEL. If, in subsequent monitoring, results indicate that an employee's exposure, as determined by two consecutive measurements taken at least seven days apart, falls from above the 8-hour TWA to between the 8-hour TWA and the action level, then monitoring need only be done annually, unless production changes lead to higher exposures. Similarly, when two consecutive measurements indicate that the exposure has dropped below the action level, further monitoring can be discontinued.

Paragraph (d)(4) allows employers to terminate monitoring for those employees whose initial monitoring results are below the action level. When the two consecutive exposure measurements (paragraph (d)(3)), taken at least seven days apart, indicate that exposure has dropped below the action level, further monitoring for these employees can be discontinued, unless production changes lead to higher exposures. OSHA recognizes that monitoring may be a time-consuming, expensive endeavor and therefore offers employers the incentive to be allowed to discontinue monitoring for employees whose sampling results indicate exposures below the action level. The intent of this provision is to allow the employer to stop monitoring employees whose exposure to BD falls below the action level. OSHA believes that this provision will encourage employers to keep exposures to BD below the action level in their workplaces, thereby keeping exposures to a minimum and saving employers the time and expense of monitoring. Moreover, employers will also benefit because most of the other requirements of the standard are not triggered when exposures are below the action level.

Employees will continue to be protected from excess BD exposure,

[10] If the monitoring required by paragraph (d)(2) of this section reveals employee exposure to be above the 8-hour TWA (or STEL), the employer shall repeat the representative monitoring required by paragraph (d)(1)(ii) (or d(1)(iii)) at least every three months until the employer has collected two samples per quarter (each at least 7 days apart) within a two-year period, after which such monitoring must occur at least every six months.

even after periodic monitoring has ceased, because of the requirements in paragraph (d)(5) (additional monitoring). Additional monitoring is required by paragraph (d)(5)(i) when there has been a process or production change or a change in control equipment, personnel or work practices which may result in new or additional exposures to BD. When the employer suspects a change which may result in new or additional BD exposure, the employer is obligated to obtain new employee exposure measurements. Instead of listing or trying to define every situation where the employer must monitor for new or additional exposures to BD, OSHA intends by this provision that employers will institute this additional monitoring when the employer has any reason to suspect a change. It should be noted that since the PEL and action level are relatively low, even a small change in production procedures may cause employees whose exposures were below the action level to have exposures that are above the PELs.

Paragraph (d)(5)(ii) requires additional monitoring to be conducted whenever leaks, ruptures or other breakdowns occur. Such occurrences can result in very high exposures. After the clean-up or repair of the leak, employers must re-determine airborne exposure levels for those employees who may be exposed at their worksites. These additional exposure measurements provide a good method of ascertaining that proper corrective methods have been effective and employee exposures are not significantly altered from what they were prior to the leak or spill.

In commenting on the requirement to do additional monitoring after leaks or breakdowns, BP felt that ''This requirement seems arbitrary since BD is volatile and will rapidly dissipate, especially if the leak is outdoors.'' (Ex. 32–8) CMA suggested OSHA delete the requirement to ''repeat the monitoring which is required by paragraph (d)(2)(I)'' and instead require employers to ''monitor (using personal or area monitoring as appropriate) after the clean up of the spill or repair of the leak, rupture or other breakdown to insure that exposures have returned to the level that existed prior to the incident.'' (Ex. 112) The labor/industry group recommended a similar change which OSHA has determined to be appropriately protective. Paragraph (d)(5)(ii) of the final rule states:

Whenever spills, leaks, ruptures or other breakdowns occur that may lead to employee exposure above the 8-hour TWA limit or above the STEL, the employer shall monitor (using leak source (e.g., direct reading instruments), area or personal monitoring, as appropriate) after the cleanup of the spill or repair of the leak, rupture or other breakdown to ensure that exposures have returned to the level that existed prior to the incident.

OSHA believes that this provision will allow the employer greater flexibility in deciding whether additional monitoring is necessary and to determine whether the level of BD in the workplace has returned to low levels following such incidents. OSHA further notes that since the odor threshold for BD is very near the permissible limits, if the odor is detected, then a release has occurred and monitoring must take place to assure that exposure has returned to a level below the action level. OSHA recognizes that not every worker will recognize the odor of BD at a specific concentration in air.

Paragraph (d)(6) requires employers to use monitoring and analytical methods which have an accuracy (at a confidence level of 95%) of not less than plus or minus 25% for airborne concentrations of BD above a PEL and within plus or minus 35% for airborne concentrations of BD at or above the action level and below the TWA limit of 1 ppm. Methods of measurement are presently available to detect BD to this accuracy level (±25% or ±35%) at levels of 0.155 ppm. One such method is described in Appendix D.

Sampling and analysis may be performed by portable direct- reading instruments, real-time continuous monitoring systems, passive dosimeters or other suitable methods. Employers have the obligation to select a monitoring method which meets the accuracy and precision requirements of the standard under the unique conditions which exist at the worksite.

Paragraph (d)(7)(i) further requires that employers notify each of their employees in writing, either individually or by posting in an appropriate location accessible to affected employees, the results of personal monitoring samples. OSHA proposed that the employer do this within 15 working days after the receipt of the results. However, the labor/industry agreement recommended a period of 5 business days for the notification by the employer to take place. (Exs. 119, 118–12a) OSHA agrees that this will provide information to the employee in a more expedient way. The quicker notification takes place, the better. Evidence indicates that this industry can comply with a shorter, and more desirable, time period. (Ex. 118–12A)

When exposures over the PEL occur, paragraph (d)(7)(ii) requires the employer to notify affected employees in writing of what corrective action is being taken to lower exposure to BD to below the PEL, and to inform the employee of the schedule to complete this action. Such notification must be completed within 15 business days of the employer's receipt of the sampling results. (See paragraph (b) for the definition of ''business day.'') The requirement to inform employees of the corrective actions the employer is going to take to reduce the exposure level to below the PELs is necessary to assure employees that the employer is making efforts to furnish them with a safe and healthful work environment, and is required by section 8(c)(3) of the Act. Mandating the schedule for the completion of such activities is needed so that the employee can be informed when to expect correction of the situation and the employee can be assured that corrective action will take place in a specified time frame.

Paragraph (d)(8) requires employers to allow employees or their designated representatives an opportunity to observe employee exposure monitoring. This provision is also required by section 8(c)(3) of the OSH Act. The proposed rule contained this provision in a separate paragraph (paragraph (l)), however, in developing the final rule, OSHA determined that observation of monitoring more logically belonged in the paragraph dealing with exposure monitoring and has included it in paragraph (d).

E. Regulated Areas

Paragraph (e) (1) of the final rule requires employers to designate areas in which occupational exposures to BD exceed or can reasonably be expected to exceed the PELs as ''regulated areas.'' In response to comments, the wording of this requirement was made consistent with the definition of ''regulated area'' used in the standard. (Exs. 32–26; 32–27; 32–28) A similar recommendation was made by the labor/industry group. (Ex. 118–12A)

The purpose of a regulated area is to ensure that employers make employees aware of the presence of BD in the workplace at levels above either of the PELs, and to limit access to these areas to as few employees as possible. The establishment of a regulated area is an effective means of limiting the risk of exposure to substances known to pose a risk of material impairment of health or functional capacity. Because of the serious nature of the outcome of possible exposure to BD and the need for persons entering the area to be provided with properly fitted respirators, the number of persons given

access to the area must be limited to the employees needed to perform the work in the area.

Paragraphs (e)(2) and (e)(3) are identical to the proposed paragraphs. Paragraph (e)(2) limits access to regulated areas to authorized persons. This provision makes clear that exposure over the PEL triggers the need for a regulated area, but that inadvertent releases which are covered under paragraph (i), Emergency Situations, would not trigger the requirement for a regulated area.

Consistent with the performance orientation of the standard, paragraph (e)(3) does not specify how employers are to demarcate their regulated areas. Factors that the Agency believes are appropriate for employers to consider in determining how to mark their areas include consideration of the configuration of the area, whether the regulated area is permanent, the airborne BD concentration, the number of employees in adjacent areas, and the period of time the area is expected to have exposure levels above the PEL. Permitting employers to choose how best to identify and limit access to regulated areas is consistent with OSHA's belief that employers are in the best position to make such determinations, based on their knowledge of the specific conditions of their workplaces.

Paragraph (e)(4) requires that whenever an employer at a multi-employer worksite establishes a regulated area he or she must communicate effectively the location and access restrictions pertaining to the regulated area to other employers with work operations at the worksite. Such communication will lessen the possibility that unauthorized persons will enter the area or that workers not involved in BD-related operations will be inadvertently exposed. OSHA requires employers whose employees are exposed to BD at concentrations above either of the PELs to be responsible for coordinating their work with that of other employers whose employees could suffer excessive exposure because of their proximity to the source of exposure to BD. Only one comment was received on the proposed multi-employer provision. (Ex. 32–27) That commenter requested OSHA to clarify that this provision applies only to employers whose employees are potentially exposed to BD. This interpretation is correct: the intent of this provision is to ensure that employers who establish regulated areas communicate with other employers whose employees could inadvertently enter the area. However, in response to this comment and at the suggestion of the labor/industry group, OSHA has made clear that the workers who may have access to the regulated area must be told where such areas exist and of their restricted access to them. Accordingly the phrase ''whose employees may have access to these areas'' has been added to paragraph (e)(4).

The regulated area provision underscores OSHA's concern that employees at nearby sites be aware of the existence of a BD exposure hazard so that they will remain outside the boundaries delineating the regulated area. Requiring the employer who establishes a regulated area to notify other employers whose employees might be placed at risk by the presence of high concentrations of BD is consistent with other OSHA standards, e.g., 29 CFR 1910.1048 (Formaldehyde).

F. Methods of Compliance

The final standard, like the proposed standard, requires employers to institute engineering and work practice controls to reduce the exposures of employees to or below the permissible exposure limits (both the 8-hour TWA limit and the STEL), to the extent feasible. If the employer establishes that engineering and work practice controls are inadequate to lower exposures sufficiently to or below either of the PELs, the employer must nevertheless implement engineering and work practice controls to reduce exposures as low as possible and provide supplemental protection with respirators selected in accordance with paragraph (h). The methods of compliance requirements in the final rule are similar to those in all of OSHA's other substance-specific health standards.

The primary reliance on engineering and work practice controls to maintain employee exposures to or below the PELs is consistent with good industrial hygiene practice and with the Agency's traditional adherence to this hierarchy of controls. This hierarchy specifies that, in controlling exposures, engineering controls and work practices are to be used in preference to respiratory protective equipment. In this final rule, respirators may be used by employees only in emergencies; where engineering and work practice controls are not feasible, adequate, or have not yet been installed; or during intermittent, non-routine work operations that are limited in duration.

Engineering controls involve the installation of equipment, such as forced air ventilation, or the modification of a process to prevent or contain chemical releases. Work practice controls reduce employee exposures by altering the manner in which a task is performed. An example of a work practice control would be to train a tank car unloader to stand upwind rather than downwind of the tank car's hatch during the operation.

Respirators have traditionally been accorded the last position in the hierarchy of controls because of the many problems associated with their use. For example, the effective use of respirators requires that they be individually selected and fitted for each employee, conscientiously worn, carefully maintained, and replaced when necessary; these conditions may be difficult to achieve and maintain consistently in many workplace environments. Furthermore, unlike engineering and work practice controls, which permit the employer to evaluate their effectiveness directly by air monitoring and other means, it is considerably more difficult to directly measure the effectiveness of respirators on a regular basis to ensure that employees are not unknowingly being overexposed. Finally, in the case of butadiene, respirator cartridges and canisters used to purify the air inhaled by the employee have limited capacity. Data relied on by OSHA to develop the respiratory protection requirements of the final rule show that cartridges will not be able to provide adequate protection over an entire workshift (see discussion for paragraph (h), Respiratory Protection).

Industry representatives were in agreement that respirators should not be relied upon as a first line of defense if feasible engineering and work practice controls are available to protect employees from exposure to butadiene. (Ex. 34–4; 60; 61; 66A; 113). For example, James L. McGraw, representing the IISRP, commented as follows:

> It has long been recognized that engineering controls should be the primary means of reducing occupational exposures to regulated substances. Respirators are useful as supplementary controls to protect workers during emergencies, if engineering controls fail or break down, while feasible engineering controls or work practices are being designed or implemented, or for mobile or short-term work, such as some maintenance operations * * *. At ASRC and, as I understand, throughout the industry, respirators are generally used only for short-duration tasks where the potential for exposure may be relatively high, (and) * * * are generally worn by workers for only a small fraction of the shift * * *. Moreover, because they inhibit worker mobility, obstruct vision and make communication among workers difficult, serious safety risks may be posed

where respirators are used over long periods of time * * *. The required use of respirators over extensive periods of time is also psychologically stressful, especially for employees not accustomed to such use. All of these factors significantly impair worker mobility and productivity. (Ex. 34–4, pp. 7–9)

Thus, according to the hierarchy of controls concept, use of installed equipment, such as well-designed and maintained local exhaust ventilation, is a superior compliance method because its effectiveness does not depend to any marked degree on human behavior, and the operation of such equipment is not as vulnerable to human error as is the use of personal protective equipment. The Agency has also found that modified work practices can aid in achieving compliance with the PELs without introducing the safety and comfort problems inherent with respirator use.

Based upon the evidence in the rulemaking record and the Economic Analysis, OSHA finds that the use of engineering and work practice controls will reduce employee exposures to or below the butadiene PELs for practically all work situations, without having to rely on excessive respirator use. Some of the controls applicable to the production of butadiene monomer and polymers include:

—Installation of closed-loop sampling ports for quality-control sampling of process streams;
—Use of self-circulating-type sampling cylinders;
—Replacement of pumps equipped with single mechanical seals with those having dual seals;
—Use of an on-line chromatographic system to minimize the need for manual process sampling;
—Replacement of slip-tube gauges with magnetic level gauges in loading/unloading operations;
—Routine venting and purging of transfer lines between loading and unloading operations;
—Prohibiting air recirculation in quality-control laboratories (i.e., use of 100 percent make-up air);
—Ensuring that samples are removed from sample cylinders within enclosed, ventilated cabinets, and implementing closed-systems for injection into chromatographs;
—Voiding and purging sample cylinders outside of the laboratory or within an exhausted hood; and
—Purging process lines with nitrogen followed by steam or water cleaning prior to performing equipment maintenance.

OSHA recognizes that there may be situations where engineering and work practice controls are not feasible due to a unique feature or condition. These situations are recognized in paragraph (f)(1) of the final rule, which permits the use of approved respiratory protection where employers can demonstrate that engineering and work practice controls are not feasible. In such situations, the burden of proof is appropriately placed on the employer to make and support a claim of infeasibility because the employer has better access to information specific to the particular operation that is relevant to the issue of feasibility.

Paragraph (f)(2) requires employers whose employees are exposed above either of the PELs to establish and implement a written compliance plan that describes the methods to be used to reduce employee exposures to or below the PELs. The plan must provide for this to be accomplished where feasible with engineering and work practice controls, which must include surveys for leak detection on a periodic basis. The written plan must include a schedule for implementation and must be furnished upon request for examination and copying to OSHA, NIOSH, and affected employees or their representatives.

In the preamble to the proposal, OSHA raised concerns about and solicited comments on the suggestion in the JACA report that worker exposures to BD originating from pump leaks could be controlled more cost-effectively with the use of leak detection programs rather than by engineering means, such as installation of pumps with dual mechanical seals. (Ex. 30) OSHA also questioned whether use of a continuous air monitoring system equipped with an alarm might be an equally effective alternative control technology (55 FR 32736 at 32791).

In response, OSHA received many comments indicating that implementation of engineering controls is a far superior control strategy than primary reliance on leak detection, and these comments urged the Agency to retain its original performance-oriented language in the methods of compliance paragraph. For example, Michael J. Murphy of Monsanto commented as follows:

It is Monsanto's position that the actual method of maintaining the integrity of engineering controls and process equipment should not be specified by OSHA. The appropriate utilization of preventative maintenance programs, periodic leak detection surveys, continuous monitoring systems and an educated workforce should be left up to the employer's professional judgment. So long as the overall process is maintained in a fashion which minimizes employee exposures as determined by personal monitoring, the actual method of compliance should not be a specific item. (Ex. 32–19, p. 6)

In their post-hearing comments, NIOSH indicated that continuous monitoring systems might be useful in some situations, but only as an ''* * * adjunct to engineering containment features * * *.'' (Ex. 101, p. 2) Similarly, Dr. Norman Morrow, of Exxon Chemical Company and chairman of the CMA Butadiene Panel, commented that use of double seals on pumps combined with a good leak detection and repair program would provide more protection to workers than would continuous monitoring systems. (Ex. 54, p. 7) The feasibility of relying primarily on continuous monitoring systems to maintain low worker exposures was also questioned by CMA in their post-hearing submission:

In a monomer or crude facility which is out of doors and spread over a large area, a very large number of such analyzers would be required to provide any warning of potential high ambient levels. It is likely that even a very large and costly system would fail to detect butadiene excursions because of changing wind patterns, areas not covered, downtimes for maintenance, cycle times between measurements, etc. * * * [B]y contrast, engineering controls such as dual or tandem pump seals serve as a true primary safeguard against worker exposure. * * * Thus, OSHA should expressly recognize that continuous analyzers or monitoring systems, although perhaps beneficial in certain situations as part of a leak detection program, should not supplant engineering controls which directly protect workers against butadiene exposures. (Ex. 112, p. 125)

After reviewing these comments, OSHA is convinced that primary reliance on either manual leak detection programs, as suggested by JACA, or continuous monitoring systems, would not provide worker protection equivalent to that afforded by engineering and work practice controls; therefore, OSHA is retaining the performance-oriented language originally proposed for the methods of compliance requirements, which allows employers to design their own compliance programs so long as they adhere to the general principles for the hierarchy of controls set forth in paragraph (f)(1).

Furthermore, in paragraph (f)(2) of the final rule, OSHA specifies that the compliance program must include a leak detection program, but leaves the specific design of the program up to the employer. OSHA believes that leak detection is a vital element of the compliance program for butadiene, given the high volatility of the substance, and given that leaks, if not

detected in timely fashion, can be a significant source of employee exposure.

Howard Kusnetz of Shell Oil objected to the proposal's requirement that compliance programs include leak detection:

> OSHA should not require the compliance program to include a periodic leak detection survey. If this is to be an effective performance standard, the facility needs the maximum flexibility to develop an effective program. The engineering control or work practice that reduces exposure may not need leak detection to be effective. This requirement will be a significant drain of resources and not result in enhanced employee protection. This is a significant departure from other health standards such as benzene and is already being addressed by EPA requirements. (Ex. 32–27, p.2)

Other rulemaking participants identified leak detection as an important component of an effective compliance program for butadiene. For example, Frank Parker of Environmental Technologies Incorporated, testifying for OSHA, stated that use of double seals on pumps combined with a good leak detection and repair program would effectively control exposures to butadiene (Tr. 1/17/91, p. 534). In post-hearing testimony, NIOSH explained that leaks from process equipment were one of the major sources of employee exposure:

> NIOSH supports the contention that 1,3-butadiene processing involves closed systems and that exposures are the direct result of leaks in these systems. There are only relatively few points * * * in which the integrity of these closed systems are likely to be (intentionally) broken. * * * Prompt repair of leaks can appreciably reduce exposures, and techniques such as Hazard and Operability Studies * * * should help even more by anticipating and preventing the leaks. (Ex. 101, pp. 1–2)

Similarly, as discussed above, several participants agreed that leak detection programs combined with primary reliance on engineering controls were the most effective approach for maintaining low employee exposures to BD; a routine leak detection program is one of the control elements specified in the exposure goal program recommended in the joint labor/industry agreement. (Ex. 118–13A) Furthermore, contrary to Mr. Kusnetz's assertion, OSHA has required compliance programs to contain provision for leak detection in its final rule for another highly volatile carcinogen, ethylene oxide (See 29 CFR 1910.1047(f)(2)(ii)).

OSHA believes that the language contained in paragraph (f)(2) of the final rule gives employers considerable latitude in designing effective leak detection programs. OSHA has not specified a minimum frequency for performing leak detection, the methods to be used by employers for performing leak detection, nor the locations where periodic leak detection must be performed. OSHA believes that the employer, with his or her knowledge of specific processes and workplace conditions, is in the best position to make these decisions. The employer must perform leak detection as often as is reasonable, given the specific circumstances of the work operation. The intent of the provision as worded in the proposal was to ensure that employers include a leak detection program as appropriate to their workplace within the compliance program, and that this information be available to affected employees or their representatives. Because the preponderance of professional opinion contained in the record provides support that leak detection programs are important supplements to engineering control programs, OSHA has accordingly retained this requirement in the final rule.

The paragraph describing the proposed written compliance program requirements also contained a cross reference to paragraph (h) of the proposed standard dealing with written emergency plans. OSHA has deleted this cross reference in the final rule, recognizing that the written emergency plan is required regardless of whether the requirement for a written compliance program is triggered by exposures exceeding the PELs. This deletion was also included in the regulatory text from the joint labor/industry agreement.

Paragraph (f)(2)(iv) prohibits the use of employee rotation as a method of reducing exposure to BD to or below the PELs. This requirement, which remains unchanged from the proposal, reflects a long-standing Agency policy that rotation of employees is an unacceptable practice for reducing exposures of employees to potential carcinogens. Although this approach may reduce the risk of cancer among individual workers who are periodically rotated out of tasks involving such exposure, the practice places a larger pool of workers at risk. OSHA received no objection to retaining this requirement for the butadiene standard, and its inclusion was supported by the joint labor/industry agreement. OSHA wishes to make clear that other kinds of administrative controls are acceptable so long as they do not involve exposing employees who would otherwise not be exposed. Acceptable practices include methods such as scheduling certain maintenance tasks where there is a potential for high exposures during the work shift where there are the fewest employees present in the area.

The text of the joint labor/industry joint recommendations included one other change in the language of proposed paragraph (f), clarifying that no written compliance program would be required ''if the initial (exposure) reading has been reliably determined to have been in error.'' (Ex. 118–13A) None of the participants of the joint agreement provided a specific rationale explaining the need to include this language; however, one rulemaking participant, Richard Olson of Dow Chemical, offered an explanation after reviewing a draft of the agreement:

> Occasionally, one sample may be over a permissible exposure level because of some circumstance such as an analytical error or perhaps an unusual, unanticipated action taken by the employee. In such cases, the situation surrounding the data point should be investigated but that individual sample should not necessarily instigate a full-blown program as it may not be representative of actual average conditions. (Ex. 118–16, p. 6)

For these reasons, Mr. Olson suggested that the language contained in the draft regulatory text from the agreement not be limited to circumstances involving only analytical error, but also be applied to other unusual events.

In the final rule, OSHA did not include the language regarding erroneous sample results that was contained in the labor/industry regulatory text. Clearly, no employer action should ever be based on an erroneous reading. In addition, OSHA believes such language is unnecessary since it has never been the Agency's intent or practice to require employers to comply with a provision of a standard based on the results of a single sample so long as the employer has adequate documentation that the result is unusual and does not reflect typical workplace conditions. Conversely, OSHA would not expect an employer to discontinue complying with a provision of the standard simply because a single sample suggests employees are not exposed above either of the PELs, if the weight of information available to the employer indicates otherwise. Indeed, OSHA believes it more likely that gross sampling and analytical errors will tend to understate rather than overstate exposures for a variety of reasons (for example, due to sampling pump fault or failure, taking samples under conditions of high humidity or where other hydrocarbons are present, sample loss from breakthrough or due to improper sample storage or handling, or

inefficient desorption of the sample from the media).

OSHA believes that employers should base their compliance actions on the totality of information and data available to them about their workplaces and employee exposures, and on their best professional judgment. If in the employer's best judgment, a sample result is obtained that is not credible or is perceived as unlikely, the employer should, as Mr. Olson suggests, investigate the probable causes by ensuring that process and engineering equipment are functioning properly, by talking with affected employees to determine if there were any unusual occurrences or practices that may be associated with the result, and conduct repeat monitoring to help confirm that the questionable result is not representative of typical workplace conditions. On the other hand, should the employer instead choose to rely on a minimal program to assess employee exposures and a sample result indicates that an operation is associated with worker exposures above the PELs, OSHA believes it is prudent to presume that the result reflects typical exposure conditions and that a plan for implementing corrective measures is necessary.

G. Exposure Goal Program

Paragraph (g) of the final rule contains requirements for the employer to establish an exposure goal program where employee exposures are above the action level of 0.5 ppm TWA. As part of the exposure goal program, which was recommended by the labor/industry agreement, the employer must implement the following control measures:

—A leak prevention, detection, and repair program;
—A program for maintaining effectiveness of local exhaust systems;
—Use of technologies that minimize BD emissions from pumps;
—Use of gauging devices designed to limit employee exposures during loading operations;
—Use of controls such as vapor return systems to limit exposures during unloading operations; and
—A program to maintain BD concentrations below the action level in control rooms.

The employer is not required to implement the controls specified above if he or she demonstrates that the controls are not feasible, will not be effective in reducing exposures to or below the action level, or are not necessary to achieve exposures to or below the action level. In addition, nothing in the exposure goal program requires employers to use respiratory protective equipment to achieve the action level. The exposure goal program must be implemented within three years from the effective date of the standard, in accordance with paragraph (m); this is one year beyond the date that employers are required to have installed engineering and work practice controls to achieve the PELs.

The requirements in this paragraph were not originally included in the proposal, but were proposed as part of the joint labor/industry agreement for BD. In its supplemental Federal Register notice, OSHA requested comments on the exposure goal program. (61 FR 9382) Specifically, OSHA was concerned whether including specification-oriented requirements for engineering controls in the exposure goal program would lead to situations where:

—The use of alternative control methods that would be equally or more effective in reducing exposures would be discouraged or ignored;
—The employer would be unable to comply because the specified controls are not applicable to the operation(s) where exposures exceed the action level; or
—The required controls would not be needed because exposures could be reduced to or below the action level by work practices alone, thus forcing employers to spend capital resources unnecessarily to comply with the letter of the requirement.

Several other participants raised concerns similar to those of OSHA's, generally preferring a more performance-oriented approach that did not mandate the use of specific control methods. For example, Paul Bailey, representing the American Petroleum Institute, submitted the following comment:

> API has some concerns with the ''Exposure Goal Program'' * * *, particularly shifting the burden to employers (to prove that the required controls are not feasible or effective) * * *. The listed elements of the exposure goal program may be useful tools for controlling exposures, but it is important to provide flexibility for use of new exposure control technologies that may become available. (Ex.118–11)

API recommended that the specific elements of the program be contained in a non-mandatory appendix rather than specified in the regulatory text; this approach was also supported in Richard Olson's submission on behalf of Dow Chemical. (Ex. 118–16) Mr. Olson also stated that the exposure goal program would establish the action level as a ''de facto PEL,'' and expressed the concern that specifying control measures might cause employers to implement controls for operations that do not contribute to employee exposures exceeding the action level. However, Mr. Olson acknowledged that the language contained in the draft agreement would allow employers to exclude specified elements of the program where they are not needed to attain the action level. Representatives of three refineries or chemical producers submitted similar comments (Exs. 118–5, 118–6, 118–8), arguing that the program should not include specifically mandated control methods since it would ''discourage * * * (the use of) process-based controls in favor of equipment based controls * * *'' (Ex. 118–5) and would be ''* * *counterproductive to innovating new control strategies * * *'' (Ex. 118–6)

However, in describing the program further, the CMA Olefins Panel commented that the regulatory language contained in the labor/industry agreement addressed these concerns. They said:

> The program is meant to supplement, not replace, the requirement that an employer ''institute engineering controls and work practices to reduce and maintain employee exposure to or below'' the PEL * * *. Since the program is required only where exposures are above the action level, it in fact creates incentives to develop improved engineering controls or work practices that achieve greater reductions in exposure.
>
> In addition, under the program, an employer would not need to implement the listed components of an exposure goal program if the employer could show that the components are not feasible, effective, or necessary to reduce exposures to at or below the action level * * *. Thus, OSHA's concerns that the program may impose inapplicable or unwarranted requirements are unfounded. (Ex. 118–13, p. 6)

The Panel further stated that the program ''* * * is an innovative concept aimed at addressing industry feasibility concerns while creating incentives to minimize worker exposure by encouraging the use of specified engineering controls with which the industry has experience.'' According to the Panel, incentives for developing improved exposure control methods are brought about because the exposure control program would not be required where exposures are at or below the action level (Ex.118–13, p. ii).

The submission by the IISRP explained that the exposure goal program is part of a three-pronged framework developed to address concerns about minimizing worker exposures in a feasible manner. According to IISRP:

* * * OSHA's record does not demonstrate that a 2 ppm (TWA) PEL or a 10 ppm STEL is feasible in polymer operations. Recognizing, however, that union representatives wished to see butadiene exposures even lower than 1 ppm, industry worked to develop an overall standard that would minimize exposures and still be feasible. The result was a three-part framework:

(1) A PEL of 1 ppm, STEL of 5 ppm, and action level of 0.5 ppm, coupled with

(2) The flexibility to employ respirators to achieve such exposures for non-routine intermittent and limited in duration activities and

(3) The exposure goal program.

* * * [T]he exposure goal program does not raise the concerns expressed by OSHA. No goal program need be initiated when exposures are already below the action level by whatever engineering controls or work practices. Better * * * controls * * * are thus not discouraged; they may always be used to achieve (the) action level or lower exposures. (Ex. 118–12, pp. 4–5)

After considering these comments, as well as the actual regulatory language recommended in the joint labor/industry agreement, OSHA finds that it is both reasonable and appropriate to include the specified control measures in the requirement for the exposure goal program. First, OSHA finds it reasonable in that the control measures specified in the exposure goal program represent those that are readily available to industry and have been proven effective to achieve the action level in at least some workplaces. OSHA's analysis of the technological feasibility of the standard, based largely on the NIOSH study of BD plants, identified some of these controls as approaches that have been successfully used to achieve exposure levels well below the PELs (see the Economic Analysis discussion in this preamble). For example, Shell Oil in Deer Park, Texas, achieved median exposure levels of 0.3 ppm (TWA) by implementing a collection system to capture emissions from loading operations as well as a combination of magnetic and slip-tube gauges (Ex. 16–29); use of magnetic gauges for all loading operations would likely reduce exposures further. Replacement of pumps having single mechanical seals with dual-seal pumps, which is an improved pump technology specified under the exposure goal program, has been occurring within the BD industry over the past several years (see the Technological Feasibility chapter of the Economic Analysis). Other elements of the exposure goal program are not equipment-oriented, but instead are designed to ensure that process equipment and engineering controls are optimally maintained to minimize or capture BD releases; these elements include a leak prevention, detection and repair program and a program to maintain the effectiveness of local exhaust ventilation equipment. Finally, all of the control measures specified in the exposure goal program are those that labor and industry representatives jointly agreed were reasonable to include. (Ex. 118–13A)

OSHA also finds that the exposure goal program requirements are appropriate for two reasons. First, OSHA has determined that a significant risk of cancer is associated with lifetime exposure to the action level of 0.5 ppm; the estimated risk to workers exposed at this level is about 4 per 1,000 (see the Quantitative Risk Assessment section of this Preamble). OSHA finds that it is appropriate to expect employers who have not already done so to implement the commonly used approaches detailed in paragraph (g) for controlling exposures to BD in an effort to further reduce this risk. Second, OSHA believes it appropriate to craft the exposure goal program requirements in specification language because to do otherwise would effectively blur the distinction between the exposure goal program and the methods of compliance requirements of paragraph (f), a distinction that the CMA emphasized was critical. (Ex. 118–13, p. 6) OSHA has not made a determination that a 0.5 ppm TWA exposure level for BD was generally feasible in affected industry sectors; therefore, the burden of proof to demonstrate the infeasibility of engineering and work practice controls for achieving the 0.5 ppm action level in an operation cannot be placed on the employer. If the requirements for the exposure goal program were developed in performance-oriented language, even with the aid of a non-mandatory appendix to guide employers and OSHA in its interpretation, OSHA believes that the requirement would have no real meaning in terms of performance measures by which employers, employees, and OSHA could judge compliance. In this situation, the action level might well be interpreted as a ''*de facto* PEL'', as suggested by Mr. Olson. By including a minimum specification for the content of the program, employers and their employees, as well as OSHA, are provided with a clear set of performance measures while maintaining a distinction between the exposure goal program and methods of compliance requirements for the PELs.

Nevertheless, OSHA believes the final rule's requirement for the exposure goal program, as worded, provides employers with considerable flexibility in the design of the program. Key to providing this flexibility is the 3-year phase-in date for the program. OSHA believes that by extending the implementation date for the exposure goal program one year beyond the date for which employers must implement controls to achieve the PELs, employers will have sufficient time to explore whether the use of alternative engineering approaches, process modifications, or work practices will permit them to reduce exposures to or below the action level.

OSHA also finds that commenters' concerns about the program's supposed lack of flexibility in allowing for the use of alternative technologies is unwarranted, since the extended phase-in period for implementation of the exposure goal program will provide employers with additional flexibility to design their own programs using alternative engineering control methods and work practices. The longer phase-in period for the exposure goal program is also appropriate because it allows employers to focus their initial efforts on reducing employee exposures to or below the PELs, as required under paragraph (f).

However, if the required implementation date of the exposure goal program is approaching and employee exposures still remain above the action level, either because the alternative controls were not sufficiently effective or the employer was not proactive in identifying alternatives, OSHA finds it appropriate to require that the employer implement, at a minimum, the controls that have been proven effective within the BD industry and identified in the exposure goal program, to the extent that such controls are feasible and applicable to the affected operations, and will be effective in further reducing employee exposures to BD.

The exposure goal program in paragraph (g) of the final rule incorporates two modifications from the language contained in regulatory text proposed by the joint labor/industry agreement (Ex. 118–12A). The joint agreement proposed that worker rotation be permitted as part of the exposure goal program. OSHA did not include this language in the final rule because of the Agency's long-standing policy of not allowing worker rotation to be used to control employee exposures to a carcinogen. As explained above in the Summary and Explanation for paragraph (f) (Methods of Compliance), employee rotation places a larger than necessary pool of workers at risk from exposure to BD. In other words, it would result in some employees being exposed to a cancer hazard to which they might not otherwise be exposed.

Since OSHA has estimated the lifetime cancer risk from exposure to BD to be about 4 per 1,000 workers at the action level of 0.5 ppm, use of employee rotation to achieve the action level provides no assurance that employees who are rotated into jobs with exposures around the action level will not be exposed to BD at levels representing a significant risk. Therefore, OSHA finds that employee rotation is not an appropriate method for achieving the action level. The second change involves the addition of clarifying language in the exposure goal program. The regulatory text contained in the joint labor/industry agreement stated that employers need not apply the control measures specified in the exposure goal program if such methods would not be ''effective.'' OSHA modified this language to make clear that such controls need not be implemented if the employer could demonstrate that they will ''not be effective in reducing employee exposures.'' OSHA believes that this better reflects the intent expressed in the joint labor/industry agreement.

H. Respiratory Protection

The respiratory protection requirements of the final standard for BD are in keeping with the requirements for respiratory protection in other OSHA health standards (e.g., Occupational Exposure to Lead, 29 CFR 1910.1025; Occupational Exposure to Benzene, 29 CFR 1910.1028), and with recent developments in the field. The provisions contained in the final rule have been changed from the proposal in some important respects in response to information and comments placed in the record. Comments received on the proposed BD respiratory protection provisions addressed broad issues of fit testing protocols, protection factors for various respirator classes, and other general respiratory protection issues. OSHA is currently evaluating these generic issues in the context of revising 29 CFR 1910.134, which is expected to be promulgated in the near future. The discussion of the appropriate respiratory protection for BD exposure that follows will identify those areas that are relevant to the broader issues being dealt with in the revision of 29 CFR 1910.134. The respiratory protection provisions contained in the final rule on BD reflect OSHA's current thinking on how some of these respiratory protection issues should be addressed. OSHA thus believes that the final rule for BD will be consistent with the revision of 29 CFR 1910.134.

Use of Respiratory Protection. Respirators are necessary as supplementary protection to reduce employee exposures when engineering and work practice controls cannot achieve the necessary reduction to or below the PELs. Paragraph (h)(1) identifies instances where the use of respiratory protection is permitted when employee exposures exceed the PELs. These are:

1. During the time interval necessary to install or implement feasible engineering and work practice controls;
2. In work situations where feasible controls are not yet sufficient to maintain exposures below the PELs;
3. During emergency situations; and
4. During non-routine work operations that are performed infrequently and in which exposures are limited in duration.

The first three instances are identical to those that were contained in the proposal. As to the fourth instance, i.e., ''non-routine work operations,'' OSHA originally proposed that respirators would be permitted for non-routine, limited-duration work operations *if the employer could demonstrate that engineering and work practice controls were infeasible.* OSHA received numerous comments arguing that OSHA should not impose a burden of proof on employers to demonstrate the infeasibility of engineering controls during such work operations.

The CMA Panel expressed support for allowing respirator use ''during the period necessary to install feasible engineering controls and where feasible * * * controls are not yet sufficient to reduce exposures below the PEL.'' (Ex. 118–13) However, in this submission and preceding ones, they objected to the proposal, which stated that respirators shall be used ''In work operations such as maintenance and repair activities, vessel cleaning, or other activities for which engineering and work practice controls are demonstrated to be infeasible, and exposures are intermittent in nature and limited in duration.'' (55 FR at 32805, 8/10/90) CMA's concern centered on the requirement to demonstrate the infeasibility of engineering controls before respirators could be used in short-term, intermittent work. (Ex. 112, p. 141–145) They felt that there were certain activities for which the infeasibility of engineering controls could not be demonstrated in ''an absolute technological sense,'' but the use of engineering controls would nevertheless be ''highly impracticable'' because the work activities are performed infrequently and the controls would prove to be very expensive. (Ex. 112, p. 142) CMA witness, Mr. Roger Daniel, gave the following example of such an activity:

> You may have 300 (pumps) in the plant and no one of those has to have any maintenance or cleaning activities to reestablish the integrity of the signal to that instrument more frequently than every two years. But because of the nature of the material that you're handling and the fact that it can slowly accumulate material * * * Periodically this has to be dealt with * * * you could put in lines to each of these blow-downs and collect from these 200 instruments just a little bit of liquid that has to be discharged * * * but from a practical standpoint, * * * [it] doesn't seem to make good sense. (Tr. 1/18/91. p. 1234–5)

In a pre-hearing submission CMA enumerated some situations where they believed engineering controls to be ''highly impracticable.'' Two of these were discussed in some detail. (Ex. 32–28) The first, ''blowing down of meter leads'' to clear instrument lines of accumulated debris was described as occurring only once every several years per instrument. CMA felt that installation of permanent blow-down lines leading to the flare, which would ensure the containment and destruction of BD, was not justified in this case. Second, they described breaking into and degassing pumps for maintenance as a work task that is performed twice weekly and lasts less than 10 minutes per occurrence. They felt that although it might be possible to build an enclosure around each of the pumps, the high cost of doing so was unjustified, due to the short-term nature of the task. (Ex. 32–28)

During the public hearing, Charles Adkins, then Director of OSHA Health Standards Programs, stated that in the context of the BD proposal, OSHA did not intend the term ''infeasible'' to mean an absolute technological infeasibility in the strictest sense, but that the intent was to limit respirator use to intermittent short duration situations where engineering controls are impracticable. He said that OSHA has:

> * * * always recognized that there [are] some situations that you don't consider it feasible. You don't put in an elaborate ventilation system to control exposures to some device that may break once every five years * * * and you * * * spend 30 minutes repairing that device. That's an appropriate time to use personal protective equipment. (Tr. 37, 1/15/91)

OSHA witness Frank Parker, a Professional Engineer and Certified Industrial Hygienist, testified that engineering controls were generally cost-effective, but that even when engineering controls are technologically feasible, respirators are ''going to be the most useful, practical approach'' in those situations in which there is ''sporadic (exposure) under unique conditions.'' (Tr. 1/17/91, p. 546)

In several other health standards, including the benzene standard, OSHA has specified some examples of activities for which engineering controls are not feasible. In the benzene rule respirators are required, ''In work operations for which the employer establishes that compliance with either the TWA or STEL, through the use of engineering and work practice controls are not feasible, such as some maintenance and repair activities, vessel cleaning, or other operations where engineering and work practice controls are infeasible because exposures are intermittent in nature and limited in duration.'' (29 CFR 1910.1028(g)(1)(ii)).

In the preamble to the benzene standard OSHA stated that

* * * engineering controls are often infeasible when exposures are intermittent in nature and limited in duration. For the same reason as maintenance and repair activities, extensive attempts at engineering controls are often not practical where exposures are both brief and occasional. It is both difficult to keep operable and a not very productive use of valuable industrial hygiene time, as well as often very costly, to try to provide engineering controls for very brief, intermittent exposures * * * In addition, for such intermittent and irregular exposures, employees can wear respirators with less difficulty. (52 FR at 34544, 9/11/87)

The labor/industry group recommended that respirators be specifically allowed ''in non-routine work operations which are performed infrequently and in which exposures are limited in duration.'' (Ex. 118–12A) OSHA considered all available information on this issue and has determined that such a provision is justified for BD. OSHA has therefore included the above language in the final rule in paragraph (h)(1)(ii).

The intent of this provision is not to allow employers to organize their workplace operations such that work is artificially broken down into tasks of small increments of time to allow wholesale respirator use when engineering controls are clearly practicable and therefore feasible under paragraph (f).

High exposures have been documented for workers performing certain activities such as cylinder voiding and sampling. Such activities may be performed intermittently and resulting exposures have been shown to be of short duration; however, since such operations are performed routinely, engineering controls need to be used to control exposures. OSHA does not intend that such routine activities be included in the paragraph (h)(1)(ii) exemption from the usual preference for engineering and work practice controls. Rather, paragraph (h)(1)(ii) contemplates that brief incidental maintenance activities be included. On the other hand, in the case of cylinder voiding (which would not be covered by paragraph (h)(1)(ii)), NIOSH recommended use of a laboratory hood or a vacuum exhaust with an enclosure. (Ex. 16–38; 16–39) For maintenance activities, NIOSH said ''maintenance technicians should follow decontamination procedures when working on process equipment. However, if it is not possible to completely decontaminate a process prior to the procedures, then respirators with organic vapor cartridges should be worn.'' (Ex. 16–38; 16–39)

In keeping with OSHA's intention to use a performance-oriented approach, where appropriate, the Agency has not defined either ''non-routine,'' ''infrequently,'' nor ''limited in duration'' in the final rule. Reasonable interpretations must be made. To qualify for the narrow exemption that permits the use of respirators without demonstrating the infeasibility of engineering or work practice controls, the task must meet all three criteria; it must be non-routine, infrequent, and of limited duration. OSHA believes that the vast majority of such activities qualifying under paragraph (h)(1)(ii) will consist of brief, intermittent maintenance operations such as those described by CMA (e.g., blowing down meter leads for 5 minutes once a year, or opening pumps for maintenance for 1 hour quarterly). (Ex. 32–28, p. 116)

Emergency Situations. Paragraph (h)(1)(iv) requires employers to ensure that employees use respiratory protective equipment during emergencies. The joint labor/industry agreement suggested changing ''emergencies'' to ''accidental release emergencies.'' Submissions by CMA (Ex. 118–13) and IISRP (Ex. 118–12) provided no explanation supporting the need to change the language in paragraph (h)(1)(iv). OSHA did not incorporate this change in the final rule since the language suggested by the labor/industry agreement may imply to some that a release must occur before an emergency is declared and respirators would be required. The language that was originally proposed and retained in the final rule, along with the definition of ''emergency'' in paragraph (b), make clear that employers must ensure that employees use respiratory protection during an unusual condition or occurrence where there is a *potential* for a release of BD, even if an actual release has not occurred. OSHA believes that this reflects common practice in the chemical industry. This provision of the final rule is consistent with other OSHA health standards and is necessary to ensure that employees do not become exposed should an unusual condition result in a release.

Respirator Selection. Paragraph (h)(1) of the final standard requires that employers provide respirators to employees when necessary and ensure that employees use the respirators properly. As in other OSHA standards, employers are to provide the respirators at no cost to the employees. OSHA views this allocation of costs as necessary to effectuate the purposes of the Act. This requirement makes explicit an Agency position which has long been implicit in the promulgation of health standards under section 6(b) of the Act.

Employers must select respirators from those certified as being acceptable for protection against BD or organic vapors by the National Institute for Occupational Safety and Health (NIOSH), under the provisions of 42 CFR part 84.

Paragraph (h)(2) of the final rule requires employers to select and provide respirators in accordance with the criteria specified in Table 1. In the proposal, OSHA would not have permitted the use of cartridge-type negative-pressure respirators because of concern that they would not be sufficiently protective due to the short breakthrough times associated with high BD concentrations. OSHA requested additional data and comment on the issue, and asked NIOSH to conduct another breakthrough study to provide more information about the effectiveness of organic vapor cartridges in atmospheres containing lower BD concentrations.

The respirator selection table in the proposal was the subject of numerous comments addressing two principal issues. (Ex. 32–3; 32–4; 32–7; 32–8; 32–14; 32–20; 32–22; 32–25; 32–27; 32–28; 112; 118–6; 118–12; 118–16) First, commenters stated that the table should allow the use of cartridge type respirators in limited applications, and that the table should include other kinds of available respiratory protective equipment, such as half-mask supplied air respirators and loose-fitting powered air purifying respirators. (Ex. 32–4; 32–22; 32–27; 32–28; 112; 118–6; 118–12; 118–16) Second, commenters questioned the assigned protection factors (APFs) used in the proposal, stating that OSHA should use APF's similar to those used in other OSHA health standards or those of the ANSI

Z88.2–1992 standard. (Ex. 32–7; 32–25; 112; 118–6; 118–16) NIOSH stated that if respirators other than a self-contained breathing apparatus (SCBA) or a supplied air respirator with auxiliary SCBA that NIOSH recommended are permitted, OSHA should use the APFs in the 1987 NIOSH Respirator Decision Logic. (Ex. 32–25) The ANSI Z88.2–1992 standard and NIOSH decision logic apply the same APFs to half-mask, negative-pressure respirators (10) and PAPRs equipped with a tight-fitting half mask (50); for other respirator types, ANSI generally assigns a higher APF than does NIOSH.

OSHA has determined that cartridge-type respirators will provide adequate protection for BD, based on new evidence and data on breakthrough times at low BD concentrations (described in the discussion of *Service Life* below) and on comments concerning whether BD had adequate odor warning properties that would permit employees to detect breakthrough well in advance of their being overexposed. (Ex. 32–25; 32–28; 112) NIOSH stated that BD does not have adequate warning properties, citing the paper by Amoore and Hautala (Odor as an aid to chemical safety: odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. *J. Appl. Toxicol.* 3:272–290) that lists an air odor threshold of 1.6 ppm for BD. (Tr. 1/17/91. p. 741) However, this value is a geometric average of all the literature survey odor data that Amoore and Hautala used in devising their odor threshold tables. On the other hand, Tom Nelson, testifying on behalf of CMA, cited the American Industrial Hygiene Association (AIHA) report, *Odor Thresholds for Chemicals with Established Occupational Standards,* which lists BD as having a geometric mean odor threshold of 0.45 ppm for detection and 1.1 ppm for recognition. (Ex. 32–28c) According to CMA, the AIHA report represents a more recent compendium of odor threshold data for chemical agents than does the Amoore and Hautala study. (Ex. 112) Since the mean odor threshold identified by this source is about half of the 1 ppm PEL, and more than 10-fold below the 5 ppm STEL, OSHA finds that most wearers of air purifying respirators should still be able to detect breakthrough before a significant overexposure to BD occurs. Accordingly, OSHA is permitting the use of air purifying respirators equipped with either organic vapor cartridges or canisters in the final rule. In addition, OSHA will permit employers to provide single-use, half mask respirators equipped with organic vapor cartridges for employees working in environments containing up to 10 ppm BD.

In the final rule, OSHA has used the APFs for the various respirator classes contained in the NIOSH Respirator Decision Logic. (Ex. 32–25) The ANSI Z88.2–1992 APF values have not been adopted, although they were relied on in the recommended standard from the joint labor/industry agreement. As discussed earlier in this section of the preamble, OSHA is currently engaged in evaluating extensive data and evidence on APFs as part of its 29 CFR 1910.134 revision. However, in the case of the BD standard, OSHA's decision to rely on the more protective NIOSH APFs is based on evidence showing that organic-vapor cartridges and canisters have limited capacity for adsorbing BD and may have too short a service life when used in environments containing greater than 50 ppm BD. This evidence (discussed in detail in the section below entitled *Service Life of Organic Vapor Cartridges and Canisters*) consists of laboratory test data showing that organic vapor cartridges and canisters have a useful service life of no more than about 1.5 hours when challenged with air containing greater than 50 ppm BD, and that, at these concentrations, service life declines rapidly with increasing BD concentration. Allowing for a reasonable margin of protection, and given that test data were available only for a few makes of cartridges and canisters, OSHA believes that air-purifying devices should not be used for protection against BD present in concentrations greater than 50 ppm, or 50 times the 1 ppm PEL. Thus, OSHA finds that the ANSI APFs of 100 for full-facepiece, air-purifying respirators and 1,000 for PAPRs equipped with tight-fitting facepieces are inappropriate for selecting respirators for BD.

The proposal contained a provision (g)(2)(iii) requiring employers to provide employees with the option of using a positive-pressure respirator if the employee is unable to use a negative-pressure device. John Hale of Respirator Support Services objected to this provision since it would take respirator selection, the most critical aspect of a respirator program, out of the hands of the program administrator who is most knowledgeable about respirators and put it into the hands of the worker. (Ex. 32–3) Hale questioned whether the provision's language implied that the individual's medical condition would preclude the wearing of any respirator, since the breathing resistance of a modern negative pressure respirator is not a concern for a healthy worker. Mr. Hale also questioned the additional cost of supplying these alternative respirators. The International Institute of Synthetic Rubber Producers (IISRP) stated that, ''this provision is unwarranted because employees who are not medically fit should not be assigned to a job where respiratory protection is required.'' (Ex. 34–4)

OSHA has similar provisions requiring that the employer supply alternative respirators, either upon employee request or if the employee has difficulty wearing a negative-pressure device, in other substance specific standards such as inorganic arsenic (1910.1018), lead (1010.1025), cadmium (1910.1027), benzene (1910.1028), formaldehyde (1910.1048), and MDA (1910.1050). It has been OSHA's experience that this requirement has not proven to be a burden to implement and has proved to be a way to improve worker acceptance of respirator use. The language used in the BD proposal was the same as the language used in the benzene standard, 1910.1028 (g)(2)(iii). However, commenters felt the language in question implied that medically unfit workers would be allowed to wear PAPRs or supplied air respirators in place of a negative pressure respirator. (Ex. 32–3; 34–4) This is not the intent of this provision. The final provision (h)(2)(iii) has been modified to clarify that employers must determine that employees are able to use positive-pressure respiratory devices before upgrading an employee's respirator from a negative-pressure device. OSHA believes that this change in language better reflects the Agency's intent that employees who are unable to wear negative-pressure respirators be permitted to wear positive-pressure devices only after the employer takes appropriate steps to ensure the employee's ability to do so safely.

Some commenters pointed out that Table 1 of the proposal contained an error in that it would have permitted the use of PAPRs and self-contained breathing apparatus operated in a negative-pressure demand mode at any BD concentrations exceeding 50 ppm, which could result in a potentially dangerous situation since no maximum use concentration for these types of respirators was specified. (Ex. 32–28; 32–25; 32–3; 32–14) OSHA agrees that its proposed respiratory selection table was in error and has revised Table 1 of the final rule to reflect the appropriate maximum use concentration for PAPRs. OSHA deleted SCBA operated in negative-pressure demand mode from Table 1 since this type of respirator is not typically used in industrial settings.

Respirator Program. The proposal required (paragraph (g)(3)) that employers institute a respirator program in accordance with 29 CFR 1910.134 (b), (d), (e), and (f). It was pointed out by one commenter that since 29 CFR 1910.134 is under revision, these references to specific paragraphs may change. (Ex. 32–3) The language of this provision has been revised to eliminate any reference to specific paragraphs in 29 CFR 1910.134, but still retains the requirement that a respirator program in accordance with the respiratory protection standard be implemented that contains the basic requirements for proper selection, fit, use, training of employees, cleaning, and maintenance of respirators. For employers to ensure that employees use respirators properly, OSHA has found that the employees need to understand the respirator's limits and the hazard it is protecting against in order to appreciate why specific requirements must be followed when respirators are used.

Service Life of Organic Vapor Cartridges and Canisters

The proposal in paragraph (g)(4)(i) required that the air purifying filters be replaced at 90% of the expiration of service life. The service life of organic vapor cartridges and canisters relates to the amount of time that the charcoal filter effectively purifies the breathing air before contaminants break through the filter and enter the facepiece. In laboratory testing for service life, air containing a known concentration of contaminant is passed through a cartridge or canister at a predetermined flow rate. The concentration of contaminant is measured in the air exiting the filter element on the other side. The time required for the contaminant concentration to reach a target level after passing through the filter element is known as the breakthrough time, and represents a measure of the service life of the filter element when used in atmospheres containing concentrations of the contaminant near the challenge concentration.

OSHA received comments on the proposed provision that would require replacement of organic vapor filters at 90% of the service life. The joint labor/industry agreement supported the proposed provision and recommended its inclusion in the final rule. (Ex. 118–12) However, John Hale of Respirator Support Services questioned how anyone could be expected to know when an element had reached 90% of its service life, or even come close to guessing it, since service life is dependent on the filter's inherent capacity (sorbent efficiency, bed depth, and other design factors) and even more so on respirator use conditions. (Ex. 32–3) Mr. Hale recommended that OSHA simply require filter elements to be replaced at the end of each shift.

In contrast, Tom Nelson, testifying for CMA (Ex. 32–28 C; 107–22), recommended that service life be taken into account to permit the use of organic vapor cartridges against BD, pointing out that there were test data contained in the BD record that would permit employers to establish cartridge change schedules suitable for their individual workplaces (these test data are discussed below). Specifically, Mr. Nelson suggested modifying paragraph (g)(4)(iii) of the proposal to permit the use of cartridge style respirators, provided that the cartridges have a minimum service life of at least 110% the anticipated duration of respirator use. Mr. Nelson also recommended that service life be tested under worst-case conditions of use, i.e., at a flow rate of 64 lpm at 25°C and at a relative humidity of 85%.

OSHA agrees with Mr. Nelson that adequate service life data are currently available both to support the use of organic vapor cartridges for BD and to establish schedules for changing filter elements. For example, NIOSH has performed respirator cartridge breakthrough testing at various exposure levels. (Ex. 23–83; 90) The BD record also contains other reports of service life testing of organic vapor filters, one a published report by Mr. Mark Ackley (Chemical cartridge respirator performance: 1,3-butadiene. *Am. Ind. Hyg. Assoc. J.* 48:447–453 in Ex. 32–28, Vol. II, App. B), and the other an unpublished report prepared by Mr. William Myles of Dow Chemical (Ex. 32–28, Vol. II, App.C). A summary of service life test data from these reports is presented in Table 2. Most of the breakthrough tests conducted for BD used high challenge concentrations relative to the PEL (most exceeding 50 ppm). In addition, the data from Myles and those from Ackley measured breakthrough times for a target concentration of 10 ppm, which was the ACGIH TLV at the time testing was conducted. However, after the informal hearing, NIOSH conducted breakthrough tests at lower challenge (10 to 50 ppm) and target (2 to 10 ppm) concentrations; some of these data are also summarized in Table X–1. (Ex. 90)

TABLE X–1. SUMMARY OF BREAKTHROUGH TEST DATA FOR RESPIRATOR CARTRIDGES AND CANISTERS CHALLENGED AGAINST BUTADIENE

Upstream Concentration (ppm)	Breakthrough Concentration (ppm)	Temperature, Relative Humidity (RH), Flow Rate (lpm)	Breakthrough Time (min)	Reference
CARTRIDGES				
500	10	27°C, 85% RH, 64 lpm	36	Myles (Ex. 32–28C).
100	10	25°C, 50% RH, 64 lpm	132.8, 142.0	Ackley (Ex. 32–28C).
100	10	25°C, 50% RH, 32 lpm	240.7, 245.1, 260.0	Ackley (Ex. 32–28C).
100	10	27°C, 85% RH, 64 lpm	108	Myles (Ex. 32–28C).
100	10	27°C, 85% RH, 32 lpm	174	Myles (Ex. 32–28C).
75	0.75	25°C, 85% RH, 64 lpm	55	NIOSH (Ex. 23–83).
93	0.93	25°C, 85% RH, 64 lpm	92	NIOSH (Ex. 23–83).
50	2	25°C, 85% RH, 64 lpm	159.1 [a]	NIOSH (Ex. 90).
20	2	25°C, 85% RH, 64 lpm	201.1 [a]	NIOSH (Ex. 90)
10	2	25°C, 85% RH, 64 lpm	217.3 [a]	NIOSH (Ex.90).
CANISTERS				
500	10	27°C, 85% RH, 64 lpm	42	Myles (Ex. 32–28C)
100	10	27°C, 85% RH, 64 lpm	102	Myles (Ex. 32–28C)

TABLE X–1. SUMMARY OF BREAKTHROUGH TEST DATA FOR RESPIRATOR CARTRIDGES AND CANISTERS CHALLENGED AGAINST BUTADIENE—Continued

Upstream Concentration (ppm)	Breakthrough Concentration (ppm)	Temperature, Relative Humidity (RH), Flow Rate (lpm)	Breakthrough Time (min)	Reference
100	10	27°C, 85% RH, 32 lpm	234	Myles (Ex. 32–28C).

[a] Mean values reported.

The more recent NIOSH data (Ex. 90) show that organic vapor cartridges, when tested in the range of 10 to 20 ppm, can provide about 3 to 3.5 hours of protection against BD under worst case test conditions (see Table X–1). However, at concentrations above 20 ppm, NIOSH test data (Ex. 23–83, see Table X–1) show that breakthrough time begins to decline rapidly; breakthrough times of about 2.5, 1, and 1.5 hours were obtained at test concentrations of 50, 75, and 93 ppm, respectively. More limited data on canister performance provided by Myles (see Table X–1) suggest that canisters will provide little gain in service life compared to cartridges. At a challenge concentration of 100 ppm and a target concentration of 10 ppm, breakthrough of organic vapor canisters occurred in 102 minutes under worst-case test conditions.

After reviewing the record evidence and comments on filter service life for BD, OSHA has modified its proposal to include a required schedule for the replacement of organic vapor cartridges and canisters (paragraph (h)(4)(i) and Table 1). Alternatively, employers may use other existing data or conduct additional tests to evaluate cartridge or canister service life in BD-contaminated atmospheres, and establish schedules for filter replacement based on 90% of the service life (paragraph ((h)(4)(ii)), as originally proposed. Employers may adopt the second approach, rather than use the default schedule in Table 1, so long as the written respirator program clearly describes the basis for the filter replacement schedule and demonstrates that employees will be adequately protected. In conducting this evaluation, employers should consider any workplace-specific factors that may affect filter service life, such as pattern and intensity of exposure to BD, temperature and humidity, and presence of other air contaminants that may shorten service life. In addition, where air-purifying respirators are used intermittently throughout the day, the filter replacement schedule developed by the employer must consider the effects of BD migration through the filter element during periods of non-use, and the impact of this effect on service life.

Under the default schedule in the final rule, cartridges and canisters for negative- pressure respirators must be replaced every 4 hours at BD concentrations less than or equal to 5 ppm, every 3 hours at concentrations between 5 and 10 ppm, every 2 hours at 10 to 25 ppm, and every hour at 25 to 50 ppm (see Table 1 of the final rule). The record contained no specific evidence on the performance of PAPR cartridges against BD. Therefore, the default change schedule for PAPR cartridges is based on that of negative-pressure devices, i.e., PAPR cartridges must be replaced every 2 hours or every 1 hour at BD concentrations less than or equal to 25 ppm or 50 ppm, respectively. Under the default replacement schedule, the maximum service time permitted in Table 1 begins from the time that the filter seal is broken, regardless of whether the respirator is actually put into immediate use, and runs continuously regardless of the pattern of respirator use. For example, if the seals of a pair of cartridges for a negative-pressure half mask respirator are broken at 8 am and the respirator is used in atmospheres not exceeding 5 ppm BD, the cartridges must be replaced no later than 12 pm, even if the respirator was only used intermittently for a few minutes. OSHA believes that it is necessary to define the replacement schedule requirement in this manner to account for BD migration throughout the cartridge during periods of non-use, and to ensure simplicity in administering the respirator program.

In setting the service lives of air purifying respirators for BD, OSHA has taken a conservative approach in evaluating the service life testing data. Temperature, humidity, air flow through the filter, the work rate, and the presence of other potential interfering chemicals in the workplace all can have a serious effect on the service life of an air purifying cartridge or canister. High temperature and humidity directly impact the performance of the activated carbon in air purifying filters. Humidities of 85% and temperatures of 25 °C or higher are commonly reached in the summer at BD polymer processing plants located on the Gulf Coast. An air flow rate of 64 liters per minute (lpm) used to test cartridges represents an air flow that may be achieved at a moderately high work rate. In addition, filter elements from different manufacturers may exhibit different service lives depending upon the types and amounts of charcoal used. OSHA realizes that lower humidity, temperature, and air flow through the filter would increase the estimates of service life. However, OSHA believes that, in establishing a default schedule for filter replacement that applies to all work situations involving exposure to BD, it is important to base the schedule on worst case conditions found in the workplace, since this will provide the greatest margin for safety in using air purifying respirators with BD. NIOSH in its comments (Ex. 32–25) stated that filters should be tested at worst case conditions of temperature, humidity, and BD concentration, and in combination with the other gases and vapors present in the workplace, since they may drastically affect service lives.

OSHA believes that specifying a schedule for filter changes based on service life data, or allowing employers to develop schedules based on BD-specific test data, is key to permitting the use of organic vapor cartridge respirators for protection against BD, since the service life data described above clearly demonstrate that organic vapor cartridges will not provide adequate protection if used over an entire work shift. In addition, OSHA believes that specifying a default filter change schedule for organic vapor cartridges will simplify compliance for those employers who do not have access to additional breakthrough data for BD.

Furthermore, OSHA finds that the odor warning properties of BD will provide an additional margin of protection in the event that the filter replacement schedule contained in Table 1 is not adequate for certain work situations. The regulatory text recommended by the joint labor/industry agreement suggested that OSHA add language in paragraph (h)(4) to require that employers replace air-purifying elements as soon as possible if an employee detects the odor of BD while using the respirator. OSHA agrees that this is an appropriate precaution,

and has included the language in the final rule.

Respirator Use. The proposal required (paragraph (g)(4)(i)) that canisters be labeled with the date they were put into service. A date alone was all that was needed since the proposal would have allowed for their use for a full work shift before replacement. However, in the final rule, OSHA will now be allowing the use of air purifying cartridges for BD exposures, and the service life of these cartridges is less than a full work shift. Therefore, the proposed provision has been modified in the final rule (paragraph (h)(4)(iii)) to require the labeling of air purifying filter elements with both the date and the time of the start of use to allow for their prompt replacement once the service life listed in Table 1 is reached.

The final standard (paragraph (h)(4)(v)) permits employees to leave the regulated area to readjust the respirator facepiece to their faces for proper fit. The respirator wearer who detects the odor of BD or who feels eye irritation should leave the area immediately and replace the air purifying elements before reentry. It also permits employees wearing respirators to leave the regulated area to wash their faces and respirator facepieces to avoid potential skin irritation associated with respirator use.

End-of-Service-Life Indicators. End-of-service-life indicators (ESLI) for BD do not now exist. The final standard contains a provision (paragraph (h)(4)(iv)) that would allow the use of such a NIOSH-approved ESLI. OSHA originally proposed permitting the use of a NIOSH-approved ELSI for BD, and inclusion of this requirement was supported by the joint labor/industry agreement. This provision is intended to encourage respirator manufacturers to develop a reliable ESLI for organic vapor cartridges and canisters used to protect against BD. Respirator manufacturers have been reluctant to develop filter elements with ESLI without an indication from OSHA that it would allow the use of an ESLI.

In its comments on the proposed standard, NIOSH stated that if OSHA chooses to allow air purifying respirators for BD, OSHA should require the use of an ESLI along with the requirement for doing a service life determination based on the worst case BD exposure level expected, at high humidity levels and high temperatures encountered at that plant location. (Ex. 32–25) Since a NIOSH approved ESLI for BD does not yet exist, OSHA cannot make their use a prerequisite for air purifying respirator use with BD, since by doing so OSHA would preclude the use of air purifying respirators. However, OSHA does encourage employers to use ESLIs when they are approved by NIOSH.

John Hale of Respirator Support Services objected to the practice of relying on mechanical end-of-service-life indicators, stating that since mechanical devices do fail, it is preferable instead to rely upon breakthrough to dictate when to replace air purifying elements. (Ex. 32–3) However, since the permissible exposure limits for chemicals such as BD are being lowered to levels almost at the odor threshold, a reliable ESLI would not replace breakthrough detection by the wearer, but would instead provide an additional means of ensuring that air purifying elements are replaced before their service life expires.

Air purifying filter elements with end of service life indicators (ESLI) may be used until the ESLI indicates that filter replacement is necessary. For cartridges and chin style canisters this may mean that their service lives with an ESLI would be longer than the conservative service lives listed in Table 1. However, the final rule includes a requirement to replace the cartridge or canister at the beginning of the next work shift, regardless of any residual service life left, due to the problem of BD migration through the filter element during the time the previously exposed filter element is not in use (e.g., overnight).

Fit Testing. Paragraph (h)(5) of the final BD rule requires employers to perform either qualitative (QLFT) or quantitative (QNFT) fit testing at the time a tight-fitting negative-pressure respirator is first assigned to an employee who is working in atmospheres containing 10 ppm or less of BD, and annually thereafter. At BD concentrations above 10 ppm, employers must use QNFT for full-facepiece, negative-pressure respirators. In the proposal, employers would have been required to perform either QNFT or QLFT on all tight-fitting respirator facepieces, including those used for positive-pressure devices. The final rule also adds a new paragraph (h)(5)(iii) that requires employers to ensure that employees perform a fit check of the respirator facepiece before each entry into a BD-contaminated atmosphere.

OSHA received many comments on the proposed fit test requirements for BD. The IISRP stated that OSHA should not require QNFT at exposure levels above 20 ppm (i.e., an APF of 10), because it is scientifically unnecessary and much more expensive than QLFT. (Ex. 34–4) In the preamble to the BD proposal (55 FR 32793), OSHA referred to the Agency's proposed revision to 29 CFR 1910.134, which in turn discussed evidence indicating that QLFT was not reliable in achieving APFs higher than 10. (55 FR at 32793) OSHA's standards for cadmium (29 CFR 1910.27) and asbestos (29 CFR 1910.1001) require QNFT of full facepiece respirators used at APFs higher than 10. Although the Agency will make a final determination on the effectiveness of QLFT for achieving APFs higher than 10 as part of its revision of 29 CFR 1910.134, OSHA is not aware of any data or evidence presented in the BD rulemaking that suggest that OSHA should depart from the position expressed in the proposal. Therefore, the final rule for BD will require QNFT when negative-pressure respirators are to be used in atmospheres containing more than 10 ppm BD.

When tight fitting respirators are used, OSHA requires respirator fit testing because proper fit is critical to the performance of tight fitting negative pressure, air-purifying respirators. With tight fitting air-purifying respirators, a negative pressure is created within the facepiece of a properly fitted respirator when the wearer inhales. A poorly fitted respirator allows contaminated workplace air to enter the facepiece through gaps and leaks in the seal between the face and the facepiece instead of passing through the sorbent material.

The fit testing of positive pressure respirators, both half masks and full facepieces, was part of the respirator fit testing provisions in the proposal (paragraph (g)(5)(i)), based on a concern that employees may ''overbreathe'' while wearing the respirator, thus creating a temporary negative pressure within the facepiece and increasing the likelihood for leakage. Tom Nelson, testifying for CMA, questioned this requirement since the requirement had never appeared in previous OSHA standards. (Ex. 112) Mr. Nelson also claimed that requiring fit testing of positive-pressure respirators due to the potential for ''overbreathing'' was unwarranted for BD since this was likely to occur only at extremely high work rates. (Ex. 112) In addition, Mr. Nelson stated that, if OSHA does require fit testing of positive pressure respirators, then it should adopt the ANSI approach.

OSHA has previously required fit testing for positive pressure respirators in the recent cadmium standard, 29 CFR 1910.1027(g)(4) (ii), (iii), and (iv). However, OSHA is currently conducting a comprehensive evaluation of the need to require fit testing of positive-pressure facepieces as part of its rulemaking to revise 29 CFR 1910.134. Until this

evaluation is complete and OSHA has made a final determination, OSHA is not including the proposed requirement to fit test positive-pressure devices in the final rule for BD.

Some commenters objected to the requirement contained in Appendix E that employers conduct at least three separate quantitative fit tests to obtain a fit factor for a respirator, questioning the basis for the requirement and arguing that it was too costly. (Exs. 32–3, 32–28, 112, 118–6) For example, John Hale of Respirator Support Services provided the following comment in his pre-hearing submission:

> On what technical basis does OSHA impose this requirement? It is widely accepted among the health and safety professionals * * * that there is no more confidence gained from three fit test results than from one. Indeed, it would take many more than three to provide any level of statistical confidence in the actual value arrived at for a fit factor. The burden of time and expense imposed by this requirement is completely unjustified.* * * (and) there is no benefit to the respirator wearer. (Ex. 32–3)

As with other respirator issues raised in the BD record, OSHA is currently revising its required protocols for fit testing as part of the revision of 29 CFR 1910.134. At this time, OSHA has modified Appendix E in the final rule for BD to require a single test when QNFT is performed, pending OSHA's final determination for the revised 29 CFR 1910.134 standard.

Several commenters stated that the BD standard fit testing requirements did not allow the use of the Portacount fit testing device since there is no protocol for that method contained in Appendix E. (Ex. 32–3; 32–4; 32–8; 32–11; 32–27; 32–28; 112; 118–16) In 1988 OSHA issued a compliance memorandum classifying the use of the Portacount fit test as a de minimis violation for those OSHA standards that contain a mandatory appendix listing quantitative fit test protocols and instrumentation. The validation of fit testing methods such as the Portacount and appropriate protocols for such methods are to be addressed fully in the fit testing section of the 29 CFR 1910.134 respiratory protection standard revision. Shell Oil Company, in a pre-hearing submission to the BD record stated:

> In a new standard, it would seem reasonable for OSHA to recognize the Portacount system. It is improper for OSHA arbitrarily to exclude a proven fit-test system from a standard, but to encourage a technical violation by advising industry that it would consider Portacount [a de minimis violation] * * * (Ex. 32–27, p. 3)

CMA asked that OSHA allow use of ''any QNFT equipment such as the Portacount that can reliably measure a test challenge.'' (Ex. 32–28, p. 131)

TSI, Inc. (Ex. 32–11, Att. 1–3) submitted three technical papers to the BD record reporting the results of studies comparing the ''Portacount,'' condensation nuclei counting (CNC) respirator fit-test method with the aerosol/photometer method. The first, published in the Journal of the International Society for Respiratory Protection, described a U.S. Army study comparing fit factors determined by CNC and the more traditional corn oil aerosol/photometer determinations. Initial tests did not employ human subjects, but rather they used a mask/headform assembly enclosed in a plastic hood. Numerous conditions of heat and humidity were tested repeatedly.

The correlation coefficient was calculated to determine the strength of the relationship between measurements made in applying the two methods.[11] The correlation coefficients calculated in this study ranged from 0.953 to 0.996.

The Army study also fit-tested human subjects using both methods. Subjects were tested by each method sequentially and the pass-fail agreement/disagreements determined for 100 comparison tests. Agreement exceeded 95%. The author concluded that ''(CNC) was a suitable alternative to conventional photo-meter quantitative fit testing systems.'' (Ex. 32–11, Att. 1, p. 8)

The second study, performed at Shell Oil Company, described sequential fit tests of approximately 50 test subjects at each of two chemical plants. (Ex. 32–11, Att. 2) Again Portacount/CNC methodology was compared with the corn oil aerosol/photometric method. This researcher also compared fit test outcomes as pass-fail agreement/disagreement. The differences in the results obtained from the Portacount/CNC method and aerosol/photometric method shoed less than a 10% discordance and were not statistically distinguishable. The author concluded that ''the Portacount would appear to be an acceptable system for quantitative fit testing.'' (Ex. 32–11, Att. 2, p. 6)

The final submission was a paper by Rose et al. that appeared in the Journal of Applied Occupational and Environmental Hygiene in 1990. (Ex. 32–11, Att. 3) Again, sequential fit-factor measurements using both the aerosol/photometer test system and CNC (Portacount) methods were compared. They were tested at the same fitting of the respirator for each subject. The study involved 24 test subjects. It was found that fit factors determined by photometer were lower than the CNC determinations in 14 of 24 pairs. However, the correlation coefficient was over 0.85, indicating that the two sets of measurements were highly correlated. Other statistical tests were applied and no differences between the two methods were demonstrated. When pairwise comparisons of pass-fail agreement/disagreements were made, the authors concluded ''there was only one discordant pair in the 48 comparisons at the two critical fit factors.'' In reviewing the then-current literature, Rose et al. noted that several other studies had shown good agreement between the results of the 2 fit factor measurement methods also.

These findings affirm OSHA's earlier determination based on a study by Lawrence Livermore National Laboratory (as described in the above-mentioned compliance directive) that the CNC/Portacount method of fit factor determination is acceptable. Rather than continue to consider use of the CNC/Portacount method as a de minimis violation, OSHA is in this final rule accepting its use for fit testing for BD exposure and has included instructions for performing this fit test in Appendix E. These instructions are essentially the same as those of the manufacturer.

In Appendix E of the proposal, the QNFT protocol in section C(4)(xi) required that half masks and full facepiece respirators obtain a minimum fit factor of 100 during QNFT fit testing. John Hale stated that a minimum fit factor of 10 times the APF for that class of respirator is needed. (Ex. 32–3) James Kline of Wilson Safety Products pointed out that the preamble stated that a minimum fit factor of 100 for half masks and 500 for full facepieces should be obtained during fit testing, while Appendix E mentioned only a fit factor of 100. (Ex. 32–14) Mr. Kline recommended that the minimum fit factor should be ten times the applicable APF or the protection factor needed for the application, whichever is lower. NIOSH also recognized the difference in fit factor requirements between the preamble of the proposal and Appendix E and recommended a fit factor of 100 be used for quarter and half mask and that a fit factor of 500 be used for full facepieces. (Ex. 32–25) OSHA agrees that the language in the proposed Appendix E was in error, and has corrected it in the final rule to require that a minimum fit factor of 100 for half

[11] The correlation coefficient is the proportion of the total sum of the squares variation that is explained by the linear relationship. Thus, a correlation coefficient of zero indicates the two are not related, while a value close to 1 indicates a high positive correlation.

masks and 500 for full facepieces be obtained during QNFT testing.

Obtaining a proper fit for each employee may require that the employer provide two to three different sizes and types of masks so that an employee can select the most comfortable respirator that has a facepiece with the least leakage around the face seal. In past rulemaking efforts, OSHA has consistently found that this is a necessary requirement for fit testing of negative-pressure devices since the configuration of each manufacturer's facepiece varies, and it is highly unlikely that all employees will be comfortably fitted with the facepiece of a single manufacturer, even if different sizes are provided.

However, the requirement in Appendix E to use respirators from multiple manufacturers for the fit testing of positive-pressure respirators was questioned by CMA since, unlike the case for negative-pressure facepieces, most people can be adequately fitted with a single manufacturer's positive-pressure equipment. (Ex. 112) CMA was also concerned that, if employees were assigned different makes and models of positive-pressure facepieces, confusion would arise in the workplace with the use of different types of hoses specific to each manufacturer, increasing the likelihood that incompatible respirator hardware would be used, increasing risks to workers. However, as discussed above, OSHA is not now requiring fit testing of positive-pressure devices in the final rule for BD, deferring judgement until the issue is resolved in the rulemaking for 29 CFR 1910.134.

The CMA submission addressed two additional fit test issues, recommending that OSHA delete the protocol for the irritant smoke QLFT in Appendix E, due to health concerns, and that the grimace exercise be deleted from the QNFT protocols because it tends to yield an artificially low fit factor. (Ex. 32–28, Ex. 112) OSHA is evaluating both of these issues in the context of the rulemaking for 29 CFR 1910.134. At the present time, OSHA is retaining in Appendix E the irritant smoke QLFT, should employers wish to continue using it. Should OSHA determine upon promulgation of a final revision of 29 CFR 1910.134 that use of irritant smoke QLFT poses excessive risks to employees, OSHA will make appropriate changes to its final rule for BD.

Regarding the issue of the grimace test, this exercise is to determine whether the facepiece being tested will reseat itself on the face after the respirator seal is broken. In quantitative fit testing, the test instrument should show a rise in challenge agent concentration within the mask during the grimace exercise, followed by a drop once the respirator reseats itself. If the respirator fails to reseat, subsequent test exercises will show excessive leakage, resulting in a failed test. Since even a properly fitting mask may show increased penetration during the grimace exercise, the penetration observed during the exercise is not to be used in calculating the overall fit factor. OSHA has revised Appendix E in the final rule to clarify this aspect of determining fit factors for respirator facepieces.

The preamble to the proposal contained a discussion of the need to perform a facepiece fit check prior to entry into a BD exposed work area. (55 FR 32736 at 32793) The purpose of performing such a negative pressure or positive pressure fit check is to meet the objective of demonstrating that a proper facepiece seal is being obtained each time the respirator is donned. Appendix E, Section II contains descriptions of the recommended positive and negative fit check methods. This test can be either a positive pressure fit check, in which the exhalation valve is closed and the wearer exhales into the facepiece to produce a positive pressure, or a negative pressure fit check, in which the inlet is closed and the wearer inhales so that the facepiece collapses slightly. Not all tight fitting respirators can be fit checked by using one or the other of these methods, since the wearer must be able to block off either the inlet or exhalation valves. Where the fit cannot be checked using one of the above methods, the wearer shall use the fit check method recommended by the manufacturer of the respirator being used. Language has been added to the respirator fit testing section of the final BD standard at paragraph (h)(5)(iii) that contains this requirement.

I. Personal Protective Equipment

This paragraph, which in the proposed rule was included in the Respiratory Protection paragraph, has been separated into a separate paragraph to facilitate compliance. Paragraph (i)(6) (paragraph (g)(6) of the proposed rule) requires that personal protective equipment must be worn where appropriate to prevent eye contact and limit dermal exposure to liquefied BD and solutions containing BD. Furthermore, it must be provided by the employer at no cost to the employee and the employer shall ensure its use where appropriate. OSHA believes that this performance oriented approach affords employers the flexibility to provide in a given situation only the protective clothing and equipment necessary to protect employees without specifying the exact nature of protective equipment to be used. This paragraph is sufficiently performance-oriented to allow the employer adequate flexibility to provide only the personal protective equipment necessary to protect employees in each particular work operation from the BD exposure encountered. Therefore, compliance can be tailored to fit the hazards posed on a day-to-day basis.

OSHA further notes that the generic requirements for Personal Protective Equipment (PPE) (Part 1910, Subpart I) apply for BD except where a specific provisions of the BD standard would provide otherwise.

J. Emergency Situations

Under paragraph (b) of this section, OSHA defines an emergency situation to be any occurrence such as, but not limited to, equipment failure, rupture of containers, or failure of control equipment that may or does result in an uncontrolled significant release of BD.

Paragraph (j) requires that employers develop new written plans for emergency situations or modify an existing plan to contain applicable elements of 29 CFR 1910.38, Employee Emergency Plans and Fire Prevention Plans, and of 29 CFR 1910.120, Hazardous Waste Operations and Emergency Responses and how the cause of the emergency is to addressed.

Both the above-mentioned standards require written plans for emergency responses and set out their content and use; however, it is noted that paragraph (q)(1) of 1910.120 states the following:

> An emergency response plan shall be developed and implemented to handle anticipated emergencies prior to the commencement of emergency response operations. The plan shall be in writing and available for inspection and copying by employees, their representatives and OSHA personnel. Employers who will evacuate their employees from the danger area when an emergency occurs, and who do not permit any of their employees to assist in handling the emergency, are exempt from the requirements of this paragraph is they provide an emergency action plan in accordance with (29 CFR) 1910.38(a) of this part.

Thus, only one of the two standards, either 1910.38 or 1910.120, would likely apply in a single facility. OSHA believes that it is likely that smaller facilities will comply with the provisions of 29 CFR 1910.38, while employers whose facilities are large enough to have specific emergency response personnel available will comply with 29 CFR 1910.120.

OSHA recognizes that all sudden releases of BD do not constitute an emergency. For example, the accidental breaking of a sampling syringe containing a minute amount of BD would not normally constitute an emergency. On the other hand, failure of a valve on a reaction vessel, a flange, or a safety relief valve would likely constitute an emergency. OSHA believes that compliance with these requirements will ensure that affected employees are effectively protected during a BD emergency.

In the limited reopening of the BD record in March 1996, OSHA stated that it proposed to define ''Emergency'' as:

> * * * any occurrence such as, but not limited to, equipment failure, rupture of containers, or failure of control equipment that may or does result in an unexpected significant release of BD.

The agency said that it was considering limiting the emergency releases to those that are uncontrolled, so that the last phrase of the definition would read: ''* * * that may or does result in an uncontrolled significant release of BD.'' It then asked whether this addition adequately clarifies what situations OSHA considers to be emergencies, and whether the term ''significant release'' gives adequate guidance to employers as to how much BD must be released in order to constitute an emergency?

Some comment was received on this issue and it is discussed in the paragraph dealing with the definition of the term emergency situation in the definition section (b) of the Summary and Explanation.

OSHA has chosen to use the term uncontrolled occurrence because it is more descriptive and is consistent with the Hazard Communication Standard (29 CFR 1910.1200) and Hazardous Waste Operations and Emergency Response Standard (29 CFR 1920.120).

In the proposed rule, OSHA included provisions for respiratory use and for alerting employees during emergencies. These have been omitted from this section as redundant. Paragraph (j)(1)(iv) sets out the requirement for respirator use during emergencies. Paragraph (k)(4)(ii) sets out medical screening requirements for those exposed to significant releases of BD.

K. Medical Screening and Surveillance

Where appropriate, medical screening and surveillance programs are required by section 6(b)(7) of the OSH Act to be included in OSHA health standards to aid in determining whether the health of workers is adversely affected by exposure to toxic substances. The relationship between medical screening and medical surveillance was clarified in posthearing comments by Dr. William Halperin, NIOSH. (Ex. 90, p.4) According to Dr. Halperin:

> The term ''medical'' surveillance is often used to encompass two distinct activities: (1) Medical screening: the search for early disease and (2) medical surveillance: the ongoing collection, analysis and dissemination of health related information that can be applied to the promotion of health and the prevention of adverse health effects (Ex. 90, p. 4).

Paragraph (k) of this rule clarifies OSHA's intention to include both activities in a program to identify and prevent BD-related disease.[12]

Health hazards that have been shown to be associated with occupational exposure to BD include leukemia, non-Hodgkins lymphoma, and anemia. Additionally, adverse reproductive and developmental outcomes have been observed in toxicologic studies of male and female mice. The medical screening and surveillance program specified in paragraph (k) has the following goals:

1. To prevent occupational diseases related to BD exposure;
2. To detect and treat BD-related disease before a worker would routinely seek medical care; and
3. To provide information on the adequacy of the PELs for BD.

Although most of the medical screening and surveillance provisions remain the same as in the proposal, several changes have been made. These changes include:

(1) Physical examinations are required once every three years, rather than annually;

(2) An annual health questionnaire for workers exposed to BD has been added;

(3) An annual complete blood count including differential and platelet count (CBC) is required;

(4) Medical evaluation of employees required to wear respirators, including assessment of cardiopulmonary function, is no longer required in this rule, and employers are referred to 29 CFR 1910.134;

(5) Employees with past BD exposures that meet specific criteria must be offered continued participation in medical screening and surveillance programs;

(6) Activities pertaining to medical screening and medical surveillance have been more clearly delineated; and

(7) Responsibility for the program has been expanded to include other licensed health care professionals, as well as physicians.

[12] Nothing in this standards changes the meaning of the term ''medical surveillance'' as it has been used in previous standards, such as the asbestos standards, 29 CFR 1910.1001 and 1926.110.

Paragraph (k)(1) specifies the circumstances under which employers must provide medical screening and surveillance for employees exposed to BD. Under paragraph (k)(1)(i) this program must be offered to each employee with exposure to BD at concentrations at or above the action level on at least 30 days a year. Additionally, it must be made available to those employees who have or may have exposure to BD at or above the PELs on at least 10 days per year.

This provision remains the same as that contained in the proposed rule. An alternative set of criteria for employee coverage was suggested in the joint labor-management agreement submitted to OSHA by the USWA and the IISRP. (Exs. 118–12; 119) This agreement would have raised the threshold of employee exposure to BD concentrations at or above the action level for at least 60 days per year, and at or above the PELs for at least 30 days per year. OSHA's review of the record did not produce evidence of controversy for the trigger levels as originally proposed. In fact, Shell Oil Company provided written comments which stated in part,

> This is a reasonable definition of who should be covered, with a time factor (30 days a year) for exposures at or above the action level * * * and a shorter time factor (10 days a year) for exposures at or above the PEL * * * or STEL * * * (Ex. 32–27)

Additionally, designation of trigger levels for medical screening and surveillance at or above the action level for 30 days and at or above the PELs for 10 days per year is consistent with past OSHA policy. For example, in the rulemaking for occupational exposure to coke oven emissions OSHA determined that a specific time period is the most effective and administratively feasible method to adopt in order to exclude workers with very limited exposures, e.g., temporary assignments during vacation periods. (41 FR 46777) At the same time, OSHA was concerned that the selected time period be sufficiently inclusive, and chose a cut-off point of 30 days. (41 FR 46777) The rulemaking for occupational exposure to inorganic arsenic followed the same policy. (43 FR 19620) Subsequently, the health standard for occupational exposure to benzene and the proposed rule for methylene chloride used the 30/10 triggers for inclusion in the medical surveillance program. (29 CFR 1910.1028; 56 FR 57036)

This overall approach to employee selection for coverage by the medical screening and surveillance program is based, in part, on the theory that cancers

associated with BD exposure are likely to be dose-related. Thus, employees exposed for only a few days a year may be at lower risk of developing BD-related disease. This approach allows employers to concentrate valuable medical screening and surveillance resources on higher risk employees.

Another change in the coverage of the medical screening and surveillance program is the elimination of coverage based only on required respirator use. The proposal specified that each employee whose exposure to BD requires the use of a respirator, regardless of the duration of exposure, be covered by the program. In the final rule, employees using respirators will be part of the medical screening program if they are over the action level or PELs for the amount of time stated in the medical screening provisions (on least 30 or more days for the action level and on 10 or more days for the PELs). This change is consistent with the recommendations contained in the labor-management agreement, and with OSHA's intention to clearly delineate medical screening requirements for employees with chemical specific exposures and those who must wear respirators, irrespective of the specific hazard. (Ex. 118–12; 29 CFR 1910.134) OSHA believes that the medical screening requirements for respirator users must be consistent with the provisions contained in 29 CFR 1910.134. Support for this approach was received from several industry representatives. (Exs. 118–11; 118–13; 118–14)

The proposed rule also included a provision for medical evaluation of cardiopulmonary function for all employees whose exposures require them to use respirators. This evaluation was supported by Dr. Philip Landrigan of the Mount Sinai Medical Center. He stated that,

> * * * the cardiorespiratory testing for people that are going to be wearing respirators is very much indicated, that wearing a respirator increases the work of breathing. It is important to know that a person has sufficient cardiorespiratory capacity to be able safely and healthfully to be able to work with the respirator on. (Tr.1/15/91, p. 200)

However OSHA received several comments, including ones from Shell, CMA, and Dr. James A. Saunders, that disagreed with this provision. (Exs. 32–27; 112; Tr. 1/18/91, p. 1213–1214) According to CMA,

> All employees who wear respirators should not receive an evaluation of cardiopulmonary function. As in the benzene standard, a pulmonary function test should be performed every three years on employees who wear respirators for at least 30 days per year. The cardiopulmonary function of these employees should also be evaluated but no specific test should be required except as directed by the examining physician. (Ex. 112, pp. 127–128)

The testimony of Dr. Saunders, who testified on behalf of the CMA BD panel, supported the CMA position on this issue. (Tr. 1/18/91, pp. 1213–1214) Shell offered the following opinion,

> This is *not* a reasonable definition of who should be evaluated. * * * To promulgate slightly different requirements for respirator user evaluation in different individual chemical exposure standards only creates confusion and nonuniformity. OSHA needs to finalize a respirator standard rather than putting different details in each standard. * * * (Ex. 32–27, attachment II, p. 3)

In the final rule, OSHA has clarified its position on medical screening and surveillance for employees whose exposure to BD requires them to use a respirator. Determinations regarding an employee's physical ability to perform the work and use the equipment should be made pursuant to 29 CFR 1910.134. Accordingly, paragraph (k)(4)(iii) has been added to refer employers to the standard on respiratory protection, and the requirement for evaluation of cardiopulmonary function has been deleted from this standard. Comments that support these changes have also been received from labor and industry representatives in response to the limited reopening of the rulemaking record. (Exs. 118–11; 118–13; 118–14; 118–16)

The concept for paragraph (k)(1)(ii) was recommended in the labor-management agreement submitted to OSHA by the USWA and the IISRP. It requires that employers continue medical screening and surveillance for employees after they have transferred to a job without potential exposure to BD when their work histories meet specified criteria. (Ex. 118–12) These criteria are: (1) Exposure at or above the 8-hour TWA limit or STEL on 30 or more days a year for 10 or more years; (2) exposure at or above the Action level on 60 days a year for 10 or more years; or (3) exposure above 10 ppm for 30 days in any past year. (Ex. 118–12) This would also include employees who transfer to low exposure BD jobs, provided that their work histories meet the specified criteria. OSHA welcomes this new provision to the final rule because of the additional protection it affords to workers with a history of occupational exposure to BD. The relatively short latency periods associated with BD-related diseases, which range from 4–9 years to 15–20 years, provide supporting rationale for this provision.

Objections to this provision were made by Texas Petrochemicals Corporation and Hampshire Chemical Corporation on the grounds of unreliable past exposure measurements and recordkeeping. (Exs. 118–6; 118–8) The Air Transport Association objected to this provision on the grounds that including ''employees whose past exposure was over a period of 10 years seems extreme.'' (Ex. 118–18B) Instead, they suggested a ''period of 5 or 3 years'' as a selection criterion. In response to these concerns, OSHA believes that the epidemiologic evidence suggests that these workers may be at increased risk of BD-related disease. This provision narrows the coverage of previously exposed workers to those with the greatest risk. It is OSHA's opinion that this approach errs on the side of caution for this group of workers. Support for this requirement, together with the provisions of paragraph (k)(1)(i), was offered by CMA in their statement that, ''this eligibility standard is appropriate for the medical surveillance program and will effectively protect employees most at risk.'' (Ex. 118–13) OSHA is of the opinion that, when taken in conjunction with the entire labor-management agreement, the requirement to include employees with historical BD exposure will be protective for high risk employees and provide valuable data for the medical surveillance portion of this section, paragraph (k)(8)(i).

Paragraph (k)(1)(iii) requires that coverage in the medical screening and surveillance program must be extended to each employee exposed to BD following an emergency situation regardless of the airborne concentrations of BD normally present in the workplace. Where very large amounts of BD are maintained in a sealed system, routine exposure may be essentially zero. However, system failure might result in catastrophic exposures. Thus, employers who have identified operations where there is potential for an emergency involving BD must take the necessary action to implement an emergency plan, as required in 29 CFR 1910.38. Additionally, employers must ensure that emergency medical care is available to exposed employees, and that such care is rendered by physicians or other licensed health care professionals with knowledge of the acute and chronic toxicity of BD.

Paragraph (k)(2) addresses program administration. Specifically, this provision requires that the medical screening and surveillance program be provided without cost to the employee, without loss of pay, and at a reasonable time and place. It is OSHA's opinion

that this provision is necessary to encourage employee participation. This same requirement was contained in the proposal. Furthermore, it is consistent with other OSHA health standards as well as with provisions contained in the OSH Act.

Additionally, paragraph (k)(2)(ii) requires that all physical examinations, medical procedures, and health questionnaires be administered by a ''physician or other licensed health care professional,'' defined as an individual whose legally permitted scope of practice (i.e., license, registration, or certification) allows him or her to independently provide or be delegated the responsibility to provide some or all of the health care services required by paragraph (k) of this section. The proposal required that all medical procedures be performed by or under the supervision of a licensed physician.

However, OSHA has long been considering the issue of whether and how to specify the particular professionals who are to perform medical surveillance in all of its standards. The Agency has determined that other professionals who are licensed under state laws to provide medical screening and surveillance services would also be appropriate providers of such services for the purposes of the BD standard. The Agency recognizes that the personnel able to provide the required medical screening and surveillance may vary from state-to-state depending on the state's licensing laws. Under the final rule, an employer, after becoming familiar with state laws delineating scope of practice for various licensed health care professionals, has the flexibility to retain the services of a range of qualified licensed health care professionals, thus potentially reducing cost and inconvenience for employers, and easing compliance burdens.

In the future, OSHA may attempt, with the cooperation of interested stakeholders, to specify which health care professionals are the most appropriate to perform each of a variety of diagnostic, therapeutic, medical management and other services. The more generic approach contained in this standard does, however, signal OSHA's belief that employees should have access to, and that employers should retain, when feasible, those professionals with the greatest level of expertise in discriminating between medical problems associated with occupational or environmental exposures and those associated with organic conditions unrelated to exposure. While the limited numbers of occupational physicians and occupational health nurses available to perform these services is increasing, such expertise does not necessarily correlate with any particular credential.

The final program administration requirement, paragraph (k)(2)(iii), is for all laboratory tests to be conducted by an accredited laboratory. This provision is consistent with other health standards, including benzene (29 CFR 1910.1028), bloodborne pathogens (29 CFR 1910. 1030), and lead (29 CFR 1910.1025). Furthermore, OSHA believes that this requirement is a necessary element for quality control in the medical screening and surveillance program.

The required frequency of medical screening activities is shown in paragraph (k)(3). For each employee covered under paragraphs (k)(1)(i)-(ii), a health questionnaire and CBC are required every year. Additionally, physical examinations must be provided at specified intervals: (1) An initial physical examination if twelve months or more have elapsed since the last physical examination conducted as part of a medical screening program for BD exposure; (2) a preplacement examination before assumption of duties by the employee in a job with BD exposure; (3) every three years after the initial or preplacement physical examination; (4) at the discretion of the physician or other licensed health care professional; (5) a termination of exposure examination at the time of employee reassignment to an area where exposure to BD is below the Action level, if the employee's past exposure history does not meet the criteria of paragraph (k)(1)(ii) for continued participation in the program, and if twelve months or more have elapsed since the last physical examination; and (6) at termination of employment, if twelve months or more have elapsed since the last physical examination.

There are several differences between the proposed and final rules regarding the type and frequency of medical screening activities. First, the initial physical examination provided under this section must be provided only ''if twelve months or more have elapsed since the last physical examination conducted as part of a medical screening program for BD exposure.'' This addition to the proposal language was made to prevent unnecessary extra physical examinations when the medical screening and surveillance portion of the final rule becomes effective. It is OSHA's opinion that, if an employee has received a physical examination as part of a medical screening program for BD within the past year, a repeated physical examination conducted just to coincide with the promulgation of this rule would be unnecessary and costly to the employer and burdensome for the employee. However, evaluation of the data for the entire group of BD exposed workers would still need to be done to comply with the surveillance portion of this paragraph.

Second, the requirement for preplacement evaluations has been changed from ''before the time of initial assignment of the employee'' to ''before assumption of duties by the employee.'' This change reflects comments received from Shell, which stated,

> * * * before the time of initial assignment of the employee is not effective. OSHA should make clear that what is meant is at the time of initial assignment or transfer into a job meeting the entry criteria, and preferable before assumption of duties in such an assignment. (Ex. 32–27, attachment II, p. 4)

OSHA agrees that this wording more clearly reflects the intention behind this requirement for preplacement examinations. Such examinations are intended to evaluate an employee's ability to work in a safe and healthful manner in a specific work environment. Additionally, they establish a baseline of information against which future health status changes can be compared.

Third, the frequency of physical examinations has been changed from once a year to every three years following the initial or preplacement examination. Several comments were received that addressed the frequency of these examinations. For example, CMA offered the opinion that, ''requiring a complete physical examination each year is unreasonable and excessively burdensome.'' (Ex. 112, p. 131) Dr. Saunders, testifying on behalf of the CMA BD panel, also objected to annual physical examinations, stating that they are ''unreasonable and wasteful of limited medical resources.'' (Tr. 1/18/91, p. 1210) OSHA agrees that an annual physical examination is not the most effective medical screening activity to detect BD-related disease, and thus has changed this requirement. However, OSHA does not agree with CMA that physical examinations should only be provided ''where warranted by symptoms of adverse health effects that might be related to butadiene exposure.'' (Ex. 112, p. 127) Such an approach would ignore principles of medical screening and surveillance, i.e., early identification of disease before medical care would routinely be sought. Most recently, support has been expressed by both labor and industry representatives for this frequency schedule. (Exs. 118–12; 118–13)

Fourth, under the final rule employees covered by the medical screening and surveillance program must be offered an annual health questionnaire and a CBC. It is OSHA's opinion that these medical evaluation activities will be effective in detecting signs and symptoms of BD-related disease that occur in the interval between physical examinations. Furthermore, they allow for greater efficiency of medical resource utilization. Support for this approach to medical screening has been shown in the labor-management agreement submitted to OSHA. (Ex. 118–12; 118–13)

Fifth, to allow for the application of professional judgement in the care of employees exposed to BD, physical examinations are to be provided at the discretion of the physician or other licensed health care professional reviewing the annual health questionnaire and blood test results. This provision not only creates a mechanism for immediate response to abnormal questionnaire responses or laboratory results, but provides flexibility by eliminating the requirement for unnecessary physical examinations and requiring physical examinations when they are indicated.

The sixth difference between the NPRM and the final rule pertaining to the frequency of physical examinations concerns those that occur at termination of employment or at the time of employee reassignment to an area where exposure to BD is below the action level, if the employee has not been exposed over the action level or the PELs for the requisite period of time and if twelve months or more have elapsed since the last physical examination. The NPRM required a termination physical examination ''if three months or more have elapsed since (the) last annual medical examination.'' The final rule extends this time interval to a lapse of one year or more.

The frequency of medical evaluations for employees exposed to BD following an emergency situation is specified in paragraph (k)(3)(ii). Medical screening in this situation is required to be conducted as quickly as possible, but no later than 48 hours after the event. This requirement is supported in part by the labor-management agreement that recommended these medical evaluations to ''be performed as quickly as possible.'' (Ex. 118–12, p.16) OSHA has added the stipulation ''but not later than 48 hours after the exposure'' to ensure that a baseline CBC is obtained within that time period. An accurate CBC baseline reading is vital for comparison with subsequent CBC values in order to detect significant deviations from normal.

Finally, paragraph (k)(3)(iii) addresses medical evaluations for employees who must wear a respirator by referring employers to 29 CFR 1910.134. This change from the NPRM is consistent with comments received from Shell,

> * * * Respirator user medical evaluation should have some uniformity, regardless of the exposure. To promulgate slightly different requirements for respirator user evaluation in different individual chemical exposure standards only creates confusion and nonuniformity. OSHA needs to finalize a respirator standard rather than putting different details in each standard. * * * (Ex. 32–27, attachment II, p. 3)

This approach further clarifies OSHA's intention to distinguish between health-related issues of employees who wear respirators and those who are exposed to BD. Support for the separation of these issues was provided by both labor and industry representatives. (Ex. 118–12; 118–13; 118–11; 118–14; 119)

Paragraph (k)(4) covers the required content of medical screening. One of the required components is a comprehensive occupational and health history that is updated annually. This history must place particular emphasis on the hematopoietic and reticuloendothelial systems, including exposure to chemicals, in addition to BD, that may have an adverse effect on these systems, the presence of signs and symptoms that might be related to disorders of these systems, and any other information determined by the physician or other licensed health care professional to be necessary. OSHA has restated the intended focus of the occupational and health history to more clearly reflect current knowledge of BD epidemiology. While OSHA is not specifying the format of the questionnaire, samples provided in Appendix F indicate the minimum information that must be obtained through the use of any questionnaire to comply with the requirements of this paragraph.

A complete occupational and health history is one part of a thorough medical evaluation. More specifically, however, for workers who are exposed to BD this history has several focused goals. First, the initial history may identify workers who are potentially at increased risk of adverse health effects from exposure to BD. For example, as suggested by Dr. William Halperin of NIOSH on cross examination, ''[i]t may be reasonable to advise workers with a previous history of leukemia or lymphoma to avoid exposure to [BD] * * *'' (Tr. 1/17/91, p. 705) Personal risk factors, such as existing hematologic abnormalities, that also place a worker at increased risk of BD-related disease, may also be identified through the health history. Additionally, predisposition to lymphomas is associated with immune deficiency syndromes.

Second, the initial and updated occupational and health history will have a training effect on workers by educating them about the potential adverse health effects from exposure to BD. Over time OSHA believes that informed workers will be more likely to seek medial attention for signs and symptoms that may be associated with BD exposure. Third, the initial history will provide a critical baseline of health status against which any changes can be compared. Finally, the health questionnaire might also suggest to the physician or other licensed health care professional additional medical tests or procedures that would be prudent to offer to the employee.

Another required component of medical screening for BD is a complete physical examination, with special emphasis on the spleen, liver, lymph nodes and skin. The physical examination for BD exposed employees provides an opportunity for direct observation and palpation of target organs such as the lymph nodes, liver, and spleen. Specifically, the physician or other licensed health care professional would be looking for signs of lymphadenopathy (enlarged lymph nodes), splenomegaly (enlarged spleen), or hepatomegaly (enlarged liver). Although lymphadenopathy is not specific for either lymphoma or leukemia, the physical examination provides an opportunity to detect this finding before symptoms develop. This rationale was rejected by Dr. Saunders in his testimony. (Tr. 1/18/91, p. 1211–1212) However, according to Dr. Halperin of NIOSH, ''[s]ome individuals may benefit by receiving treatment at this earlier point in the course of their disease.'' (Ex. 90, p. 5) Dr. Dennis D. Weisenburger, an expert witness for OSHA, also offered testimony that supported this basis for periodic physical examination of BD exposed employees. (Tr. 1/16/91, pp. 275–276)

The final required medical screening activity is a complete blood count (CBC). A CBC consists of a white blood cell (WBC) count, hematocrit, hemoglobin, differential WBC count, platelet count, red blood cell (RBC) count, and WBC and RBC morphology. (Ex. 23–55) It is an important component of the medical screening program because acute leukemia may, in some cases, be diagnosed with the aid of a CBC prior to the onset of symptoms. Additionally, the CBC is an effective test

for the detection of anemia, which may result from BD exposure. (Tr. 1/17/91, p. 784)

Animal evidence suggests that BD affects the bone marrow, resulting in anemia. In mice, inhalation of BD at 1,250 ppm resulted in a decrease in circulating erythrocytes, total hemoglobin and hematocrit, an increase in mean corpuscular volume, and leukopenia (a decrease in the WBC count), due mainly to a decrease in segmented neutrophils. (Ex. 23–12) These findings are consistent with a diagnosis of macrocytic megaloblastic anemia, suggesting that a CBC with a leukocyte count might yield information on overexposure to BD.

Additionally, changes in hemoglobin level, thrombocyte (platelet) count, and leukocyte count occur in the presence of leukemia. However, the detection of leukemia at a pre-clinical phase, i.e., prior to onset of symptoms, may not lead to improved treatment outcomes. The value of early disease detection, in this case, is that it provides an opportunity to terminate further potential exposure to BD. An employee who already has hematologic abnormalities due to leukemia should avoid exposure to BD and any other chemicals that could accelerate or worsen cytopenias and blood cell dysfunction.

Abnormality in blood counts is found in only 37 percent of patients with bone marrow infiltration. The correlation between peripheral blood counts and marrow involvement by lymphoma is poor. However, examination of the peripheral smear in patients with non-Hodgkins lymphoma may yield evidence of malignant cells in about 15 percent of patients. (Ex. 23–52, p. 1,357)

A CBC would also be a valuable screening tool for disorders other than leukemia and lymphoma. According to testimony offered by OSHA's expert witness Dr. Dennis D. Weisenburger,

> * * * the occurrence of other diseases of the blood and blood forming organs should also be critically examined in workers with BD exposure, particularly blood cytopenias, bone marrow failure, aplastic anemia, and the myelodysplastic (pre-leukemic) syndromes, which have also been associated with other chemical agents. (Ex. 39, p. 11)

Because the latency period for development of lymphohematopoietic disorders and cancers is relatively short, e.g., death from leukemia may occur in as little as 3–4 years after initial exposure, a CBC performed annually is reasonable and prudent. (Ex. 39, p. 9)

The combination of an annual CBC and a physical examination every three years balances both the need to diagnose leukemias (CBC) and lymphomas (physical examination) at an early stage, and the limited number of cases likely to be identified through the screening program. OSHA believes that waiting for sentinel cases to be identified would place other employees at risk of chronic BD-related illnesses, such as leukemias and lymphomas. The more quickly such illnesses are recognized, the sooner workplace modifications may be instituted to protect the health of other employees. An annual CBC, in addition to a health questionnaire, is an efficient means of using medical screening resources to detect early leukemia or anemia in individuals, while simultaneously providing data that can be used to protect the whole population of exposed employees. A medical screening strategy that includes an annual CBC and health questionnaire with physical examinations provided every three years has received support from both labor and industry representatives. (Exs. 118–12; 118–13)

To allow for individual differences among covered employees, as well as professional judgement, provision is made for inclusion of any other test which the examining physician or other licensed health care professional deems necessary. This requirement is provided to ensure that adequate flexibility is incorporated into the standard, so that any occupational diseases due to BD exposure are adequately diagnosed and treated. Furthermore, this provision is consistent with previously promulgated health standards.

Medical screening requirements for employees exposed to BD in an emergency situation focus on the acute effects of BD exposure. These effects include: Irritation of the eyes, nose, throat, lungs, or skin; blurred vision; coughing; drowsiness; nausea; and headache. At a minimum, the required medical screening components include: A CBC within 48 hours of the exposure and then monthly for three months; and a physical examination if the employee reports symptoms related to any of the acute effects. Employee participation in the medical screening and surveillance program, subsequent to a BD exposure from an emergency situation, need not continue for the duration of employment. This limitation on employee inclusion after emergency exposure is supported in comments received from Shell. (Ex. 32–27, Att. II, pp. 3–4) However, to accommodate management of individual cases, continued employee participation in the medical screening and surveillance program, beyond the minimum requirements, is left to the discretion of the physician or other health care professional.

Additionally, the time frame for the collection of the blood specimen has been extended from immediately after the emergency to ''within 48 hours of the exposure and then monthly for three months.'' Again, support for this approach was provided by Shell,

> ''Immediately'' after every emergency may not be possible or even reasonable. We suggest ''as soon as possible'' after a *significant exposure* from an emergency event and at least within 48 hours. * * * (Ex. 32–27, attachment II, p.4)

Further support for this medical screening strategy following an emergency situation was provided by Dr. William Halperin, NIOSH,

> The life span of a red blood cell is approximately 120 days. Thus, the results of a medical examination shortly after a high exposure may be normal despite severely compromised blood-producing capacity. If an exposure is high enough to warrant a medical examination, then it would be reasonable to obtain a baseline hematologic examination at the time of exposure, followed by reexaminations at 30, 60, and 90 days. (Ex. 90)

A physical examination is required only if the employee reports symptoms related to the acute effects after exposure to BD in an emergency situation. Comments submitted by Shell support the idea that not every exposure in an emergency situation necessitates a physical examination. (Ex. 32–27, attachment II, p. 4) It is OSHA's opinion that this approach provides flexibility, as suggested by Dr. Saunders. (Tr. 1/18/91, p. 1214–1213) Contrary to the suggestion by CMA, it does not leave the need and frequency for medical examinations following an emergency situation completely to the judgement of the physician. (Ex. 112, p. 128) Thus, OSHA believes the final rule adopts a moderate, yet protective, approach for medical evaluation requirements for employees exposed to BD in an emergency situation.

Paragraph (k)(5) addresses additional medical evaluations and referrals. Whenever the results of medical screening indicate abnormalities of the hematopoietic or reticuloendothelial systems, for which a non-occupational cause is not readily apparent to the health care professional, the employee shall be referred to an appropriate specialist, e.g., hematologist, for further evaluation. The content of the evaluation is left to the professional judgement of the specialist to whom the employee is referred. This provision is essential to ensure that employees receive prompt diagnosis at the earliest stage possible, when treatment is most likely to be effective.

In the NPRM, the paragraph on additional examinations and referrals contained a provision for the content of the medical examinations or consultations to include, ''evaluation of fertility and other tests, if requested by the employee and deemed appropriate by the physician.'' (55 FR 32736 at 32806) After evaluation of all factors presented in the rulemaking, the Agency has deleted the provision for fertility testing from the final rule. However, given the observations in experimental animals, the medical screening and surveillance program provided by the employer should address the potential reproductive and developmental problems of workers exposed to BD. (The reader is referred to the Health Effects section of this preamble.) The sample health questionnaires provided in Appendix F include examples of questions that address reproductive and developmental health concerns.

Information that the employer must provide to the examining physician or other licensed health care provider is listed in paragraph (k)(6). Specifically, that information includes: (1) A copy of the BD standard; (2) a description of the employee's duties as they relate to BD exposure; (3) the employee's actual or representative BD exposure level; (4) a description of required pertinent personal protective equipment; and (5) information from previous employment-related medical evaluations which the physician or other licensed health care professional may not otherwise have available. The purpose of this requirement is to provide information necessary for the physician or other licensed health care professional to make an informed determination regarding whether the employee may be at increased risk from exposure to BD.

Paragraph (k)(7) requires employers to ensure that the physician or other licensed health care professional produces a written opinion of the evaluation results and provides a copy to the employer and employee within 15 business days of the medical evaluation. OSHA rejected Shell's suggestion of extending the time frame for provision of the written opinion to the employee from 15 to 30 days. (Ex. 32–27) In OSHA's opinion 30 days is too long to wait to inform employees of the results of the medical evaluation. However, OSHA agrees with the recommendation made in the labor-management agreement to specify ''business days.'' (Ex. 118–12, p.18) It is OSHA's opinion that this recommendation does not adversely impact the health of employees in the medical screening and surveillance program and, yet, it provides a more practical time frame for the communication of this information.

The written opinion must contain the results of the medical evaluation that are pertinent to BD exposure, an opinion concerning whether the employee has any detected medical conditions which would place the employee's health at increased risk of material impairment from exposure to BD, and any recommended limitations on the employee's exposure to BD. This opinion must be developed with consideration given to a comparison of all available medical evaluation results for occupational exposure to BD. OSHA recommends that the physician or other licensed health care professional use a flow sheet to chart temporal changes in the CBC. The occurrence of temporal changes in the CBC indices, even if the actual results remain within normal limits, should be considered when evaluating risk of material impairment to health, as well as the overall medical opinion.

Additionally, the written opinion must include a statement that the employee has been informed of the medical evaluation results and any conditions resulting from BD exposure that require further explanation or treatment. This written opinion shall not contain any information that is not related to the employee's ability to work with BD. In rendering this opinion, the physician or other licensed health care professional must rely on the results obtained from the medical evaluation. This provision does not negate the ethical obligation of the physician or other health care professional to transmit any other adverse findings directly to the employee.

Medical surveillance requirements are specified in paragraph (k)(8). This provision requires the employer to ensure periodic review of information obtained from the medical screening program activities to determine whether the health of the employee population of that employer is adversely affected by exposure to BD. This requirement is meant to clarify OSHA's longstanding policy that individual data collected during medical screening activities should be examined in the aggregate, with personal identifiers removed, so that population trends or patterns can be observed and appropriately managed. This medical surveillance provision does not require employers to conduct epidemiologic or any other type of research studies, although such studies are certainly not precluded.

It is OSHA's opinion that this information review will provide employers with supplemental evidence of the effectiveness of their exposure control strategies. The employer's obligations regarding medical surveillance may be limited to a determination that all medical evaluation results are within normal limits and temporal changes in these results have not occurred. However, should a pattern of abnormal findings be identified, the employer may have an opportunity for primary prevention of BD-related disease. Information learned from medical surveillance activities must be disseminated to employees covered by the medical screening and surveillance program provision, as defined in paragraph (k)(1).

L. Hazard Communication

The requirements for hazard communication have been moved from proposed paragraph (j), redesignated and promulgated as paragraph (l) of the final rule. The paragraph addressing hazard communication in the final BD rule is consistent with the requirements of OSHA's Hazard Communication Standard (HCS). The HCS requires all employers to provide information concerning the hazards of workplace chemicals to their employees. The transmittal of hazard information to employees is to be accomplished by such means as container labeling and other forms of warning, material safety data sheets, and employee training.

Signs and Labels

Since the HCS is ''intended to address comprehensively the issue of evaluating the potential hazard of chemicals and communicating information concerning hazards and appropriate protective measures to employees,'' OSHA is including paragraph (l)(1) only to reference HCS requirements for labels and material safety data sheets. Employers who have already met their longstanding requirements to comply with the HCS will have no additional duties with regard to labels and MSDSs under the BD rule.

The warning sign and labels for BD which OSHA proposed in 1990 have been deleted from the final rule in response to the recommendation of various commenters, including the labor/industry group, who suggested that no requirements were needed beyond those already listed in the HCS. (Tr. 1/18/91, p. 1169; Tr. 1/22/91, pp. 1348–1249; Ex. 112, 32–17, 32–19, 32–22, 32–27, 108, 118–12A) Therefore, the final rule now references the HCS.

Employee Information and Training

OSHA is also referencing the HCS for employee information and training, but is specifying additional provisions applicable when employee exposures

are likely to exceed the action level or STEL. Paragraph (l)(2) reiterates that training must be afforded employees in accordance with the HCS and contains various provisions which apply when exposure limits are exceeded. The first of these is the requirement that a training program be instituted and that employee participation in it be assured by the employer (paragraph (l)(2)(i)).

OSHA believes that training is not a passive process. The information provided employees in training requires their comprehension of the material and subsequent use of what they have learned while performing their duties in the workplace. There are many different ways to accomplish training effectively, but it cannot be a mechanical transfer of information such as giving someone a written document. OSHA's voluntary guidelines, which are found in OSHA publication No. 2252, are available to provide employers with additional guidance in setting up and implementing an appropriate employee training program. An effective training program is a critical component of any safety and health program in the workplace. Workers who are fully informed and engaged in the protective measures established by the employer will play a significant role in the prevention of adverse health effects. Ineffective training will not serve the purpose of making workers full participants in the program, and the likelihood of a successful program for safety and health in the absence of an effectively-trained workforce is remote.

OSHA expects that employers will ensure that the information and training is effective. Although not specifically required in the standard, any good training program should include an evaluation component to help ensure effectiveness. The voluntary training guidelines previously recommended can provide additional guidance in this respect.

Paragraph (l)(2)(ii) requires employers to provide the required information and training prior to or at the time of initial assignment to work with BD. This paragraph also requires that such training be repeated annually when employees are exposed over the action level or STEL ((l)(2)(iii)). OSHA notes that annual training for workers exposed above an action level is also required in other standards e.g., benzene (29 CFR 1910.1028), asbestos (29 CFR 1910.1001), cadmium (29 CFR 1910.1027), formaldehyde (29 CFR 1910.1048).

CMA requested that OSHA correct the final rule to require annual training only when the employee is assigned to a job where the potential exposure is above the action level or STEL. OSHA has included this provision in paragraph (l)(2)(iii). (Ex. 112, p. 116) OSHA notes, however that all employees potentially exposed to BD must receive training at least once as provided by the HCS. Those employees whose tasks place them at risk of higher exposure (above the action level or STEL) need training at least annually to review the nature of the hazards of BD exposure and the methods to be used to minimize exposure and to maintain a continuing awareness of the potential dangers associated with exposure.

In its submission, CMA also requested that OSHA specify in the final rule that where the BD standard does not apply because objective data are used to exempt a material or process from the standard, the hazard communication requirements would come from the HCS. (Ex. 112, p. 178) OSHA does not believe this is necessary and that it might lead to greater confusion. Clearly, exemption from the BD standard does not imply exemption from the HCS.

OSHA notes that materials containing less than 0.1% BD are exempt from the BD standard unless there is evidence which indicates that the action level or STEL can reasonably be expected to be exceeded during the job. On the other hand, the HCS contains no exemption from employee information and training provisions for materials containing less than 0.1% of a carcinogen (BD).

Paragraph (l)(2)(iv) indicates that employers must ensure that the information and training is presented in a manner that is understandable to employees, and lists topics which must be included in the training program.

The labor/industry agreement recommended deletion of the proposed requirement that: ''The training program shall be conducted in a manner that the employee is able to understand.'' (Ex. 118–12A) No explanation for this suggestion was offered in submissions to the record. OSHA believes that it is essential that training be understood by the employee. Thus, OSHA has not deleted the requirement from the standard.

Paragraph (l)(2)(iv) also addresses the items upon which employees are to be trained and includes training regarding specific measures employees can take to protect themselves from the effects of BD exposure. Paragraphs (l)(2)(iv)(A) through (F) set forth the basic topics to be covered during the requisite training program. CMA asked that OSHA delete most of this list of training topics. (Ex. 112, p. 177) CMA felt that the HCS provisions were adequate. However, the labor/industry group did not make a similar recommendation, and the final rule contains basic guidance to employers establishing an employee training program as to what subjects must be included. OSHA believes that these requirements build upon the HCS and provide BD-specific information needed by the employee to reduce exposure to BD, and therefore prevent adverse health effects from occurring.

Upon recommendation of the labor/industry group, OSHA has consolidated some of the training topics and made them more concise and clearer. (Ex. 118–12A) The labor/industry group recommended deletion of proposed paragraph (k)(4)(iii)(D), which stated that the training must cover

> The measure employees can take to protect themselves from exposure to BD, including a review of their habits, such as smoking and personal hygiene; and specific procedures the employer has implemented to protect employees from exposure to BD, such as appropriate work practices, emergency procedures, and personal protective equipment. (55 FR 32736 at 32807)

OSHA agrees that most of this material is to be covered under the other topics listed in the final rule, but has determined that the training must include information regarding what employees themselves can do to assist in protecting themselves from exposure to BD. Additionally, as recommended in the labor/industry agreement, reference to personal habits and hygiene has been deleted. (Ex. 118–12A) OSHA has concluded that there is little data regarding the relationship of personal habits to the hazards associated with BD exposure to justify the inclusion of this provision in the final rule. Therefore this subject is not included among those required in the training program.

Paragraph (l)(3)(i) requires the employer to give copies of the BD standard in its entirety, including all appendices, to employees. In response to the labor/industry group recommendation, OSHA has included in the provision that the standard must also be provided by the employer to persons designated as employee representative(s). (Ex. 118–12A) Further, the copy must be provided at no cost to the employee.

In paragraph (l)(3)(ii) OSHA has indicated that the Assistant Secretary or the Director may access all materials relating to employee information and training in the workplace. This would be done in conjunction with an inspection to ascertain compliance with the rule, or in the event of a NIOSH health hazard evaluation. Review of the available materials regarding information and training will help evaluate whether the program has been properly conducted, as well as ascertain

what could be improved if employees do not appear to be effectively trained. As in previous paragraph (l)(3)(i), and at the suggestion of the labor/industry group, designated employee representatives are to be provided all materials relating to information and training. (Ex. 118–12A) This will be useful to them in helping to assure that their members are benefitting from all the protection the BD standard affords.

The training provisions of this final rule are performance-oriented because employees may be exposed to BD in a variety of circumstances. Thus, the standard lists the topics of information to be transmitted to the employees, but does not specify the ways in which it is to be transmitted.

M. Recordkeeping

Section 8(c)(3) of the Act provides for the promulgation of ''regulations requiring employers to maintain accurate records of employee exposures to potentially toxic materials or harmful physical agents which are required to be monitored or measured under section 6.'' All employers with BD in their workplace must do initial monitoring or reasonably rely on objective data that show that workplace exposures to BD are at or below the action level. Paragraph (m)(1) of the final rule requires employers who are relying on objective data (under paragraph (d)(2)) to avoid the initial monitoring requirements of the final rule, to maintain records that show the basis for their reliance and the reasoning used in reaching the conclusion that such monitoring is not necessary.

The objective data must provide the same degree of assurance that employees are not being significantly exposed to butadiene as monitoring would. Thus, such data should include information about the materials, product, activity, or process tested and found to qualify for exemptions; the source (e.g., manufacturer, testing laboratory, research study) of the objective data; the protocol used to obtain the results; a description of the product(s), materials(s), activities, or processes to which the relied upon data applies and an explanation of why such data are worthy of being relied upon; and any other data the employer believes are relevant to the exemption. This documentation is intended to demonstrate the appropriateness of the employer's reliance on objective data in lieu of the initial monitoring of employee exposure to BD.

The Agency has made a determination that significant employee exposures to BD should be closely monitored. Therefore it is appropriate to require the employer to carefully document and keep records of the data that are being relied upon in lieu of actual monitoring.

At the suggestion of the labor/industry group and for consistency with other provisions of the standard, the word ''streams'' has been included in paragraph (m)(1), since it is part of the exemptions in paragraph (a)(2) of this section.[13] (Ex. 118–12A)

Paragraph (m)(1)(iii) requires the employer to keep records of the objective data relied upon for as long as the employer continues to rely on such data.

Paragraph (m)(2) requires that employers keep records of all exposure monitoring required by the final rule. The provisions in this paragraph are consistent with those of 29 CFR 1910.1020, OSHA's Access to Employee Exposure and Medical Records standard. Paragraph (m)(2) specifies what information related to employee exposure monitoring must be kept. For example, it requires retention of information on the sampling and analytical methods, as well as information about the employee(s) sampled and their use of protective equipment. At the recommendation of the labor/industry group, records must also be maintained on written corrective action to be taken when monitoring indicates exposures over the PEL. (Ex. 118–12A) In addition, OSHA has also included a requirement that the schedule for completing the corrective action also be maintained.

A new paragraph, (m)(3), has been added to the final rule, which requires that records of respirator fit tests be maintained by the employer until the next fit test is administered to the employee. In the proposal, this provision was included in the mandatory appendix for respirator fit testing. OSHA believes that it will be more convenient for those using the standard to have all recordkeeping provisions together in the standard. Therefore recordkeeping provisions from other parts of the standard are being moved to paragraph (m) of the final rule.

Paragraph (m)(4) requires that the employer keep accurate medical records for each employee subject to medical screening and surveillance under the standard. Section 8(c) of the Act authorizes the promulgation of regulations requiring an employer to keep necessary and appropriate records regarding activities to permit the enforcement of the Act or to develop information regarding the causes and prevention of occupational illnesses. OSHA has determined that, in this context, requiring employers to maintain both medical and exposure measurement records is necessary and appropriate, and paragraph (m)(3) simply details what information must be kept.

Paragraph (m)(5)(i) states that all records required to be maintained by the standard must be made available to the Assistant Secretary and Director of NIOSH for examination and copying if such records are requested in writing. Access to these records is necessary for compliance monitoring. These records also contain information that the agencies may need to carry out other statutory responsibilities.

Paragraph (m)(5)(ii) provides that employees, former employees, and their designated representatives have access upon request to all exposure and medical records required by the standard. This provision is consistent with 29 CFR 1910.1020 (e). Section 8(c)(3) and other provisions of the Act make clear that employees and their representatives are expected to have an active and meaningful role in workplace safety and health. Employees and their representatives need information about employee exposures to toxic substances and their potential effects on health and safety if they are to benefit fully from these statutorily created rights.

OSHA's generic rule (29 CFR 1910.1020) permitting access to employee exposure and medical records was issued on May 23, 1980. (45 FR 35212) This rule applies to records created pursuant to specific standards and to records that are voluntarily created by employers. OSHA retains unrestricted access to medical and exposure records, but the Agency's access to personally identifiable records is subject to the Agency's rules of practice and procedure concerning OSHA access to employee medical records, which are codified at 29 CFR 1913.10.

Paragraph (m)(6) of the final rule addresses transfer of records. Under paragraph (m)(6)(i), when an employer ceases to do business, the employer must transfer records required by this section to the successor employer, who shall receive and maintain such records. If there is no successor employer, the employer shall notify the Director of NIOSH at least three months prior to anticipated disposal of the records, and shall transmit the records to the Director, if so requested. Under paragraph (m)(6)(ii), the employer is required to transfer medical and exposure records in accordance with

[13] Paragraph (m)(1)(i) now reads in pertinent part: ''Where the processing, use, or handling of products *or streams* made from or containing BD * * *

requirements set forth in 29 CFR 1910.1020(h).

The Agency believes it is necessary to keep certain records for extended periods of time because of the long latency periods commonly observed for the induction of cancer caused by exposures to carcinogens. Cancer often is not detected until 20 or more years after onset of exposure. The extended record retention period required by 29 CFR 1910.1020 therefore is needed for two purposes. First, possession of past and present exposure data and medical records aids in the diagnosis of workers' disease and determination of work-relatedness. In addition, retaining records for extended periods make possible future review to determine the effectiveness and adequacy of OSHA's final rules.

The time periods required for retention of exposure records and medical records are thirty years and the period of employment plus thirty years, respectively. These retention requirements are consistent with those in the OSHA exposure and medical records access standard.

N. Dates

This paragraph establishes the effective date of the final rule for butadiene and sets out start-up dates for various provisions of the standard. The final rule becomes effective 90 days following publication in the Federal Register. This period enables employers to familiarize themselves with the final rule. In addition, individual provisions, where appropriate, have delayed start-up dates. In addition, the Agency has established delayed start-up dates for several provisions of the final rule, based on evidence submitted to the record demonstrating that compliance with some provisions may require longer times than compliance with other provisions. These dates are based on the record in this rulemaking and on the Agency's experience with other standards concerning the amount of time required for employers to perform initial employee monitoring, institute medical surveillance programs, implement emergency procedures, etc.

The effective date, in conjunction with the start-up dates, will allow sufficient time for employers to achieve compliance with the substantive requirements of the final rule.

Paragraph (n)(2)(i) requires that initial monitoring shall be completed within sixty days of the effective date of the standard or within 60 days of the introduction of BD into the workplace. In the proposed rule, this paragraph was designated as paragraph (d)(2)(ii); it has been moved to paragraph (n) in the final rule to consolidate all effective date information in one section.

Dow Chemical Company objected to the 60 day start-up date for initial monitoring as being inadequate to set up such a program. (Ex. 118–16) OSHA believes that 60 days after the effective date of the standard is sufficient time to carry out initial monitoring. OSHA believes that much of the required monitoring may have already been performed by employers.

Final rule paragraph (n)(2)(iii) requires that the feasible engineering controls required by paragraph (f)(1) be implemented within two years after the effective date of the standard. This represents an extension of 12 months beyond that proposed for engineering controls. In testimony, the CMA Panel Chair, Dr. Norman Morrow, said that it was necessary to extend the one year start-up date to two years because of the time needed to identify those areas needing control, to determine the appropriate control measure to use, and to procure and install the equipment. (Tr. 1/18/91, p. 1168)

Other submissions contained similar requests for extension of the period to comply with controls. (Ex. 28–32; 112) OSHA agrees that additional time may be needed to come into full compliance and thus the final rule permits a full 24 months for compliance with the engineering controls provision of the final rule. During the period in which employers are implementing these controls, additional respirator use may be required to comply with the new exposure limits.

Paragraph (n)(2)(iii) also has a start-up date of within three years of the effective date of the standard to implement the exposure goal program (paragraph (g)). This is the length of time agreed upon by the labor/industry group who developed the provisions for the exposure goal program and submitted them to OSHA. (Ex. 118–12A) OSHA believes that this will provide ample time for employers to install or otherwise comply with the provisions in the program.

Final rule paragraph (n)(2)(ii), which covers start-up dates for paragraphs (c) through (m), including those for feasible work practice controls but not for the engineering controls specified in the paragraph (f)(1), requires that employers attain compliance within 180 days of the effective date of the BD standard. This provision is identical to proposed paragraph (n)(2)(i).

The rest of the provisions of the standard must be implemented within 180 days of the effective date.

O. Appendices

Six appendices have been included at the end of this standard. Appendices A, B, C, D, and F are included primarily for purposes of information and compliance assistance and should not be construed as establishing a mandatory requirement not otherwise imposed by the standard, or as detracting from an obligation which the standard does impose. However, the protocols for respiratory fit testing in Appendix E are binding.

The appendices have been updated from the proposal to reflect the final rule. Additionally, a number of technical and typographical corrections have been made in them. Appendix A contains information briefly describing the properties of BD and its hazards, and describes in general terms the provisions of the standard. Further, it contains the procedures to be used during emergencies, fires, and other situations in which there is potential for BD exposure.

Appendix B describes more fully the chemical and physical properties of BD and gives procedures to use when leaks or spills occur. Correct disposal is also outlined. Additional information is given on ways to safely handle BD.

Appendix C provides medical screening and surveillance guidelines for BD. The appendix describes the effects of BD exposure on the body and gives an overview of the medical screening and surveillance provisions of the standard. In general terms, it provides the physician or other licensed healthcare professional with an outline of the requirements of the rule.

Appendix D contains the sampling method developed and validated by the OSHA laboratory for use with BD. This is a non-mandatory appendix—the use of other measurement methods is allowed when accuracy levels required in the standard are met. Paragraph (d)(6) states that monitoring shall be accurate, at a confidence level of 95 percent, to within plus or minus 25 percent for airborne concentrations of BD at or above the 1 ppm TWA limit and to within plus or minus 35 percent for airborne concentrations of BD at or above the action level of 0.5 ppm and below the 1 ppm TWA limit. In addition, paragraph (m)(2)(ii)(C) requires that the exposure measurement record include sampling and analytical methods used and evidence of their accuracy.

Supplementary data used by the OSHA laboratory in developing the analytical method were included in the proposal, but have been deleted from the final rule. (55 FR 32736 at 32814.)

Basically, the OSHA method is a charcoal tube (CT)-gas chromatography (GC)-mass spectrometry (MS) (CT–GC–MS) method. It involves the use of charcoal tubes and sampling pumps, followed by analysis of the samples by gas chromatography and a confirmation of GC peak by MS when it is necessary. The charcoal is coated with 4-tert-butylcatechol to inhibit the polymerization of BD, in order to increase the stability of the sample. (Ex. 118–9) Since BD often is present in a complex mixture which may make it difficult to adequately evaluate due to interferences, MS is used in GC–MS combination to identify the GC chemical peak and to make sure that there is no interferences and to identify any interferences that occur.

OSHA agrees with API that no single CT–GC–MS method can be used as a ''cookbook'' for all situations. (Ex. 118–11) The American Petroleum Institute (API) developed a method to ''resolve interferences for complex mixtures found in the petroleum industry'' in 1991 and refined the method in 1996. (Exs. 108 and 118–11) The API method uses a long length of capillary column with different configurations for a greater separation ability from other isomers/interferences found in the petroleum industry. API asked OSHA's acceptance of the API BD monitoring method. (Ex. 118–11) OSHA believes that the API method, as well as other methods which may be developed that accurately measure BD levels in the breathing zone of exposed workers, are acceptable.

Since many of the duties relating to employee exposure are dependent on the results of measurement procedures, employers must assure that the evaluation of employee exposure is performed by a technically qualified person.

Appendix E is the only mandatory appendix to the BD rule. This appendix has been revised somewhat from the proposal throughout, primarily for clarity. However, it now contains a protocol for using ambient aerosol condensation nuclei counter (CNC) quantitative fit testing, which was not included in the proposal.

Appendix F contains sample questionnaires for use in medical screening and surveillance. The appendix contains two sample questionnaires, one for the initial medical evaluation and the other for the annual updating of the medical evaluations. These are included to provide medical personnel information to assist them in complying with the standard.

Authority and Signature

This document was prepared under the direction of Joseph A. Dear, Assistant Secretary of Labor for Occupational Safety and Health, U.S. Department of Labor, 200 Constitution Avenue, N.W., Washington, D.C. 20210

Pursuant to sections 4, 6(b), 8(c) and 8(g) of the Occupational Safety and Health Action (29 U.S.C. 653, 655, 657), section 107 of the Contract Work Hours and Safety Standards Act (the Construction Safety Act) (40 U.S.C. 333); the Longshore and Harbor Workers' Compensation Act (33 U.S.C. 941); the Secretary of Labor's Order No. 1–90 (55 FR 9033); and 29 CFR part 1911; 29 CFR parts 1910, 1915 and 1926 are amended as set forth below.

List of Subjects in 29 CFR Parts 1910, 1915 and 1926

1,3–Butadiene, Cancer, Chemicals, Health risk-assessment, Occupational safety and health.

Signed at Washington, DC, this 24th day of October 1996.

Joseph A. Dear,

Assistant Secretary of Labor.

PART 1910—[AMENDED]

Part 1910 of Title 29 of the Code of Federal Regulations is hereby amended as follows:

Subpart B—[Amended]

1. The authority citation for subpart B of Part 1910 is revised to read as follows:

Authority: Secs. 4, 6 and 8 of the Occupational Safety and Health Act, 29 U.S.C. 653, 655; 657; Walsh-Healey Act, 41 U.S.C. 35 *et seq;* Service Contract Act of 1965, 41 U.S.C. 351 *et seq;* sec. 107, Contract Work Hours and Safety Standards Act (Construction Safety Act), 40 U.S.C. 333; sec. 41, Longshore and Harbor Workers' Compensation Act, 33 U.S.C. 941; National Foundation of Arts and Humanities Act, 20 U.S.C. 951 et seq.; Secretary of Labor's Order No. 12–71 (36 FR 8754); 8–76 (41 FR 25059); 9–83 (48 FR 35736) or 1–90 (55 FR 9033), as applicable; and 29 CFR part 1911.

2. A new paragraph (l) is added to § 1910.19 to read as follows:

§ 1910.19 Special provisions for air contaminants.

* * * * *

(l) 1,3-Butadiene (BD): Section 1910.1051 shall apply to the exposure of every employee to BD in every employment and place of employment covered by §§ 1910.12, 1910.13, 1910.14, 1910.15, or § 1910.16, in lieu of any different standard on exposure to BD which would otherwise be applicable by virtue of those sections.

Subpart Z—Toxic and Hazardous Substances—[Amended]

3. The authority citation for subpart Z of part 1910 continues to read as follows:

Authority: Secs. 4, 6, and 8 of the Occupational Safety and Health Act of 1970 (29 U.S.C. 653, 655, and 657); Secretary of Labor's Order No. 12–71 (36 FR 8754), 8–76 (41 FR 25059), 9–83 (48 FR 35736), of 1–90 (55 FR 9033) as applicable; and 29 CFR part 1911.

Section 1910.1000, Tables Z–1, Z–2, and Z–3 also issued under 5 U.S.C. 553. Section 1910.1000, Tables Z–1, Z–2, and Z–3 not issued under 29 CFR Part 1911 except for the arsenic (organic compounds), benzene, cotton dust, and 1,3-butadiene listings.

Section 1910.1001 also issued under section 107 of the Contract Work Hours and Safety Standards Act (40 U.S.C. 333) and 5 U.S.C. 553.

Section 1910.1002 not issued under 29 U.S.C. 655 or 29 CFR 1911; also issued under 5 U.S.C. 553.

Section 1910.1200 also issued under 5 U.S.C. 553.

§ 1910.1000 [Amended]

4. The entry in Table Z–1 of § 1910.1000, ''Butadiene (1,3-Butadiene)'' is amended as follows: remove the ''1000'' and ''2200'' from the columns entitled ppm(a)[1] and mg/m^3 (b)[1] respectively, add ''1 ppm/5 ppm STEL'' in the ppm (a)[1] column; and add the following to the butadiene entry ''; See 29 CFR 1910.1051; 29 CFR 1910.19(l)'' so that the entry reads as follows: ''Butadiene (1,3-Butadiene); See 29 CFR 1910.1051; 29 CFR 1910.19(l).''

5. A new 1910.1051 is added to read as follows:

§ 1910.1051 1,3-Butadiene.

(a) *Scope and application.* (1) This section applies to all occupational exposures to 1,3-Butadiene (BD), Chemical Abstracts Service Registry No. 106–99–0, except as provided in paragraph (a)(2) of this section.

(2)(i) Except for the recordkeeping provisions in paragraph (m)(1) of this section, this section does not apply to the processing, use, or handling of products containing BD or to other work operations and streams in which BD is present where objective data are reasonably relied upon that demonstrate the work operation or the product or the group of products or operations to which it belongs may not reasonably be foreseen to release BD in airborne concentrations at or above the action level or in excess of the STEL under the expected conditions of processing, use, or handling that will cause the greatest possible release or in any plausible accident.

(ii) This section also does not apply to work operations, products or streams where the only exposure to BD is from liquid mixtures containing 0.1% or less of BD by volume or the vapors released from such liquids, unless objective data become available that show that airborne concentrations generated by such mixtures can exceed the action level or STEL under reasonably predictable conditions of processing, use or handling that will cause the greatest possible release.

(iii) Except for labeling requirements and requirements for emergency response, this section does not apply to the storage, transportation, distribution or sale of BD or liquid mixtures in intact containers or in transportation pipelines sealed in such a manner as to fully contain BD vapors or liquid.

(3) Where products or processes containing BD are exempted under paragraph (a)(2) of this section, the employer shall maintain records of the objective data supporting that exemption and the basis for the employer's reliance on the data, as provided in paragraph (m)(1) of this section.

(b) *Definitions:* For the purpose of this section, the following definitions shall apply:

Action level means a concentration of airborne BD of 0.5 ppm calculated as an eight (8)-hour time-weighted average.

Assistant Secretary means the Assistant Secretary of Labor for Occupational Safety and Health, U.S. Department of Labor, or designee.

Authorized person means any person specifically designated by the employer, whose duties require entrance into a regulated area, or a person entering such an area as a designated representative of employees to exercise the right to observe monitoring and measuring procedures under paragraph (d)(8) of this section, or a person designated under the Act or regulations issued under the Act to enter a regulated area.

1,3–Butadiene means an organic compound with chemical formula $CH_2{=}CH{-}CH{=}CH_2$ that has a molecular weight of approximately 54.15 gm/mole.

Business day means any Monday through Friday, except those days designated as federal, state, local or company specific holidays.

Complete Blood Count (CBC) means laboratory tests performed on whole blood specimens and includes the following: White blood cell count (WBC), hematocrit (Hct), red blood cell count (RBC), hemoglobin (Hgb), differential count of white blood cells, red blood cell morphology, red blood cell indices, and platelet count.

Day means any part of a calendar day.

Director means the Director of the National Institute for Occupational Safety and Health (NIOSH), U.S. Department of Health and Human Services, or designee.

Emergency situation means any occurrence such as, but not limited to, equipment failure, rupture of containers, or failure of control equipment that may or does result in an uncontrolled significant release of BD.

Employee exposure means exposure of a worker to airborne concentrations of BD which would occur if the employee were not using respiratory protective equipment.

Objective data means monitoring data, or mathematical modelling or calculations based on composition, chemical and physical properties of a material, stream or product.

Permissible Exposure Limits, PELs means either the 8 hour Time Weighted Average (8-hr TWA) exposure or the Short-Term Exposure Limit (STEL).

Physician or other licensed health care professional is an individual whose legally permitted scope of practice (i.e., license, registration, or certification) allows him or her to independently provide or be delegated the responsibility to provide one or more of the specific health care services required by paragraph (k) of this section.

Regulated area means any area where airborne concentrations of BD exceed or can reasonably be expected to exceed the 8-hour time weighted average (8-hr TWA) exposure of 1 ppm or the short-term exposure limit (STEL) of 5 ppm for 15 minutes.

This section means this 1,3-butadiene standard.

(c) *Permissible exposure limits (PELs).*—(1) *Time-weighted average (TWA) limit.* The employer shall ensure that no employee is exposed to an airborne concentration of BD in excess of one (1) part BD per million parts of air (ppm) measured as an eight (8)-hour time-weighted average.

(2) *Short-term exposure limit (STEL).* The employer shall ensure that no employee is exposed to an airborne concentration of BD in excess of five parts of BD per million parts of air (5 ppm) as determined over a sampling period of fifteen (15) minutes.

(d) *Exposure monitoring*—(1) *General.* (i) Determinations of employee exposure shall be made from breathing zone air samples that are representative of the 8-hour TWA and 15-minute short-term exposures of each employee.

(ii) Representative 8-hour TWA employee exposure shall be determined on the basis of one or more samples representing full-shift exposure for each shift and for each job classification in each work area.

(iii) Representative 15-minute short-term employee exposures shall be determined on the basis of one or more samples representing 15-minute exposures associated with operations that are most likely to produce exposures above the STEL for each shift and for each job classification in each work area.

(iv) Except for the initial monitoring required under paragraph (d)(2) of this section, where the employer can document that exposure levels are equivalent for similar operations on different work shifts, the employer need only determine representative employee exposure for that operation from the shift during which the highest exposure is expected.

(2) *Initial monitoring.* (i) Each employer who has a workplace or work operation covered by this section, shall perform initial monitoring to determine accurately the airborne concentrations of BD to which employees may be exposed, or shall rely on objective data pursuant to paragraph (a)(2)(i) of this section to fulfill this requirement.

(ii) Where the employer has monitored within two years prior to the effective date of this section and the monitoring satisfies all other requirements of this section, the employer may rely on such earlier monitoring results to satisfy the requirements of paragraph (d)(2)(i) of this section, provided that the conditions under which the initial monitoring was conducted have not changed in a manner that may result in new or additional exposures.

(3) *Periodic monitoring and its frequency.* (i) If the initial monitoring required by paragraph (d)(2) of this section reveals employee exposure to be at or above the action level but at or below both the 8-hour TWA limit and the STEL, the employer shall repeat the representative monitoring required by paragraph (d)(1) of this section every twelve months.

(ii) If the initial monitoring required by paragraph (d)(2) of this section reveals employee exposure to be above the 8-hour TWA limit, the employer shall repeat the representative monitoring required by paragraph (d)(1)(ii) of this section at least every three months until the employer has collected two samples per quarter (each at least 7 days apart) within a two-year period, after which such monitoring must occur at least every six months.

(iii) If the initial monitoring required by paragraph (d)(2) of this section reveals employee exposure to be above the STEL, the employer shall repeat the

representative monitoring required by paragraph (d)(1)(iii) of this section at least every three months until the employer has collected two samples per quarter (each at least 7 days apart) within a two-year period, after which such monitoring must occur at least every six months.

(iv) The employer may alter the monitoring schedule from every six months to annually for any required representative monitoring for which two consecutive measurements taken at least 7 days apart indicate that employee exposure has decreased to or below the 8-hour TWA, but is at or above the action level.

(4) *Termination of monitoring.* (i) If the initial monitoring required by paragraph (d)(2) of this section reveals employee exposure to be below the action level and at or below the STEL, the employer may discontinue the monitoring for employees whose exposures are represented by the initial monitoring.

(ii) If the periodic monitoring required by paragraph (d)(3) of this section reveals that employee exposures, as indicated by at least two consecutive measurements taken at least 7 days apart, are below the action level and at or below the STEL, the employer may discontinue the monitoring for those employees who are represented by such monitoring.

(5) *Additional monitoring.* (i) The employer shall institute the exposure monitoring required under paragraph (d) of this section whenever there has been a change in the production, process, control equipment, personnel or work practices that may result in new or additional exposures to BD or when the employer has any reason to suspect that a change may result in new or additional exposures.

(ii) Whenever spills, leaks, ruptures or other breakdowns occur that may lead to employee exposure above the 8-hr TWA limit or above the STEL, the employer shall monitor [using leak source, such as direct reading instruments, area or personal monitoring], after the cleanup of the spill or repair of the leak, rupture or other breakdown, to ensure that exposures have returned to the level that existed prior to the incident.

(6) *Accuracy of monitoring.* Monitoring shall be accurate, at a confidence level of 95 percent, to within plus or minus 25 percent for airborne concentrations of BD at or above the 1 ppm TWA limit and to within plus or minus 35 percent for airborne concentrations of BD at or above the action level of 0.5 ppm and below the 1 ppm TWA limit.

(7) *Employee notification of monitoring results.* (i) The employer shall, within 5 business days after the receipt of the results of any monitoring performed under this section, notify the affected employees of these results in writing either individually or by posting of results in an appropriate location that is accessible to affected employees.

(ii) The employer shall, within 15 business days after receipt of any monitoring performed under this section indicating the 8-hour TWA or STEL has been exceeded, provide the affected employees, in writing, with information on the corrective action being taken by the employer to reduce employee exposure to or below the 8-hour TWA or STEL and the schedule for completion of this action.

(8) *Observation of monitoring.*—(i) *Employee observation.* The employer shall provide affected employees or their designated representatives an opportunity to observe any monitoring of employee exposure to BD conducted in accordance with paragraph (d) of this section.

(ii) *Observation procedures.* When observation of the monitoring of employee exposure to BD requires entry into an area where the use of protective clothing or equipment is required, the employer shall provide the observer at no cost with protective clothing and equipment, and shall ensure that the observer uses this equipment and complies with all other applicable safety and health procedures.

(e) *Regulated areas.* (1) The employer shall establish a regulated area wherever occupational exposures to airborne concentrations of BD exceed or can reasonably be expected to exceed the permissible exposure limits, either the 8-hr TWA or the STEL.

(2) Access to regulated areas shall be limited to authorized persons.

(3) Regulated areas shall be demarcated from the rest of the workplace in any manner that minimizes the number of employees exposed to BD within the regulated area.

(4) An employer at a multi-employer worksite who establishes a regulated area shall communicate the access restrictions and locations of these areas to other employers with work operations at that worksite whose employees may have access to these areas.

(f) *Methods of compliance.*—(1) *Engineering controls and work practices.* (i) The employer shall institute engineering controls and work practices to reduce and maintain employee exposure to or below the PELs, except to the extent that the employer can establish that these controls are not feasible or where paragraph (h)(1)(i) of this section applies.

(ii) Wherever the feasible engineering controls and work practices which can be instituted are not sufficient to reduce employee exposure to or below the 8-hour TWA or STEL, the employer shall use them to reduce employee exposure to the lowest levels achievable by these controls and shall supplement them by the use of respiratory protection that complies with the requirements of paragraph (h) of this section.

(2) *Compliance plan.* (i) Where any exposures are over the PELs, the employer shall establish and implement a written plan to reduce employee exposure to or below the PELs primarily by means of engineering and work practice controls, as required by paragraph (f)(1) of this section, and by the use of respiratory protection where required or permitted under this section. No compliance plan is required if all exposures are under the PELs.

(ii) The written compliance plan shall include a schedule for the development and implementation of the engineering controls and work practice controls including periodic leak detection surveys.

(iii) Copies of the compliance plan required in paragraph (f)(2) of this section shall be furnished upon request for examination and copying to the Assistant Secretary, the Director, affected employees and designated employee representatives. Such plans shall be reviewed at least every 12 months, and shall be updated as necessary to reflect significant changes in the status of the employer's compliance program.

(iv) The employer shall not implement a schedule of employee rotation as a means of compliance with the PELs.

(g) *Exposure Goal Program.* (1) For those operations and job classifications where employee exposures are greater than the action level, in addition to compliance with the PELs, the employer shall have an exposure goal program that is intended to limit employee exposures to below the action level during normal operations.

(2) Written plans for the exposure goal program shall be furnished upon request for examination and copying to the Assistant Secretary, the Director, affected employees and designated employee representatives.

(3) Such plans shall be updated as necessary to reflect significant changes in the status of the exposure goal program.

(4) Respirator use is not required in the exposure goal program.

(5) The exposure goal program shall include the following items unless the employer can demonstrate that the item is not feasible, will have no significant effect in reducing employee exposures, or is not necessary to achieve exposures below the action level:

(i) A leak prevention, detection, and repair program.

(ii) A program for maintaining the effectiveness of local exhaust ventilation systems.

(iii) The use of pump exposure control technology such as, but not limited to, mechanical double-sealed or seal-less pumps.

(iv) Gauging devices designed to limit employee exposure, such as magnetic gauges on rail cars.

(v) Unloading devices designed to limit employee exposure, such as a vapor return system.

(vi) A program to maintain BD concentration below the action level in control rooms by use of engineering controls.

(h) *Respiratory protection.*—(1) *General.* The employer shall provide respirators that comply with the requirements of this paragraph, at no cost to each affected employee, and ensure that each affected employee uses such respirator where required by this section. Respirators shall be used in the following circumstances:

(i) During the time interval necessary to install or implement feasible engineering and work practice controls;

(ii) In non-routine work operations which are performed infrequently and in which exposures are limited in duration.

(iii) In work situations where feasible engineering controls and work practice controls are not yet sufficient to reduce exposures to or below the PELs; or

(iv) In emergencies.

(2) *Respirator selection.* (i) Where respirators are required, the employer shall select and provide the appropriate respirator as specified in Table 1 in paragraph (h)(5)(ii) of this section, and ensure its use.

(ii) The employer shall select respirators from among those approved by the National Institute for Occupational Safety and Health (NIOSH) under the provisions of 42 CFR Part 84, ''Respiratory Protective Devices.'' Air purifying respirators shall have filter element(s) approved by NIOSH for organic vapors or BD.

(iii) If an employee whose job requires the use of a respirator cannot use a negative pressure respirator, the employee must be provided with a respirator having less breathing resistance, such as a powered air-purifying respirator or supplied air respirator, if the employee is able to use it and if it will provide adequate protection.

(3) *Respirator program.* Where respiratory protection is required, the employer shall institute a respirator program in accordance with 29 CFR 1910.134.

(4) *Respirator use.* (i) Where air-purifying respirators are used, the employer shall replace the air purifying filter element(s) according to the replacement life interval set for the class of respirator listed in Table 1 in paragraph (h)(5) of this section and at the beginning of each work shift.

(ii) In lieu of the replacement intervals listed in Table 1, the employer may replace cartridges or canisters at 90% of the expiration of service life, provided the employer can demonstrate that employees will be adequately protected. BD breakthrough data relied upon by the employer must derive from tests conducted under worst case conditions of humidity, temperature, and air flow rate through the filter element. The employer shall describe the data supporting the cartridge/canister change schedule and the basis for reliance on the data in the employer's respirator program.

(iii) A label shall be attached to the filter element(s) to indicate the date and time it is first installed on the respirator. If an employee detects the odor of BD, the employer shall replace the air-purifying element(s) immediately.

(iv) If a NIOSH-approved end of service life indicator (ESLI) for BD becomes available for an air-purifying filter element, the element may be used until such time as the indicator shows no further useful service life or until replaced at the beginning of the next work shift, whichever comes first. If an employee detects the odor of BD, the employer shall replace the air-purifying element(s) immediately.

(v) The employer shall permit employees who wear respirators to leave the regulated area to wash their faces and respirator facepieces as necessary in order to prevent skin irritation associated with respirator use or to change the filter elements of air-purifying respirators whenever they detect a change in breathing resistance or whenever the odor of BD is detected.

(5) *Respirator fit testing.* (i) The employer shall perform either qualitative fit testing (QLFT) or quantitative fit testing (QNFT), as required in Appendix E to this section, at the time of initial fitting and at least annually thereafter for employees who wear tight-fitting negative pressure respirators. Fit testing shall be used to select a respirator facepiece which exhibits minimum leakage and provides the required protection as prescribed in Table 1 in paragraph (h)(5)(ii) of this section.

(ii) For each employee wearing a tight-fitting full facepiece negative pressure respirator who is exposed to airborne concentrations of BD that exceed 10 times the TWA PEL (10 ppm), the employer shall perform quantitative fit testing as required in Appendix E to this section, at the time of initial fitting and at least annually thereafter.

TABLE 1.—MINIMUM REQUIREMENTS FOR RESPIRATORY PROTECTION FOR AIRBORNE BD

Concentration of airborne BD (ppm) or condition of use	Minimum required respirator
Less than or equal to 5 ppm (5 times PEL).	(a) Air-purifying half mask or full facepiece respirator equipped with approved BD or organic vapor cartridges or canisters. Cartridges or canisters shall be replaced every 4 hours.
Less than or equal to 10 ppm (10 times PEL).	(a) Air-purifying half mask or full facepiece respirator equipped with approved BD or organic vapor cartridges or canisters. Cartridges or canisters shall be replaced every 3 hours.
Less than or equal to 25 ppm (25 times PEL).	(a) Air-purifying full facepiece respirator equipped with approved BD or organic vapor cartridges or canisters. Cartridges or canisters shall be replaced every 2 hours.
	(b) Any powered air-purifying respirator equipped with approved BD or organic vapor cartridges. PAPR cartridges shall be replaced every 2 hours.
	(c) Continuous flow supplied air respirator equipped with a hood or helmet.
Less than or equal to 50 ppm (50 times PEL).	(a) Air-purifying full facepiece respirator equipped with approved BD or organic vapor cartridges or canisters. Cartridges or canisters shall be replaced every (1) hour.
	(b) Powered air-purifying respirator equipped with a tight-fitting facepiece and an approved BD or organic vapor cartridges. PAPR cartridges shall be replaced every (1) hour.

TABLE 1.—MINIMUM REQUIREMENTS FOR RESPIRATORY PROTECTION FOR AIRBORNE BD—Continued

Concentration of airborne BD (ppm) or condition of use	Minimum required respirator
Less than or equal to 1,000 ppm (1,000 times PEL).	(a) Supplied air respirator equipped with a half mask of full facepiece and operated in a pressure demand or other positive pressure mode.
Greater than 1000 ppm	(a) Self-contained breathing unknown concentration, or apparatus equipped with a firefighting full facepiece and operated in a pressure demand or other positive pressure mode. (b) Any supplied air respirator equipped with a full facepiece and operated in a pressure demand or other positive pressure mode in combination with an auxiliary self-contained breathing apparatus operated in a pressure demand or other positive pressure mode.
Escape from IDLH conditions	(a) Any positive pressure self-contained breathing apparatus with an appropriate service life. (b) A air-purifying full facepiece respirator equipped with a front or back mounted BD or organic vapor canister.

Notes: Respirators approved for use in higher concentrations are permitted to be used in lower concentrations. Full facepiece is required when eye irritation is anticipated.

(iii) The employer shall ensure that employees wearing tight fitting respirators perform a facepiece seal fit check to ensure that a proper facepiece seal is obtained prior to entry into a BD atmosphere. The recommended positive or negative pressure fit check procedures listed in Appendix E to this section or the respirator manufacturer's recommended fit check procedure shall be used.

(i) *Protective clothing and equipment.* Where appropriate to prevent eye contact and limit dermal exposure to BD, the employer shall provide protective clothing and equipment at no cost to the employee and shall ensure its use. Eye and face protection shall meet the requirements of 29 CFR 1910.133.

(j) *Emergency situations. Written plan.* A written plan for emergency situations shall be developed, or an existing plan shall be modified, to contain the applicable elements specified in 29 CFR 1910.38, ''Employee Emergency Plans and Fire Prevention Plans,'' and in 29 CFR 1910.120 ''Hazardous Waste Operations and Emergency Responses,'' for each workplace where there is a possibility of an emergency.

(k) *Medical screening and surveillance.*—(1) *Employees covered.* The employer shall institute a medical screening and surveillance program as specified in this paragraph for:

(i) Each employee with exposure to BD at concentrations at or above the action level on 30 or more days or for employees who have or may have exposure to BD at or above the PELs on 10 or more days a year;

(ii) Employers (including successor owners) shall continue to provide medical screening and surveillance for employees, even after transfer to a non-BD exposed job and regardless of when the employee is transferred, whose work histories suggest exposure to BD:

(A) At or above the PELs on 30 or more days a year for 10 or more years;

(B) At or above the action level on 60 or more days a year for 10 or more years; or

(C) Above 10 ppm on 30 or more days in any past year; and

(iii) Each employee exposed to BD following an emergency situation.

(2) *Program administration.* (i) The employer shall ensure that the health questionnaire, physical examination and medical procedures are provided without cost to the employee, without loss of pay, and at a reasonable time and place.

(ii) Physical examinations, health questionnaires, and medical procedures shall be performed or administered by a physician or other licensed health care professional.

(iii) Laboratory tests shall be conducted by an accredited laboratory.

(3) *Frequency of medical screening activities.* The employer shall make medical screening available on the following schedule:

(i) For each employee covered under paragraphs (j)(1) (i)–(ii) of this section, a health questionnaire and complete blood count with differential and platelet count (CBC) every year, and a physical examination as specified below:

(A) An initial physical examination that meets the requirements of this rule, if twelve months or more have elapsed since the last physical examination conducted as part of a medical screening program for BD exposure;

(B) Before assumption of duties by the employee in a job with BD exposure;

(C) Every 3 years after the initial physical examination;

(D) At the discretion of the physician or other licensed health care professional reviewing the annual health questionnaire and CBC;

(E) At the time of employee reassignment to an area where exposure to BD is below the action level, if the employee's past exposure history does not meet the criteria of paragraph (j)(1)(ii) of this section for continued coverage in the screening and surveillance program, and if twelve months or more have elapsed since the last physical examination; and

(F) At termination of employment if twelve months or more have elapsed since the last physical examination.

(ii) Following an emergency situation, medical screening shall be conducted as quickly as possible, but not later than 48 hours after the exposure.

(iii) For each employee who must wear a respirator, physical ability to perform the work and use the respirator must be determined as required by 29 CFR 1910.134.

(4) *Content of medical screening.* (i) Medical screening for employees covered by paragraphs (j)(1) (i)–(ii) of this section shall include:

(A) A baseline health questionnaire that includes a comprehensive occupational and health history and is updated annually. Particular emphasis shall be placed on the hematopoietic and reticuloendothelial systems, including exposure to chemicals, in addition to BD, that may have an adverse effect on these systems, the presence of signs and symptoms that might be related to disorders of these systems, and any other information determined by the examining physician or other licensed health care professional to be necessary to evaluate whether the employee is at increased risk of material impairment of health from BD exposure. Health questionnaires shall consist of the sample forms in Appendix C to this section, or be equivalent to those samples;

(B) A complete physical examination, with special emphasis on the liver, spleen, lymph nodes, and skin;

(C) A CBC; and

(D) Any other test which the examining physician or other licensed health care professional deems necessary to evaluate whether the

employee may be at increased risk from exposure to BD.

(ii) Medical screening for employees exposed to BD in an emergency situation shall focus on the acute effects of BD exposure and at a minimum include: A CBC within 48 hours of the exposure and then monthly for three months; and a physical examination if the employee reports irritation of the eyes, nose throat, lungs, or skin, blurred vision, coughing, drowsiness, nausea, or headache. Continued employee participation in the medical screening and surveillance program, beyond these minimum requirements, shall be at the discretion of the physician or other licensed health care professional.

(5) *Additional medical evaluations and referrals.* (i) Where the results of medical screening indicate abnormalities of the hematopoietic or reticuloendothelial systems, for which a non-occupational cause is not readily apparent, the examining physician or other licensed health care professional shall refer the employee to an appropriate specialist for further evaluation and shall make available to the specialist the results of the medical screening.

(ii) The specialist to whom the employee is referred under this paragraph shall determine the appropriate content for the medical evaluation, e.g., examinations, diagnostic tests and procedures, etc.

(6) *Information provided to the physician or other licensed health care professional.* The employer shall provide the following information to the examining physician or other licensed health care professional involved in the evaluation:

(i) A copy of this section including its appendices;

(ii) A description of the affected employee's duties as they relate to the employee's BD exposure;

(iii) The employee's actual or representative BD exposure level during employment tenure, including exposure incurred in an emergency situation;

(iv) A description of pertinent personal protective equipment used or to be used; and

(v) Information, when available, from previous employment-related medical evaluations of the affected employee which is not otherwise available to the physician or other licensed health care professional or the specialist.

(7) *The written medical opinion.* (i) For each medical evaluation required by this section, the employer shall ensure that the physician or other licensed health care professional produces a written opinion and provides a copy to the employer and the employee within 15 business days of the evaluation. The written opinion shall be limited to the following information:

(A) The occupationally pertinent results of the medical evaluation;

(B) A medical opinion concerning whether the employee has any detected medical conditions which would place the employee's health at increased risk of material impairment from exposure to BD;

(C) Any recommended limitations upon the employee's exposure to BD; and

(D) A statement that the employee has been informed of the results of the medical evaluation and any medical conditions resulting from BD exposure that require further explanation or treatment.

(ii) The written medical opinion provided to the employer shall not reveal specific records, findings, and diagnoses that have no bearing on the employee's ability to work with BD.

Note: However, this provision does not negate the ethical obligation of the physician or other licensed health care professional to transmit any other adverse findings directly to the employee.

(8) *Medical surveillance.* (i) The employer shall ensure that information obtained from the medical screening program activities is aggregated (with all personal identifiers removed) and periodically reviewed, to ascertain whether the health of the employee population of that employer is adversely affected by exposure to BD.

(ii) Information learned from medical surveillance activities must be disseminated to covered employees, as defined in paragraph (k)(1) of this section, in a manner that ensures the confidentiality of individual medical information.

(l) *Communication of BD hazards to employees.*—(1) *Hazard communication.* The employer shall communicate the hazards associated with BD exposure in accordance with the requirements of the Hazard Communication Standard, 29 CFR 1910.1200, 29 CFR 1915.1200, and 29 CFR 1926.59.

(2) *Employee information and training.* (i) The employer shall provide all employees exposed to BD with information and training in accordance with the requirements of the Hazard Communication Standard, 29 CFR 1910.1200, 29 CFR 1915.1200, and 29 CFR 1926.59.

(ii) The employer shall institute a training program for all employees who are potentially exposed to BD at or above the action level or the STEL, ensure employee participation in the program and maintain a record of the contents of such program.

(iii) Training shall be provided prior to or at the time of initial assignment to a job potentially involving exposure to BD at or above the action level or STEL and at least annually thereafter.

(iv) The training program shall be conducted in a manner that the employee is able to understand. The employee shall ensure that each employee exposed to BD over the action level or STEL is informed of the following:

(A) The health hazards associated with BD exposure, and the purpose and a description of the medical screening and surveillance program required by this section;

(B) The quantity, location, manner of use, release, and storage of BD and the specific operations that could result in exposure to BD, especially exposures above the PEL or STEL;

(C) The engineering controls and work practices associated with the employee's job assignment, and emergency procedures and personal protective equipment;

(D) The measures employees can take to protect themselves from exposure to BD.

(E) The contents of this standard and its appendices, and

(F) The right of each employee exposed to BD at or above the action level or STEL to obtain:

(*1*) medical examinations as required by paragraph (j) of this section at no cost to the employee;

(*2*) the employee's medical records required to be maintained by paragraph (m)(4) of this section; and

(*3*) all air monitoring results representing the employee's exposure to BD and required to be kept by paragraph (m)(2) of this section.

(3) *Access to information and training materials.* (i) The employer shall make a copy of this standard and its appendices readily available without cost to all affected employees and their designated representatives and shall provide a copy if requested.

(ii) The employer shall provide to the Assistant Secretary or the Director, or the designated employee representatives, upon request, all materials relating to the employee information and the training program.

(m) *Recordkeeping.*—(1) *Objective data for exemption from initial monitoring.* (i) Where the processing, use, or handling of products or streams made from or containing BD are exempted from other requirements of this section under paragraph (a)(2) of this section, or where objective data have been relied on in lieu of initial

monitoring under paragraph (d)(2)(ii) of this section, the employer shall establish and maintain a record of the objective data reasonably relied upon in support of the exemption.

(ii) This record shall include at least the following information:

(A) The product or activity qualifying for exemption;

(B) The source of the objective data;

(C) The testing protocol, results of testing, and analysis of the material for the release of BD;

(D) A description of the operation exempted and how the data support the exemption; and

(E) Other data relevant to the operations, materials, processing, or employee exposures covered by the exemption.

(iii) The employer shall maintain this record for the duration of the employer's reliance upon such objective data.

(2) *Exposure measurements.* (i) The employer shall establish and maintain an accurate record of all measurements taken to monitor employee exposure to BD as prescribed in paragraph (d) of this section.

(ii) The record shall include at least the following information:

(A) The date of measurement;

(B) The operation involving exposure to BD which is being monitored;

(C) Sampling and analytical methods used and evidence of their accuracy;

(D) Number, duration, and results of samples taken;

(E) Type of protective devices worn, if any; and

(F) Name, social security number and exposure of the employees whose exposures are represented.

(G) The written corrective action and the schedule for completion of this action required by paragraph (d)(7)(ii) of this section.

(iii) The employer shall maintain this record for at least 30 years in accordance with 29 CFR 1910.20.

(3) *Respirator Fit-test.* (i) The employer shall establish a record of the fit tests administered to an employee including:

(A) The name of the employee,

(B) Type of respirator,

(C) Brand and size of respirator,

(D) Date of test, and

(E) Where QNFT is used, the fit factor, strip chart recording or other recording of the results of the test.

(ii) Fit test records shall be maintained for respirator users until the next fit test is administered.

(4) *Medical screening and surveillance.* (i) The employer shall establish and maintain an accurate record for each employee subject to medical screening and surveillance under this section.

(ii) The record shall include at least the following information:

(A) The name and social security number of the employee;

(B) Physician's or other licensed health care professional's written opinions as described in paragraph (k)(7) of this section;

(C) A copy of the information provided to the physician or other licensed health care professional as required by paragraphs (k)(7)(ii)–(iv) of this section.

(iii) Medical screening and surveillance records shall be maintained for each employee for the duration of employment plus 30 years, in accordance with 29 CFR 1910.20.

(5) *Availability.* (i) The employer, upon written request, shall make all records required to be maintained by this section available for examination and copying to the Assistant Secretary and the Director.

(ii) Access to records required to be maintained by paragraphs (l)(1)–(3) of this section shall be granted in accordance with 29 CFR 1910.20(e).

(6) *Transfer of records.* (i) Whenever the employer ceases to do business, the employer shall transfer records required by this section to the successor employer. The successor employer shall receive and maintain these records. If there is no successor employer, the employer shall notify the Director, at least three (3) months prior to disposal, and transmit them to the Director if requested by the Director within that period.

(ii) The employer shall transfer medical and exposure records as set forth in 29 CFR 1910.20(h).

(n) *Dates.*—(1) *Effective date.* This section shall become effective ninety (90) days after the date of publication in the Federal Register.

(2) *Start-up dates.* (i) The initial monitoring required under paragraph (d)(2) of this section shall be completed within sixty (60) days of the effective date of this standard or the introduction of BD into the workplace.

(ii) The requirements of paragraphs (c) through (m) of this section, including feasible work practice controls but not including engineering controls specified in paragraph (f)(1) of this section, shall be complied with within one-hundred and eighty (180) days after the effective date of this section.

(iii) Engineering controls specified by paragraph (f)(1) of this section shall be implemented within two (2) years after the effective date of this section, and the exposure goal program specified in paragraph (g) of this section shall be implemented within three (3) years after the effective date of this section.

(o) *Appendices.* (1) Appendix E to this section is mandatory.

(2) Appendices A, B, C, D, and F to this section are informational and are not intended to create any additional obligations not otherwise imposed or to detract from any existing obligations.

Appendix A. Substance Safety Data Sheet For 1,3-Butadiene (Non-Mandatory)

I. Substance Identification

A. Substance: 1,3-Butadiene (CH_2=CH-CH=CH_2).

B. Synonyms: 1,3-Butadiene (BD); butadiene; biethylene; bi-vinyl; divinyl; butadiene-1,3; buta-1,3-diene; erythrene; NCI–C50602; CAS–106–99–0.

C. BD can be found as a gas or liquid.

D. BD is used in production of styrene-butadiene rubber and polybutadiene rubber for the tire industry. Other uses include copolymer latexes for carpet backing and paper coating, as well as resins and polymers for pipes and automobile and appliance parts. It is also used as an intermediate in the production of such chemicals as fungicides.

E. Appearance and odor: BD is a colorless, non-corrosive, flammable gas with a mild aromatic odor at standard ambient temperature and pressure.

F. Permissible exposure: Exposure may not exceed 1 part BD per million parts of air averaged over the 8-hour workday, nor may short-term exposure exceed 5 parts of BD per million parts of air averaged over any 15-minute period in the 8-hour workday.

II. Health Hazard Data

A. BD can affect the body if the gas is inhaled or if the liquid form, which is very cold (cryogenic), comes in contact with the eyes or skin.

B. Effects of overexposure: Breathing very high levels of BD for a short time can cause central nervous system effects, blurred vision, nausea, fatigue, headache, decreased blood pressure and pulse rate, and unconsciousness. There are no recorded cases of accidental exposures at high levels that have caused death in humans, but this could occur. Breathing lower levels of BD may cause irritation of the eyes, nose, and throat. Skin contact with liquefied BD can cause irritation and frostbite.

C. Long-term (chronic) exposure: BD has been found to be a potent carcinogen in rodents, inducing neoplastic lesions at multiple target sites in mice and rats. A recent study of BD-exposed workers showed that exposed workers have an increased risk of developing leukemia. The risk of leukemia increases with increased exposure to BD. OSHA has concluded that there is strong evidence that workplace exposure to BD poses an increased risk of death from cancers of the lymphohematopoietic system.

D. Reporting signs and symptoms: You should inform your supervisor if you develop any of these signs or symptoms and suspect that they are caused by exposure to BD.

III. Emergency First Aid Procedures

In the event of an emergency, follow the emergency plan and procedures designated for your work area. If you have been trained

in first aid procedures, provide the necessary first aid measures. If necessary, call for additional assistance from co-workers and emergency medical personnel.

A. Eye and Skin Exposures: If there is a potential that liquefied BD can come in contact with eye or skin, face shields and skin protective equipment must be provided and used. If liquefied BD comes in contact with the eye, immediately flush the eyes with large amounts of water, occasionally lifting the lower and the upper lids. Flush repeatedly. Get medical attention immediately. Contact lenses should not be worn when working with this chemical. In the event of skin contact, which can cause frostbite, remove any contaminated clothing and flush the affected area repeatedly with large amounts of tepid water.

B. Breathing: If a person breathes in large amounts of BD, move the exposed person to fresh air at once. If breathing has stopped, begin cardiopulmonary resuscitation (CPR) if you have been trained in this procedure. Keep the affected person warm and at rest. Get medical attention immediately.

C. Rescue: Move the affected person from the hazardous exposure. If the exposed person has been overcome, call for help and begin emergency rescue procedures. Use extreme caution so that you do not become a casualty. Understand the plant's emergency rescue procedures and know the locations of rescue equipment before the need arises.

IV. Respirators and Protective Clothing

A. Respirators: Good industrial hygiene practices recommend that engineering and work practice controls be used to reduce environmental concentrations to the permissible exposure level. However, there are some exceptions where respirators may be used to control exposure. Respirators may be used when engineering and work practice controls are not technically feasible, when such controls are in the process of being installed, or when these controls fail and need to be supplemented or during brief, non-routine, intermittent exposure. Respirators may also be used in situations involving non-routine work operations which are performed infrequently and in which exposures are limited in duration, and in emergency situations. In some instances cartridge respirator use is allowed, but only with strict time constraints. For example, at exposure below 5 ppm BD, a cartridge (or canister) respirator, either full or half face, may be used, but the cartridge must be replaced at least every 4 hours, and it must be replaced every 3 hours when the exposure is between 5 and 10 ppm. If the use of respirators is necessary, the only respirators permitted are those that have been approved by the National Institute for Occupational Safety and Health (NIOSH). In addition to respirator selection, a complete respiratory protection program must be instituted which includes regular training, maintenance, fit testing, inspection, cleaning, and evaluation of respirators. If you can smell BD while wearing a respirator, proceed immediately to fresh air, and change cartridge (or canister) before re-entering an area where there is BD exposure. If you experience difficulty in breathing while wearing a respirator, tell your supervisor.

B. Protective Clothing: Employees should be provided with and required to use impervious clothing, gloves, face shields (eight-inch minimum), and other appropriate protective clothing necessary to prevent the skin from becoming frozen by contact with liquefied BD (or a vessel containing liquid BD).

Employees should be provided with and required to use splash-proof safety goggles where liquefied BD may contact the eyes.

V. Precautions for Safe Use, Handling, and Storage

A. Fire and Explosion Hazards: BD is a flammable gas and can easily form explosive mixtures in air. It has a lower explosive limit of 2%, and an upper explosive limit of 11.5%. It has an autoignition temperature of 420° C (788° F). Its vapor is heavier than air (vapor density, 1.9) and may travel a considerable distance to a source of ignition and flash back. Usually it contains inhibitors to prevent self-polymerization (which is accompanied by evolution of heat) and to prevent formation of explosive peroxides. At elevated temperatures, such as in fire conditions, polymerization may take place. If the polymerization takes place in a container, there is a possibility of violent rupture of the container.

B. Hazard: Slightly toxic. Slight respiratory irritant. Direct contact of liquefied BD on skin may cause freeze burns and frostbite.

C. Storage: Protect against physical damage to BD containers. Outside or detached storage of BD containers is preferred. Inside storage should be in a cool, dry, well-ventilated, noncombustible location, away from all possible sources of ignition. Store cylinders vertically and do not stack. Do not store with oxidizing material.

D. Usual Shipping Containers: Liquefied BD is contained in steel pressure apparatus.

E. Electrical Equipment: Electrical installations in Class I hazardous locations, as defined in Article 500 of the National Electrical Code, should be in accordance with Article 501 of the Code. If explosion-proof electrical equipment is necessary, it shall be suitable for use in Group B. Group D equipment may be used if such equipment is isolated in accordance with Section 501–5(a) by sealing all conduit ½- inch size or larger. See Venting of Deflagrations (NFPA No. 68, 1994), National Electrical Code (NFPA No. 70, 1996), Static Electricity (NFPA No. 77, 1993), Lightning Protection Systems (NFPA No. 780, 1995), and Fire Hazard Properties of Flammable Liquids, Gases and Volatile Solids (NFPA No. 325, 1994).

F. Fire Fighting: Stop flow of gas. Use water to keep fire-exposed containers cool. Fire extinguishers and quick drenching facilities must be readily available, and you should know where they are and how to operate them.

G. Spill and Leak: Persons not wearing protective equipment and clothing should be restricted from areas of spills or leaks until clean-up has been completed. If BD is spilled or leaked, the following steps should be taken:

1. Eliminate all ignition sources.
2. Ventilate area of spill or leak.
3. If in liquid form, for small quantities, allow to evaporate in a safe manner.
4. Stop or control the leak if this can be done without risk. If source of leak is a cylinder and the leak cannot be stopped in place, remove the leaking cylinder to a safe place and repair the leak or allow the cylinder to empty.

H. Disposal: This substance, when discarded or disposed of, is a hazardous waste according to Federal regulations (40 CFR part 261). It is listed as hazardous waste number D001 due to its ignitability. The transportation, storage, treatment, and disposal of this waste material must be conducted in compliance with 40 CFR parts 262, 263, 264, 268 and 270. Disposal can occur only in properly permitted facilities. Check state and local regulation of any additional requirements as these may be more restrictive than federal laws and regulation.

I. You should not keep food, beverages, or smoking materials in areas where there is BD exposure, nor should you eat or drink in such areas.

J. Ask your supervisor where BD is used in your work area and ask for any additional plant safety and health rules.

VI. Medical Requirements

Your employer is required to offer you the opportunity to participate in a medical screening and surveillance program if you are exposed to BD at concentrations exceeding the action level (0.5 ppm BD as an 8-hour TWA) on 30 days or more a year, or at or above the 8 hr TWA (1 ppm) or STEL (5 ppm for 15 minutes) on 10 days or more a year. Exposure for any part of a day counts. If you have had exposure to BD in the past, but have been transferred to another job, you may still be eligible to participate in the medical screening and surveillance program. The OSHA rule specifies the past exposures that would qualify you for participation in the program. These past exposure are work histories that suggest the following: (1) That you have been exposed at or above the PELs on 30 days a year for 10 or more years; (2) that you have been exposed at or above the action level on 60 days a year for 10 or more years; or (3) that you have been exposed above 10 ppm on 30 days in any past year. Additionally, if you are exposed to BD in an emergency situation, you are eligible for a medical examination within 48 hours. The basic medical screening program includes a health questionnaire, physical examination, and blood test. These medical evaluations must be offered to you at a reasonable time and place, and without cost or loss of pay.

VII. Observation of Monitoring

Your employer is required to perform measurements that are representative of your exposure to BD and you or your designated representative are entitled to observe the monitoring procedure. You are entitled to observe the steps taken in the measurement procedure, and to record the results obtained. When the monitoring procedure is taking place in an area where respirators or personal protective clothing and equipment are required to be worn, you or your representative must also be provided with,

and must wear, the protective clothing and equipment.

VIII. Access to Information

A. Each year, your employer is required to inform you of the information contained in this appendix. In addition, your employer must instruct you in the proper work practices for using BD, emergency procedures, and the correct use of protective equipment.

B. Your employer is required to determine whether you are being exposed to BD. You or your representative has the right to observe employee measurements and to record the results obtained. Your employer is required to inform you of your exposure. If your employer determines that you are being overexposed, he or she is required to inform you of the actions which are being taken to reduce your exposure to within permissible exposure limits and of the schedule to implement these actions.

C. Your employer is required to keep records of your exposures and medical examinations. These records must be kept by the employer for at least thirty (30) years.

D. Your employer is required to release your exposure and medical records to you or your representative upon your request.

Appendix B. Substance Technical Guidelines for 1,3-Butadiene (Non-Mandatory)

I. Physical and Chemical Data

A. Substance identification:

1. Synonyms: 1,3-Butadiene (BD); butadiene; biethylene; bivinyl; divinyl; butadiene-1,3; buta-1,3-diene; erythrene; NCI-C50620; CAS–106–99–0.

2. Formula: CH_2=CH-CH=CH_2.

3. Molecular weight: 54.1.

B. Physical data:

1. Boiling point (760 mm Hg): −4.7 °C (23.5 °F).

2. Specific gravity (water=1): 0.62 at 20 °C (68 °F).

3. Vapor density (air=1 at boiling point of BD): 1.87.

4. Vapor pressure at 20 °C (68 °F): 910 mm Hg.

5. Solubility in water, g/100 g water at 20 °C (68 °F): 0.05.

6. Appearance and odor: Colorless, flammable gas with a mildly aromatic odor. Liquefied BD is a colorless liquid with a mildly aromatic odor.

II. Fire, Explosion, and Reactivity Hazard Data

A. Fire:

1. Flash point: −76 °C (−105 °F) for take out; liquefied BD; Not applicable to BD gas.

2. Stability: A stabilizer is added to the monomer to inhibit formation of polymer during storage. Forms explosive peroxides in air in absence of inhibitor.

3. Flammable limits in air, percent by volume: Lower: 2.0; Upper: 11.5.

4. Extinguishing media: Carbon dioxide for small fires, polymer or alcohol foams for large fires.

5. Special fire fighting procedures: Fight fire from protected location or maximum possible distance. Stop flow of gas before extinguishing fire. Use water spray to keep fire-exposed cylinders cool.

6. Unusual fire and explosion hazards: BD vapors are heavier than air and may travel to a source of ignition and flash back. Closed containers may rupture violently when heated.

7. For purposes of compliance with the requirements of 29 CFR 1910.106, BD is classified as a flammable gas. For example, 7,500 ppm, approximately one-fourth of the lower flammable limit, would be considered to pose a potential fire and explosion hazard.

8. For purposes of compliance with 29 CFR 1910.155, BD is classified as a Class B fire hazard.

9. For purposes of compliance with 29 CFR 1910.307, locations classified as hazardous due to the presence of BD shall be Class I.

B. Reactivity:

1. Conditions contributing to instability: Heat. Peroxides are formed when inhibitor concentration is not maintained at proper level. At elevated temperatures, such as in fire conditions, polymerization may take place.

2. Incompatibilities: Contact with strong oxidizing agents may cause fires and explosions. The contacting of crude BD (not BD monomer) with copper and copper alloys may cause formations of explosive copper compounds.

3. Hazardous decomposition products: Toxic gases (such as carbon monoxide) may be released in a fire involving BD.

4. Special precautions: BD will attack some forms of plastics, rubber, and coatings. BD in storage should be checked for proper inhibitor content, for self-polymerization, and for formation of peroxides when in contact with air and iron. Piping carrying BD may become plugged by formation of rubbery polymer.

C. Warning Properties:

1. Odor Threshold: An odor threshold of 0.45 ppm has been reported in The American Industrial Hygiene Association (AIHA) Report, *Odor Thresholds for Chemicals with Established Occupational Health Standards.* (Ex. 32–28C)

2. Eye Irritation Level: Workers exposed to vapors of BD (concentration or purity unspecified) have complained of irritation of eyes, nasal passages, throat, and lungs. Dogs and rabbits exposed experimentally to as much as 6700 ppm for 7½ hours a day for 8 months have developed no histologically demonstrable abnormality of the eyes.

3. Evaluation of Warning Properties: Since the mean odor threshold is about half of the 1 ppm PEL, and more than 10-fold below the 5 ppm STEL, most wearers of air purifying respirators should still be able to detect breakthrough before a significant overexposure to BD occurs.

III. Spill, Leak, and Disposal Procedures

A. Persons not wearing protective equipment and clothing should be restricted from areas of spills or leaks until cleanup has been completed. If BD is spilled or leaked, the following steps should be taken:

1. Eliminate all ignition sources.

2. Ventilate areas of spill or leak.

3. If in liquid form, for small quantities, allow to evaporate in a safe manner.

4. Stop or control the leak if this can be done without risk. If source of leak is a cylinder and the leak cannot be stopped in place, remove the leaking cylinder to a safe place and repair the leak or allow the cylinder to empty.

B. Disposal: This substance, when discarded or disposed of, is a hazardous waste according to Federal regulations (40 CFR part 261). It is listed by the EPA as hazardous waste number D001 due to its ignitability. The transportation, storage, treatment, and disposal of this waste material must be conducted in compliance with 40 CFR parts 262, 263, 264, 268 and 270. Disposal can occur only in properly permitted facilities. Check state and local regulations for any additional requirements because these may be more restrictive than federal laws and regulations.

IV. Monitoring and Measurement Procedures

A. Exposure above the Permissible Exposure Limit (8-hr TWA) or Short-Term Exposure Limit (STEL):

1. 8-hr TWA exposure evaluation: Measurements taken for the purpose of determining employee exposure under this standard are best taken with consecutive samples covering the full shift. Air samples must be taken in the employee's breathing zone (air that would most nearly represent that inhaled by the employee).

2. STEL exposure evaluation: Measurements must represent 15 minute exposures associated with operations most likely to exceed the STEL in each job and on each shift.

3. Monitoring frequencies: Table 1 gives various exposure scenarios and their required monitoring frequencies, as required by the final standard for occupational exposure to butadiene.

TABLE 1.—FIVE EXPOSURE SCENARIOS AND THEIR ASSOCIATED MONITORING FREQUENCIES

Action level	8-hr TWA	STEL	Required monitoring activity
−*	−	−	No 8-hr TWA or STEL monitoring required.
+*	−	−	No STEL monitoring required. Monitor 8-hr TWA annually.
+	+	−	No STEL monitoring required. Periodic monitoring 8-hr TWA, in accordance with (d)(3)(ii).**
+	+	+	Periodic monitoring 8-hr TWA, in accordance with (d)(3)(ii)**. Periodic monitoring STEL, in accordance with (d)(3)(iii).

TABLE 1.—FIVE EXPOSURE SCENARIOS AND THEIR ASSOCIATED MONITORING FREQUENCIES—Continued

Action level	8-hr TWA	STEL	Required monitoring activity
+	–	+	Periodic monitoring STEL, in accordance with (d)(3)(iii). Monitor 8-hr TWA, annually.

*Exposure Scenario, Limit Exceeded: + = Yes, – = No.

**The employer may decrease the frequency of exposure monitoring to annually when at least 2 consecutive measurements taken at least 7 days apart show exposures to be below the 8 hr TWA, but at or above the action level.

4. Monitoring techniques: Appendix D describes the validated method of sampling and analysis which has been tested by OSHA for use with BD. The employer has the obligation of selecting a monitoring method which meets the accuracy and precision requirements of the standard under his or her unique field conditions. The standard requires that the method of monitoring must be accurate, to a 95 percent confidence level, to plus or minus 25 percent for concentrations of BD at or above 1 ppm, and to plus or minus 35 percent for concentrations below 1 ppm.

V. Personal Protective Equipment

A. Employees should be provided with and required to use impervious clothing, gloves, face shields (eight-inch minimum), and other appropriate protective clothing necessary to prevent the skin from becoming frozen from contact with liquid BD.

B. Any clothing which becomes wet with liquid BD should be removed immediately and not re-worn until the butadiene has evaporated.

C. Employees should be provided with and required to use splash proof safety goggles where liquid BD may contact the eyes.

VI. Housekeeping and Hygiene Facilities

For purposes of complying with 29 CFR 1910.141, the following items should be emphasized:

A. The workplace should be kept clean, orderly, and in a sanitary condition.

B. Adequate washing facilities with hot and cold water are to be provided and maintained in a sanitary condition.

VII. Additional Precautions

A. Store BD in tightly closed containers in a cool, well-ventilated area and take all necessary precautions to avoid any explosion hazard.

B. Non-sparking tools must be used to open and close metal containers. These containers must be effectively grounded.

C. Do not incinerate BD cartridges, tanks or other containers.

D. Employers must advise employees of all areas and operations where exposure to BD might occur.

Appendix C. Medical Screening and Surveillance for 1,3-Butadiene (Non-Mandatory)

I. Basis for Medical Screening and Surveillance Requirements

A. Route of Entry Inhalation

B. Toxicology

Inhalation of BD has been linked to an increased risk of cancer, damage to the reproductive organs, and fetotoxicity. Butadiene can be converted via oxidation to epoxybutene and diepoxybutane, two genotoxic metabolites that may play a role in the expression of BD's toxic effects.

BD has been tested for carcinogenicity in mice and rats. Both species responded to BD exposure by developing cancer at multiple primary organ sites. Early deaths in mice were caused by malignant lymphomas, primarily lymphocytic type, originating in the thymus.

Mice exposed to BD have developed ovarian or testicular atrophy. Sperm head morphology tests also revealed abnormal sperm in mice exposed to BD; lethal mutations were found in a dominant lethal test. In light of these results in animals, the possibility that BD may adversely affect the reproductive systems of male and female workers must be considered.

Additionally, anemia has been observed in animals exposed to butadiene. In some cases, this anemia appeared to be a primary response to exposure; in other cases, it may have been secondary to a neoplastic response.

C. Epidemiology

Epidemiologic evidence demonstrates that BD exposure poses an increased risk of leukemia. Mild alterations of hematologic parameters have also been observed in synthetic rubber workers exposed to BD.

II. Potential Adverse Health Effects

A. Acute

Skin contact with liquid BD causes characteristic burns or frostbite. BD is gaseous form can irritate the eyes, nasal passages, throat, and lungs. Blurred vision, coughing, and drowsiness may also occur. Effects are mild at 2,000 ppm and pronounced at 8,000 ppm for exposures occurring over the full workshift.

At very high concentrations in air, BD is an anesthetic, causing narcosis, respiratory paralysis, unconsciousness, and death. Such concentrations are unlikely, however, except in an extreme emergency because BD poses an explosion hazard at these levels.

B. Chronic

The principal adverse health effects of concern are BD-induced lymphoma, leukemia and potential reproductive toxicity. Anemia and other changes in the peripheral blood cells may be indicators of excessive exposure to BD.

C. Reproductive

Workers may be concerned about the possibility that their BD exposure may be affecting their ability to procreate a healthy child. For workers with high exposures to BD, especially those who have experienced difficulties in conceiving, miscarriages, or stillbirths, appropriate medical and laboratory evaluation of fertility may be necessary to determine if BD is having any adverse effect on the reproductive system or on the health of the fetus.

III. Medical Screening Components At-A–Glance

A. Health Questionnaire

The most important goal of the health questionnaire is to elicit information from the worker regarding potential signs or symptoms generally related to leukemia or other blood abnormalities. Therefore, physicians or other licensed health care professionals should be aware of the presenting symptoms and signs of lymphohematopoietic disorders and cancers, as well as the procedures necessary to confirm or exclude such diagnoses. Additionally, the health questionnaire will assist with the identification of workers at greatest risk of developing leukemia or adverse reproductive effects from their exposures to BD.

Workers with a history of reproductive difficulties or a personal or family history of immune deficiency syndromes, blood dyscrasias, lymphoma, or leukemia, and those who are or have been exposed to medicinal drugs or chemicals known to affect the hematopoietic or lymphatic systems may be at higher risk from their exposure to BD. After the initial administration, the health questionnaire must be updated annually.

B. Complete Blood Count (CBC)

The medical screening and surveillance program requires an annual CBC, with differential and platelet count, to be provided for each employee with BD exposure. This test is to be performed on a blood sample obtained by phlebotomy of the venous system or, if technically feasible, from a fingerstick sample of capillary blood. The sample is to be analyzed by an accredited laboratory.

Abnormalities in a CBC may be due to a number of different etiologies. The concern for workers exposed to BD includes, but is not limited to, timely identification of lymphohematopoietic cancers, such as leukemia and non-Hodgkin's lymphoma. Abnormalities of portions of the CBC are identified by comparing an individual's results to those of an established range of normal values for males and females. A substantial change in any individual employee's CBC may also be viewed as ''abnormal'' for that individual even if all measurements fall within the population-based range of normal values. It is suggested that a flowsheet for laboratory values be included in each employee's medical record so that comparisons and trends in annual CBCs can be easily made.

A determination of the clinical significance of an abnormal CBC shall be the responsibility of the examining physician, other licensed health care professional, or medical specialist to whom the employee is referred. Ideally, an abnormal CBC should be compared to previous CBC measurements for the same employee, when available. Clinical common sense may dictate that a CBC value

that is very slightly outside the normal range does not warrant medical concern. A CBC abnormality may also be the result of a temporary physical stressor, such as a transient viral illness, blood donation, or menorrhagia, or laboratory error. In these cases, the CBC should be repeated in a timely fashion, i.e., within 6 weeks, to verify that return to the normal range has occurred. A clinically significant abnormal CBC should result in removal of the employee from further exposure to BD. Transfer of the employee to other work duties in a BD-free environment would be the preferred recommendation.

C. Physical Examination

The medical screening and surveillance program requires an initial physical examination for workers exposed to BD; this examination is repeated once every three years. The initial physical examination should assess each worker's baseline general health and rule out clinical signs of medical conditions that may be caused by or aggravated by occupational BD exposure. The physical examination should be directed at identification of signs of lymphohematopoietic disorders, including lymph node enlargement, splenomegaly, and hepatomegaly.

Repeated physical examinations should update objective clinical findings that could be indicative of interim development of a lymphohematopoietic disorder, such as lymphoma, leukemia, or other blood abnormality. Physical examinations may also be provided on an as needed basis in order to follow up on a positive answer on the health questionnaire, or in response to an abnormal CBC. Physical examination of workers who will no longer be working in jobs with BD exposure are intended to rule out lymphohematopoietic disorders.

The need for physical examinations for workers concerned about adverse reproductive effects from their exposure to BD should be identified by the physician or other licensed health care professional and provided accordingly. For these workers, such consultations and examinations may relate to developmental toxicity and reproductive capacity.

Physical examination of workers acutely exposed to significant levels of BD should be especially directed at the respiratory system, eyes, sinuses, skin, nervous system, and any region associated with particular complaints. If the worker has received a severe acute exposure, hospitalization may be required to assure proper medical management. Since this type of exposure may place workers at greater risk of blood abnormalities, a CBC must be obtained within 48 hours and repeated at one, two, and three months.

Appendix D: Sampling and Analytical Method for 1,3-Butadiene (Non-Mandatory)

OSHA Method No.: 56.

Matrix: Air.

Target concentration: 1 ppm (2.21 mg/m^3)

Procedure: Air samples are collected by drawing known volumes of air through sampling tubes containing charcoal adsorbent which has been coated with 4-tert-butylcatechol. The samples are desorbed with carbon disulfide and then analyzed by gas chromatography using a flame ionization detector.

Recommended sampling rate and air volume: 0.05 L/min and 3 L.

Detection limit of the overall procedure: 90 ppb (200 ug/m^3) (based on 3 L air volume).

Reliable quantitation limit: 155 ppb (343 ug/m^3) (based on 3 L air volume).

Standard error of estimate at the target concentration: 6.5%.

Special requirements: The sampling tubes must be coated with 4-tert-butylcatechol. Collected samples should be stored in a freezer.

Status of method: A sampling and analytical method has been subjected to the established evaluation procedures of the Organic Methods Evaluation Branch, OSHA Analytical Laboratory, Salt Lake City, Utah 84165.

1. Background

This work was undertaken to develop a sampling and analytical procedure for BD at 1 ppm. The current method recommended by OSHA for collecting BD uses activated coconut shell charcoal as the sampling medium (Ref. 5.2). This method was found to be inadequate for use at low BD levels because of sample instability.

The stability of samples has been significantly improved through the use of a specially cleaned charcoal which is coated with 4-tert-butylcatechol (TBC). TBC is a polymerization inhibitor for BD (Ref. 5.3).

1.1.1 Toxic effects

Symptoms of human exposure to BD include irritation of the eyes, nose and throat. It can also cause coughing, drowsiness and fatigue. Dermatitis and frostbite can result from skin exposure to liquid BD. (Ref. 5.1)

NIOSH recommends that BD be handled in the workplace as a potential occupational carcinogen. This recommendation is based on two inhalation studies that resulted in cancers at multiple sites in rats and in mice. BD has also demonstrated mutagenic activity in the presence of a liver microsomal activating system. It has also been reported to have adverse reproductive effects. (Ref. 5.1)

1.1.2. Potential workplace exposure

About 90% of the annual production of BD is used to manufacture styrene-butadiene rubber and Polybutadiene rubber. Other uses include: Polychloroprene rubber, acrylonitrile butadiene-stryene resins, nylon intermediates, styrene-butadiene latexes, butadiene polymers, thermoplastic elastomers, nitrile resins, methyl methacrylate-butadiene styrene resins and chemical intermediates. (Ref. 5.1)

1.1.3. Physical properties (Ref. 5.1)

CAS No.: 106–99–0

Molecular weight: 54.1

Appearance: Colorless gas

Boiling point: −4.41 °C (760 mm Hg)

Freezing point: −108.9 °C

Vapor pressure: 2 atm @ 15.3 °C; 5 atm @ 47 °C

Explosive limits: 2 to 11.5% (by volume in air)

Odor threshold: 0.45 ppm

Structural formula: $H_2C{:}CHCH{:}CH_2$

Synonyms: BD; biethylene; bivinyl; butadiene; divinyl; buta-1,3-diene; alpha-gamma-butadiene; erythrene; NCI–C50602; pyrrolylene; vinylethylene.

1.2. Limit defining parameters

The analyte air concentrations listed throughout this method are based on an air volume of 3 L and a desorption volume of 1 mL. Air concentrations listed in ppm are referenced to 25 °C and 760 mm Hg.

1.2.1. Detection limit of the analytical procedure

The detection limit of the analytical procedure was 304 pg per injection. This was the amount of BD which gave a response relative to the interferences present in a standard.

1.2.2. Detection limit of the overall procedure

The detection limit of the overall procedure was 0.60 µg per sample (90 ppb or 200 µg/m^3). This amount was determined graphically. It was the amount of analyte which, when spiked on the sampling device, would allow recovery approximately equal to the detection limit of the analytical procedure.

1.2.3. Reliable quantitation limit

The reliable quantitation limit was 1.03 µg per sample (155 ppb or 343 µg/m^3). This was the smallest amount of analyte which could be quantitated within the limits of a recovery of at least 75% and a precision (±1.96 SD) of ±25% or better.

1.2.4. Sensitivity [1]

The sensitivity of the analytical procedure over a concentration range representing 0.6 to 2 times the target concentration, based on the recommended air volume, was 387 area units per µg/mL. This value was determined from the slope of the calibration curve. The sensitivity may vary with the particular instrument used in the analysis.

1.2.5. Recovery

The recovery of BD from samples used in storage tests remained above 77% when the samples were stored at ambient temperature and above 94% when the samples were stored at refrigerated temperature. These values were determined from regression lines which were calculated from the storage data. The recovery of the analyte from the collection device must be at least 75% following storage.

1.2.6. Precision (analytical method only)

The pooled coefficient of variation obtained from replicate determinations of analytical standards over the range of 0.6 to 2 times the target concentration was 0.011.

1.2.7. Precision (overall procedure)

The precision at the 95% confidence level for the refrigerated temperature storage test

[1] The reliable quantitation limit and detection limits reported in the method are based upon optimization of the instrument for the smallest possible amount of analyte. When the target concentration of an analyte is exceptionally higher than these limits, they may not be attainable at the routine operation parameters.

was ±12.7%. This value includes an additional ±5% for sampling error. The overall procedure must provide results at the target concentrations that are ±25% at the 95% confidence level.

1.2.8. Reproducibility

Samples collected from a controlled test atmosphere and a draft copy of this procedure were given to a chemist unassociated with this evaluation. The average recovery was 97.2% and the standard deviation was 6.2%.

2. Sampling procedure

2.1. Apparatus

2.1.1. Samples are collected by use of a personal sampling pump that can be calibrated to within ±5% of the recommended 0.05 L/min sampling rate with the sampling tube in line.

2.1.2. Samples are collected with laboratory prepared sampling tubes. The sampling tube is constructed of silane-treated glass and is about 5-cm long. The ID is 4 mm and the OD is 6 mm. One end of the tube is tapered so that a glass wool end plug will hold the contents of the tube in place during sampling. The opening in the tapered end of the sampling tube is at least one-half the ID of the tube (2 mm). The other end of the sampling tube is open to its full 4-mm ID to facilitate packing of the tube. Both ends of the tube are fire-polished for safety. The tube is packed with 2 sections of pretreated charcoal which has been coated with TBC. The tube is packed with a 50-mg backup section, located nearest the tapered end, and with a 100-mg sampling section of charcoal. The two sections of coated adsorbent are separated and retained with small plugs of silanized glass wool. Following packing, the sampling tubes are sealed with two 7⁄32 inch OD plastic end caps. Instructions for the pretreatment and coating of the charcoal are presented in Section 4.1 of this method.

2.2. Reagents

None required.

2.3. Technique

2.3.1. Properly label the sampling tube before sampling and then remove the plastic end caps.

2.3.2. Attach the sampling tube to the pump using a section of flexible plastic tubing such that the larger front section of the sampling tube is exposed directly to the atmosphere. Do not place any tubing ahead of the sampling tube. The sampling tube should be attached in the worker's breathing zone in a vertical manner such that it does not impede work performance.

2.3.3. After sampling for the appropriate time, remove the sampling tube from the pump and then seal the tube with plastic end caps. Wrap the tube lengthwise.

2.3.4. Include at least one blank for each sampling set. The blank should be handled in the same manner as the samples with the exception that air is not drawn through it.

2.3.5. List any potential interferences on the sample data sheet.

2.3.6. The samples require no special shipping precautions under normal conditions. The samples should be refrigerated if they are to be exposed to higher than normal ambient temperatures. If the samples are to be stored before they are shipped to the laboratory, they should be kept in a freezer. The samples should be placed in a freezer upon receipt at the laboratory.

2.4. Breakthrough

(Breakthrough was defined as the relative amount of analyte found on the backup section of the tube in relation to the total amount of analyte collected on the sampling tube. Five-percent breakthrough occurred after sampling a test atmosphere containing 2.0 ppm BD for 90 min at 0.05 L/min. At the end of this time 4.5 L of air had been sampled and 20.1 µg of the analyte was collected. The relative humidity of the sampled air was 80% at 23 °C.)

Breakthrough studies have shown that the recommended sampling procedure can be used at air concentrations higher than the target concentration. The sampling time, however, should be reduced to 45 min if both the expected BD level and the relative humidity of the sampled air are high.

2.5. Desorption efficiency

The average desorption efficiency for BD from TBC coated charcoal over the range from 0.6 to 2 times the target concentration was 96.4%. The efficiency was essentially constant over the range studied.

2.6. Recommended air volume and sampling rate

2.6.1. The recommended air volume is 3L.

2.6.2. The recommended sampling rate is 0.05 L/min for 1 hour.

2.7. Interferences

There are no known interferences to the sampling method.

2.8. Safety precautions

2.8.1. Attach the sampling equipment to the worker in such a manner that it will not interfere with work performance or safety.

2.8.2. Follow all safety practices that apply to the work area being sampled.

3. Analytical procedure

3.1. Apparatus

3.1.1. A gas chromatograph (GC), equipped with a flame ionization detector (FID).[2]

3.1.2. A GC column capable of resolving the analytes from any interference.[3]

3.1.3. Vials, glass 2-mL with Teflon-lined caps.

3.1.4. Disposable Pasteur-type pipets, volumetric flasks, pipets and syringes for preparing samples and standards, making dilutions and performing injections.

3.2. Reagents

3.2.1. Carbon disulfide.[4]

The benzene contaminant that was present in the carbon disulfide was used as an internal standard (ISTD) in this evaluation.

3.2.2. Nitrogen, hydrogen and air, GC grade.

3.2.3. BD of known high purity.[5]

3.3. Standard preparation

3.3.1. Prepare standards by diluting known volumes of BD gas with carbon disulfide. This can be accomplished by injecting the appropriate volume of BD into the headspace above the 1-mL of carbon disulfide contained in sealed 2-mL vial. Shake the vial after the needle is removed from the septum.[6]

3.3.2. The mass of BD gas used to prepare standards can be determined by use of the following equations:

MV=(760/BP)(273+t)/(273)(22.41)

Where:

MV=ambient molar volume
BP=ambient barometric pressure
T=ambient temperature
µg/µL=54.09/MV
µg/standard=(µg/µL)(µL) BD used to prepare the standard

3.4. Sample preparation

3.4.1. Transfer the 100-mg section of the sampling tube to a 2-mL vial. Place the 50-mg section in a separate vial. If the glass wool plugs contain a significant amount of charcoal, place them with the appropriate sampling tube section.

3.4.2. Add 1-mL of carbon disulfide to each vial.

3.4.3. Seal the vials with Teflon-lined caps and then allow them to desorb for one hour. Shake the vials by hand vigorously several times during the desorption period.

3.4.4. If it is not possible to analyze the samples within 4 hours, separate the carbon disulfide from the charcoal, using a disposable Pasteur-type pipet, following the one hour. This separation will improve the stability of desorbed samples.

3.4.5. Save the used sampling tubes to be cleaned and repacked with fresh adsorbent.

3.5. Analysis

3.5.1. GC Conditions
Column temperature: 95 °C
Injector temperature: 180 °C
Detector temperature: 275 °C
Carrier gas flow rate: 30 mL/min
Injection volume: 0.80 µL
GC column: 20-ft x ⅛-in OD stainless steel GC column containing 20%
FFAP on 80/100 Chromabsorb W–AW–DMCS.

3.5.2. Chromatogram. See Section 4.2.

3.5.3. Use a suitable method, such as electronic or peak heights, to measure detector response.

[2] A Hewlett-Packard Model 5840A GC was used for this evaluation. Injections were performed using a Hewlett-Packard Model 7671A automatic sampler.

[3] A 20-ft x ⅛-inch OD stainless steel GC column containing 20% FFAP on 80/100 mesh Chromabsorb W–AW–DMCS was used for this evaluation.

[4] Fisher Scientific Company A.C.S. Reagent Grade solvent was used in this evaluation.

[5] Matheson Gas Products, CP Grade 1,3-butadiene was used in this study.

[6] A standard containing 7.71 µg/mL (at ambient temperature and pressure) was prepared by diluting 4 µL of the gas with 1-mL of carbon disulfide.

3.5.4. Prepare a calibration curve using several standard solutions of different concentrations. Prepare the calibration curve daily. Program the integrator to report the results in µg/mL.

3.5.5. Bracket sample concentrations with standards.

3.6. Interferences (analytical)

3.6.1. Any compound with the same general retention time as the analyte and which also gives a detector response is a potential interference. Possible interferences should be reported by the industrial hygienist to the laboratory with submitted samples.

3.6.2. GC parameters (temperature, column, etc.) may be changed to circumvent interferences.

3.6.3. A useful means of structure designation is GC/MS. It is recommended that this procedure be used to confirm samples whenever possible.

3.7. Calculations

3.7.1. Results are obtained by use of calibration curves. Calibration curves are prepared by plotting detector response against concentration for each standard. The best line through the data points is determined by curve fitting.

3.7.2. The concentration, in ug/mL, for a particular sample is determined by comparing its detector response to the calibration curve. If any analyte is found on the backup section, this amount is added to the amount found on the front section. Blank corrections should be performed before adding the results together.

3.7.3. The BD air concentration can be expressed using the following equation:

$mg/m^3=(A)(B)/(C)(D)$

Where:

A=µg/mL from Section 3.7.2
B=volume
C=L of air sampled
D=efficiency

3.7.4. The following equation can be used to convert results in mg/m^3 to ppm:

$ppm=(mg/m^3)(24.46)/54.09$

Where:

mg/m^3=result from Section 3.7.3.
24.46=molar volume of an ideal gas at 760 mm Hg and 25°C.

3.8. Safety precautions (analytical)

3.8.1. Avoid skin contact and inhalation of all chemicals.

3.8.2. Restrict the use of all chemicals to a fume hood whenever possible.

3.8.3. Wear safety glasses and a lab coat in all laboratory areas.

4. Additional Information

4.1. A procedure to prepare specially cleaned charcoal coated with TBC

4.1.1. Apparatus.

4.1.1.1. Magnetic stirrer and stir bar.

4.1.1.2. Tube furnace capable of maintaining a temperature of 700°C and equipped with a quartz tube that can hold 30 g of charcoal.[8]

4.1.1.3. A means to purge nitrogen gas through the charcoal inside the quartz tube.

4.1.1.4. Water bath capable of maintaining a temperature of 60°C.

4.1.1.5. Miscellaneous laboratory equipment: One-liter vacuum flask, 1–L Erlenmeyer flask, 350–M1 Buchner funnel with a coarse fitted disc, 4-oz brown bottle, rubber stopper, Teflon tape etc.

4.1.2. Reagents

4.1.2.1. Phosphoric acid, 10% by weight, in water.[9]

4.1.2.2. 4-tert-Butylcatechol (TBC).[10]

4.1.2.3. Specially cleaned coconut shell charcoal, 20/40 mesh.[11]

4.1.2.4. Nitrogen gas, GC grade.

4.1.3. Procedure.

Weigh 30g of charcoal into a 500-mL Erlenmeyer flask. Add about 250 mL of 10% phosphoric acid to the flask and then swirl the mixture. Stir the mixture for 1 hour using a magnetic stirrer. Filter the mixture using a fitted Buchner funnel. Wash the charcoal several times with 250-mL portions of deionized water to remove all traces of the acid. Transfer the washed charcoal to the tube furnace quartz tube. Place the quartz tube in the furnace and then connect the nitrogen gas purge to the tube. Fire the charcoal to 700 °C. Maintain that temperature for at least 1 hour. After the charcoal has cooled to room temperature, transfer it to a tared beaker. Determine the weight of the charcoal and then add an amount of TBC which is 10% of the charcoal, by weight.

CAUTION-TBC is toxic and should only be handled in a fume hood while wearing gloves.

Carefully mix the contents of the beaker and then transfer the mixture to a 4-oz bottle. Stopper the bottle with a clean rubber stopper which has been wrapped with Teflon tape. Clamp the bottle in a water bath so that the water level is above the charcoal level. Gently heat the bath to 60 °C and then maintain that temperature for 1 hour. Cool the charcoal to room temperature and then transfer the coated charcoal to a suitable container.

The coated charcoal is now ready to be packed into sampling tubes. The sampling tubes should be stored in a sealed container to prevent contamination. Sampling tubes should be stored in the dark at room temperature. The sampling tubes should be segregated by coated adsorbent lot number.

4.2 Chromatograms

The chromatograms were obtained using the recommended analytical method. The chart speed was set at 1 cm/min for the first three min and then at 0.2 cm/min for the time remaining in the analysis.

The peak which elutes just before BD is a reaction product between an impurity on the charcoal and TBC. This peak is always present, but it is easily resolved from the analyte. The peak which elutes immediately before benzene is an oxidation product of TBC.

5. References

5.1. ''Current Intelligence Bulletin 41, 1,3-Butadiene'', U.S. Dept. of Health and Human Services, Public Health Service, Center for Disease Control, NIOSH.

5.2. ''NIOSH Manual of Analytical Methods'', 2nd ed; U.S. Dept. of Health Education and Welfare, National Institute for Occupational Safety and Health: Cincinnati, OH. 1977, Vol. 2, Method No. S91 DHEW (NIOSH) Publ. (US), No. 77–157–B.

5.3. Hawley, G.C., Ed. ''The Condensed Chemical Dictionary'', 8th ed.; Van Nostrand Rienhold Company: New York, 1971; 139.5.4. *Chem. Eng. News* (June 10, 1985), (63), 22–66.

Appendix E: Respirator Fit Testing Procedures (Mandatory)

A. The Employer Shall Conduct Fit Testing Using the Following Procedures

These provisions apply to both QLFT and QNFT

1. The test subject shall be allowed to pick the most comfortable respirator from a selection of respirators of various sizes and models.

2. Prior to the selection process, the test subject shall be shown how to put on a respirator, how it should be positioned on the face, how to set strap tension and how to determine a comfortable fit. A mirror shall be available to assist the subject in evaluating the fit and positioning the respirator. This instruction may not constitute the subject's formal training on respirator use, because it is only a review.

3. The test subject shall be informed that he/she is being asked to select the respirator which provides the most comfortable fit. Each respirator represents a different size and shape, and if fitted and used properly, will provide adequate protection.

4. The test subject shall be instructed to hold each chosen facepiece up to the face and eliminate those which obviously do not give a comfortable fit.

5. The more comfortable facepieces are noted; the most comfortable mask is donned and worn at least five minutes to assess comfort. Assistance in assessing comfort can be given by discussing the points in item 6 below. If the test subject is not familiar with using a particular respirator, the test subject shall be directed to don the mask several times and to adjust the straps each time to become adept at setting proper tension on the straps.

6. Assessment of comfort shall include reviewing the following points with the test subject and allowing the test subject adequate time to determine the comfort of the respirator:

(a) Position of the mask on the nose.
(b) Room for eye protection.
(c) Room to talk.
(d) Position of mask on face and cheeks.

7. The following criteria shall be used to help determine the adequacy of the respirator fit:

(a) Chin properly placed;
(b) Adequate strap tension, not overly tightened;

[8] A Lindberg Type 55035 Tube furnace was used in this evaluation.

[9] Baker Analyzed'' Reagent grade was diluted with water for use in this evaluation.

[10] The Aldrich Chemical Company 99% grade was used in this evaluation.

[11] Specially cleaned charcoal was obtained from Supelco, Inc. for use in this evaluation. The cleaning process used by Supelco is proprietary.

(c) Fit across nose bridge;

(d) Respirator of proper size to span distance from nose to chin;

(e) Tendency of respirator to slip;

(f) Self-observation in mirror to evaluate fit and respirator position.

8. The test subject shall conduct the negative and positive pressure fit checks using procedures in Appendix A or those recommended by the respirator manufacturer. Before conducting the negative or positive pressure fit checks, the subject shall be told to seat the mask on the face by moving the head from side-to-side and up and down slowly while taking in a few slow deep breaths. Another facepiece shall be selected and retested if the test subject fails the fit check tests.

9. The test shall not be conducted if there is any hair growth between the skin and the facepiece sealing surface, such as stubble beard growth, beard, or sideburns which cross the respirator sealing surface. Any type of apparel which interferes with a satisfactory fit shall be altered or removed.

10. If a test subject exhibits difficulty in breathing during the tests, she or he shall be referred to a physician to determine whether the test subject can wear a respirator while performing her or his duties.

11. If the employee finds the fit of the respirator unacceptable, the test subject shall be given the opportunity to select a different respirator and to be retested.

12. Exercise regimen. Prior to the commencement of the fit test, the test subject shall be given a description of the fit test and the test subject's responsibilities during the test procedure. The description of the process shall include a description of the test exercises that the subject will be performing. The respirator to be tested shall be worn for at least 5 minutes before the start of the fit test.

13. Test Exercises. The test subject shall perform exercises, in the test environment, while wearing any applicable safety equipment that may be worn during actual respirator use which could interfere with fit, in the manner described below:

(a) Normal breathing. In a normal standing position, without talking, the subject shall breathe normally.

(b) Deep breathing. In a normal standing position, the subject shall breathe slowly and deeply, taking caution so as to not hyperventilate.

(c) Turning head side to side. Standing in place, the subject shall slowly turn his/her head from side to side between the extreme positions on each side. The head shall be held at each extreme momentarily so the subject can inhale at each side.

(d) Moving head up and down. Standing in place, the subject shall slowly move his/her head up and down. The subject shall be instructed to inhale in the up position (i.e., when looking toward the ceiling).

(e) Talking. The subject shall talk out loud slowly and loud enough so as to be heard clearly by the test conductor. The subject can read from a prepared text such as the Rainbow Passage, count backward from 100, or recite a memorized poem or song.

Rainbow Passage

When the sunlight strikes raindrops in the air, they act like a prism and form a rainbow. The rainbow is a division of white light into many beautiful colors. These take the shape of a long round arch, with its path high above, and its two ends apparently beyond the horizon. There is, according to legend, a boiling pot of gold at one end. People look, but no one ever finds it. When a man looks for something beyond reach, his friends say he is looking for the pot of gold at the end of the rainbow.

(f) Grimace. The test subject shall grimace by smiling or frowning. (Only for QNFT testing, not performed for QLFT)

(g) Bending over. The test subject shall bend at the waist as if he/she were to touch his/her toes. Jogging in place shall be substituted for this exercise in those test environments such as shroud type QNFT units which prohibit bending at the waist.

(h) Normal breathing. Same as exercise (a). Each test exercise shall be performed for one minute except for the grimace exercise which shall be performed for 15 seconds.

The test subject shall be questioned by the test conductor regarding the comfort of the respirator upon completion of the protocol. If it has become uncomfortable, another model of respirator shall be tried.

B. Qualitative Fit Test (QLFT) Protocols

1. General

(a) The employer shall assign specific individuals who shall assume full responsibility for implementing the respirator qualitative fit test program.

(b) The employer shall ensure that persons administering QLFT are able to prepare test solutions, calibrate equipment and perform tests properly, recognize invalid tests, and assure that test equipment is in proper working order.

(c) The employer shall assure that QLFT equipment is kept clean and well maintained so as to operate within the parameters for which it was designed.

2. Isoamyl Acetate Protocol

(a) Odor threshold screening.

The odor threshold screening test, performed without wearing a respirator, is intended to determine if the individual tested can detect the odor of isoamyl acetate.

(1) Three 1 liter glass jars with metal lids are required.

(2) Odor free water (e.g. distilled or spring water) at approximately 25 degrees C shall be used for the solutions.

(3) The isoamyl acetate (IAA) (also known at isopentyl acetate) stock solution is prepared by adding 1 cc of pure IAA to 800 cc of odor free water in a 1 liter jar and shaking for 30 seconds. A new solution shall be prepared at least weekly.

(4) The screening test shall be conducted in a room separate from the room used for actual fit testing. The two rooms shall be well ventilated to prevent the odor of IAA from becoming evident in the general room air where testing takes place.

(5) The odor test solution is prepared in a second jar by placing 0.4 cc of the stock solution into 500 cc of odor free water using a clean dropper or pipette. The solution shall be shaken for 30 seconds and allowed to stand for two to three minutes so that the IAA concentration above the liquid may reach equilibrium. This solution shall be used for only one day.

(6) A test blank shall be prepared in a third jar by adding 500 cc of odor free water.

(7) The odor test and test blank jars shall be labeled 1 and 2 for jar identification. Labels shall be placed on the lids so they can be periodically peeled off and switched to maintain the integrity of the test.

(8) The following instruction shall be typed on a card and placed on the table in front of the two test jars (i.e., 1 and 2): ''The purpose of this test is to determine if you can smell banana oil at a low concentration. The two bottles in front of you contain water. One of these bottles also contains a small amount of banana oil. Be sure the covers are on tight, then shake each bottle for two seconds. Unscrew the lid of each bottle, one at a time, and sniff at the mouth of the bottle. Indicate to the test conductor which bottle contains banana oil.''

(9) The mixtures used in the IAA odor detection test shall be prepared in an area separate from where the test is performed, in order to prevent olfactory fatigue in the subject.

(10) If the test subject is unable to correctly identify the jar containing the odor test solution, the IAA qualitative fit test shall not be performed.

(11) If the test subject correctly identifies the jar containing the odor test solution, the test subject may proceed to respirator selection and fit testing.

(b) Isoamyl acetate fit test

(1) The fit test chamber shall be similar to a clear 55-gallon drum liner suspended inverted over a 2-foot diameter frame so that the top of the chamber is about 6 inches above the test subject's head. The inside top center of the chamber shall have a small hook attached.

(2) Each respirator used for the fitting and fit testing shall be equipped with organic vapor cartridges or offer protection against organic vapors.

(3) After selecting, donning, and properly adjusting a respirator, the test subject shall wear it to the fit testing room. This room shall be separate from the room used for odor threshold screening and respirator selection, and shall be well ventilated, as by an exhaust fan or lab hood, to prevent general room contamination.

(4) A copy of the test exercises and any prepared text from which the subject is to read shall be taped to the inside of the test chamber.

(5) Upon entering the test chamber, the test subject shall be given a 6-inch by 5-inch piece of paper towel, or other porous, absorbent, single-ply material, folded in half and wetted with 0.75 cc of pure IAA. The test subject shall hang the wet towel on the hook at the top of the chamber.

(6) Allow two minutes for the IAA test concentration to stabilize before starting the fit test exercises. This would be an appropriate time to talk with the test subject; to explain the fit test, the importance of his/her cooperation, and the purpose for the test

exercises; or to demonstrate some of the exercises.

(7) If at any time during the test, the subject detects the banana like odor of IAA, the test is failed. The subject shall quickly exit from the test chamber and leave the test area to avoid olfactory fatigue.

(8) If the test is failed, the subject shall return to the selection room and remove the respirator. The test subject shall repeat the odor sensitivity test, select and put on another respirator, return to the test area and again begin the fit test procedure described in (1) through (7) above. The process continues until a respirator that fits well has been found. Should the odor sensitivity test be failed, the subject shall wait about 5 minutes before retesting. Odor sensitivity will usually have returned by this time.

(9) When the subject wearing the respirator passes the test, its efficiency shall be demonstrated for the subject by having the subject break the face seal and take a breath before exiting the chamber.

(10) When the test subject leaves the chamber, the subject shall remove the saturated towel and return it to the person conducting the test, so there is no significant IAA concentration buildup in the chamber during subsequent tests. The used towels shall be kept in a self sealing bag to keep the test area from being contaminated.

3. Saccharin Solution Aerosol Protocol

The entire screening and testing procedure shall be explained to the test subject prior to the conduct of the screening test.

(a) Taste threshold screening. The saccharin taste threshold screening, performed without wearing a respirator, is intended to determine whether the individual being tested can detect the taste of saccharin.

(1) During threshold screening as well as during fit testing, subjects shall wear an enclosure about the head and shoulders that is approximately 12 inches in diameter by 14 inches tall with at least the front portion clear and that allows free movements of the head when a respirator is worn. An enclosure substantially similar to the 3M hood assembly, parts # FT 14 and # FT 15 combined, is adequate.

(2) The test enclosure shall have a ¾-inch hole in front of the test subject's nose and mouth area to accommodate the nebulizer nozzle.

(3) The test subject shall don the test enclosure. Throughout the threshold screening test, the test subject shall breathe through his/her slightly open mouth with tongue extended.

(4) Using a DeVilbiss Model 40 Inhalation Medication Nebulizer or equivalent the test conductor shall spray the *threshold check solution* into the enclosure. This nebulizer shall be clearly marked to distinguish it from the fit test solution nebulizer.

(5) The *threshold check solution* consists of 0.83 grams of sodium saccharin USP in 100 ml of warm water. It can be prepared by putting 1 ml of the fit test solution (see (b)(5) below) in 100 ml of distilled water.

(6) To produce the aerosol, the nebulizer bulb is firmly squeezed so that it collapses completely, then released and allowed to fully expand.

(7) Ten squeezes are repeated rapidly and then the test subject is asked whether the saccharin can be tasted.

(8) If the first response is negative, ten more squeezes are repeated rapidly and the test subject is again asked whether the saccharin is tasted.

(9) If the second response is negative, ten more squeezes are repeated rapidly and the test subject is again asked whether the saccharin is tasted.

(10) The test conductor will take note of the number of squeezes required to solicit a taste response.

(11) If the saccharin is not tasted after 30 squeezes (step 10), the test subject may not perform the saccharin fit test.

(12) If a taste response is elicited, the test subject shall be asked to take note of the taste for reference in the fit test.

(13) Correct use of the nebulizer means that approximately 1 ml of liquid is used at a time in the nebulizer body.

(14) The nebulizer shall be thoroughly rinsed in water, shaken dry, and refilled at least each morning and afternoon or at least every four hours.

(b) Saccharin solution aerosol fit test procedure

(1) The test subject may not eat, drink (except plain water), smoke, or chew gum for 15 minutes before the test.

(2) The fit test uses the same enclosure described in (a) above.

(3) The test subject shall don the enclosure while wearing the respirator selected in section (a) above. The respirator shall be properly adjusted and equipped with a particulate filter(s).

(4) A second DeVilbiss Model 40 Inhalation Medication Nebulizer or equivalent is used to spray the fit test solution into the enclosure. This nebulizer shall be clearly marked to distinguish it from the screening test solution nebulizer.

(5) The fit test solution is prepared by adding 83 grams of sodium saccharin to 100 ml of warm water.

(6) As before, the test subject shall breathe through the slightly open mouth with tongue extended.

(7) The nebulizer is inserted into the hole in the front of the enclosure and the fit test solution is sprayed into the enclosure using the same number of squeezes required to elicit a taste response in the screening test. A minimum of 10 squeezes is required.

(8) After generating the aerosol the test subject shall be instructed to perform the exercises in section I. A. 13 above.

(9) Every 30 seconds the aerosol concentration shall be replenished using one half the number of squeezes as initially.

(10) The test subject shall indicate to the test conductor if at any time during the fit test the taste of saccharin is detected.

(11) If the taste of saccharin is detected, the fit is deemed unsatisfactory and a different respirator shall be tried.

4. Irritant Fume Protocol

(a) The respirator to be tested shall be equipped with high-efficiency particulate air (HEPA) filters.

(b) No form of test enclosure or hood for the test subject shall be used.

(c) The test subject shall be allowed to smell a weak concentration of the irritant smoke before the respirator is donned to become familiar with its irritating properties.

(d) Break both ends of a ventilation smoke tube containing stannic chloride. Attach one end of the smoke tube to an aspirator squeeze bulb and cover the other end with a short piece of tubing to prevent potential injury from the jagged end of the smoke tube.

(d) Advise the test subject that the smoke can be irritating to the eyes and instruct the subject to keep his/her eyes closed while the test is performed.

(e) The test conductor shall direct the stream of irritant smoke from the smoke tube towards the face seal area of the test subject. He/She shall begin at least 12 inches from the facepiece and gradually move to within one inch, moving around the whole perimeter of the mask.

(f) The exercises identified in section I. A. 13 above shall be performed by the test subject while the respirator seal is being challenged by the smoke.

(g) Each test subject passing the smoke test without evidence of a response (involuntary cough) shall be given a sensitivity check of the smoke from the same tube once the respirator has been removed to determine whether he/she reacts to the smoke. Failure to evoke a response shall void the fit test.

(h) The fit test shall be performed in a location with exhaust ventilation sufficient to prevent general contamination of the testing area by the test agent.

C. Quantitative Fit Test (QNFT) Protocols

The following quantitative fit testing procedures have been demonstrated to be acceptable.

(1) Quantitative fit testing using a non-hazardous challenge aerosol (such as corn oil or sodium chloride) generated in a test chamber, and employing instrumentation to quantify the fit of the respirator.

(2) Quantitative fit testing using ambient aerosol as the challenge agent and appropriate instrumentation (condensation nuclei counter) to quantify the respirator fit.

(3) Quantitative fit testing using controlled negative pressure and appropriate instrumentation to measure the volumetric leak rate of a facepiece to quantify the respirator fit.

1. General

(a) The employer shall assign specific individuals who shall assume full responsibility for implementing the respirator quantitative fit test program.

(b) The employer shall ensure that persons administering QNFT are able to calibrate equipment and perform tests properly, recognize invalid tests, calculate fit factors properly and assure that test equipment is in proper working order.

(c) The employer shall assure that QNFT equipment is kept clean, maintained and calibrated according to the manufacturer's instructions so as to operate at the parameters for which it was designed.

2. Generated aerosol quantitative fit testing protocol

Apparatus

(a) Instrumentation. Aerosol generation, dilution, and measurement systems using particulates (corn oil or sodium chloride) or gases or vapors as test aerosols shall be used for quantitative fit testing.

(b) Test chamber. The test chamber shall be large enough to permit all test subjects to perform freely all required exercises without disturbing the challenge agent concentration or the measurement apparatus. The test chamber shall be equipped and constructed so that the challenge agent is effectively isolated from the ambient air, yet uniform in concentration throughout the chamber.

(c) When testing air-purifying respirators, the normal filter or cartridge element shall be replaced with a high-efficiency particulate air (HEPA) filter supplied by the same manufacturer in the case of particulate QNFT aerosols or a sorbent offering contaminant penetration protection equivalent to high-efficiency filters where the QNFT test agent is a gas or vapor.

(d) The sampling instrument shall be selected so that a computer record or strip chart record may be made of the test showing the rise and fall of the challenge agent concentration with each inspiration and expiration at fit factors of at least 2,000. Integrators or computers which integrate the amount of test agent penetration leakage into the respirator for each exercise may be used provided a record of the readings is made.

(e) The combination of substitute air-purifying elements, challenge agent and challenge agent concentration shall be such that the test subject is not exposed in excess of an established exposure limit for the challenge agent at any time during the testing process based upon the length of the exposure and the exposure limit duration.

(f) The sampling port on the test specimen respirator shall be placed and constructed so that no leakage occurs around the port (e.g. where the respirator is probed), a free air flow is allowed into the sampling line at all times and so that there is no interference with the fit or performance of the respirator. The in-mask sampling device (probe) shall be designed and used so that the air sample is drawn from the breathing zone of the test subject, midway between the nose and mouth and with the probe extending into the facepiece cavity at least ¼ inch.

(g) The test set up shall permit the person administering the test to observe the test subject inside the chamber during the test.

(h) The equipment generating the challenge atmosphere shall maintain the concentration of challenge agent constant to within a 10 percent variation for the duration of the test.

(I) The time lag (interval between an event and the recording of the event on the strip chart or computer or integrator) shall be kept to a minimum. There shall be a clear association between the occurrence of an event and its being recorded.

(j) The sampling line tubing for the test chamber atmosphere and for the respirator sampling port shall be of equal diameter and of the same material. The length of the two lines shall be equal.

(k) The exhaust flow from the test chamber shall pass through a high-efficiency filter before release.

(l) When sodium chloride aerosol is used, the relative humidity inside the test chamber shall not exceed 50 percent.

(m) The limitations of instrument detection shall be taken into account when determining the fit factor.

(n) Test respirators shall be maintained in proper working order and inspected for deficiencies such as cracks, missing valves and gaskets, etc.

4. Procedural Requirements

(a) When performing the initial positive or negative pressure fit check the sampling line shall be crimped closed in order to avoid air pressure leakage during either of these fit checks.

(b) The use of an abbreviated screening QLFT test is optional and may be utilized in order to quickly identify poor fitting respirators which passed the positive and/or negative pressure test and thus reduce the amount of QNFT time. The use of the CNC QNFT instrument in the count mode is another optional method to use to obtain a quick estimate of fit and eliminate poor fitting respirators before going on to perform a full QNFT.

(c) A reasonably stable challenge agent concentration shall be measured in the test chamber prior to testing. For canopy or shower curtain type of test units the determination of the challenge agent stability may be established after the test subject has entered the test environment.

(d) Immediately after the subject enters the test chamber, the challenge agent concentration inside the respirator shall be measured to ensure that the peak penetration does not exceed 5 percent for a half mask or 1 percent for a full facepiece respirator.

(e) A stable challenge concentration shall be obtained prior to the actual start of testing.

(f) Respirator restraining straps shall not be over tightened for testing. The straps shall be adjusted by the wearer without assistance from other persons to give a reasonably comfortable fit typical of normal use.

(g) The test shall be terminated whenever any single peak penetration exceeds 5 percent for half masks and 1 percent for full facepiece respirators. The test subject shall be refitted and retested.

(I) Calculation of fit factors.

(1) The fit factor shall be determined for the quantitative fit test by taking the ratio of the average chamber concentration to the concentration measured inside the respirator for each test exercise except the grimace exercise.

(2) The average test chamber concentration shall be calculated as the arithmetic average of the concentration measured before and after each test (i.e. 8 exercises) or the arithmetic average of the concentration measured before and after each exercise or the true average measured continuously during the respirator sample.

(3) The concentration of the challenge agent inside the respirator shall be determined by one of the following methods:

(i) Average peak penetration method means the method of determining test agent penetration into the respirator utilizing a strip chart recorder, integrator, or computer. The agent penetration is determined by an average of the peak heights on the graph or by computer integration, for each exercise except the grimace exercise. Integrators or computers which calculate the actual test agent penetration into the respirator for each exercise will also be considered to meet the requirements of the average peak penetration method. .

(ii) Maximum peak penetration method means the method of determining test agent penetration in the respirator as determined by strip chart recordings of the test. The highest peak penetration for a given exercise is taken to be representative of average penetration into the respirator for that exercise.

(iii) Integration by calculation of the area under the individual peak for each exercise except the grimace exercise. This includes computerized integration.

(iv) The calculation of the overall fit factor using individual exercise fit factors involves first converting the exercise fit factors to penetration values, determining the average, and then converting that result back to a fit factor. This procedure is described in the following equation:

$$\text{Overall Fit Factor} = \frac{\text{Number of exercises}}{1/ff_1 + 1/ff_2 + 1/ff_3 + 1/ff_4 + 1/ff_5 + 1/ff_7 + 1/ff_8}$$

Where ff_1, ff_2, ff_3, etc. are the fit factors for exercise 1,2,3, etc. [Results of the grimace exercise (7) are not used in this calculation.]

(j) The test subject shall not be permitted to wear a half mask or quarter facepiece respirator unless a minimum fit factor of 100 is obtained, or a full facepiece respirator unless a minimum fit factor of 500 is obtained.

(k) Filters used for quantitative fit testing shall be replaced whenever increased breathing resistance is encountered, or when the test agent has altered the integrity of the filter media. Organic vapor cartridges/canisters shall be replaced if there is any indication of breakthrough by a test agent.

2. Ambient aerosol condensation nuclei counter (CNC) quantitative fit testing protocol

The ambient aerosol condensation nuclei counter (CNC) quantitative fit testing

(Portacount™) protocol quantitatively fit tests respirators with the use of a probe. The probed respirator is only used for quantitative fit tests. A probed respirator has a special sampling device, installed on the respirator, that allows the probe to sample the air from inside the mask. A probed respirator is required for each make, model, and size in which your company requires and can be obtained from the respirator manufacturer or distributor. The CNC instrument manufacturer Dynatech Nevada also provides probe attachments (TSI sampling adapters) that permits fit testing in an employee's own respirator. A fit factor pass level of 100 is necessary for a half-mask respirator and a fit factor of at least 10 times greater than the assigned protection factor for any other negative pressure respirator. The Agency does not recommend the use of homemade sampling adapters. The entire screening and testing procedure shall be explained to the test subject prior to the conduct of the screening test.

(a) Portacount Fit Test Requirements.

(1) Check the respirator to make sure the respirator is fitted with a high efficiency filter and that the sampling probe and line are properly attached to the facepiece.

(2) Instruct the person to be tested to don the respirator several minutes before the fit test starts. This purges the particles inside the respirator and permits the wearer to make certain the respirator is comfortable. This individual should have already been trained on how to wear the respirator properly.

(3) Check the following conditions for the adequacy of the respirator fit: Chin properly placed; Adequate strap tension, not overly tightened; Fit across nose bridge; Respirator of proper size to span distance from nose to chin; Tendencies for the respirator to slip, Self-observation in a mirror to evaluate fit and respirator position.

(4) Have the person wearing the respirator do a fit check. If leakage is detected, determine the cause. If leakage is from a poorly fitting facepiece, try another size of the same type of respirator.

(5) Follow the instructions for operating the Portacount and proceed with the test.

(b) Portacount Test Exercises.

(1) *Normal breathing.* In a normal standing position, without talking, the subject shall breathe normally for 1 minute.

(2) *Deep breathing.* In a normal standing position, the subject shall breathe slowly and deeply for 1 minute, taking caution so as too not hyperventilate.

(3) *Turning head side to side.* Standing in place, the subject shall slowly turn his or her head from side to side between the extreme positions on each side for 1 minute. The head shall be held at each extreme momentarily so the subject can inhale at each side.

(4) *Moving head up and down.* Standing in place, the subject shall slowly move his or her head up and down for 1 minute. The subject shall be instructed to inhale in the up position (i.e., when looking toward the ceiling).

(5) *Talking.* The subject shall talk out loud slowly and loud enough so as to be heard clearly by the test conductor. The subject can read from a prepared text such as the Rainbow Passage, count backward from 100, or recite a memorized poem or song for 1 minute.

(6) *Grimace.* The test subject shall grimace by smiling or frowning for 15 seconds.

(7) *Bending Over.* The test subject shall bend at the waist as if he or she were to touch his or her toes for 1 minute. Jogging in place shall be substituted for this exercise in those test environments such as shroud type QNFT units which prohibit bending at the waist.

(8) *Normal Breathing.* Remove and re-don the respirator within a one-minute period. Then, in a normal standing position, without talking, the subject shall breathe normally for 1 minute.

After the test exercises, the test subject shall be questioned by the test conductor regarding the comfort of the respirator upon completion of the protocol. If it has become uncomfortable, another model of respirator shall be tried.

(c) Portacount Test Instrument.

(1) The Portacount will automatically stop and calculate the overall fit factor for the entire set of exercises. The overall fit factor is what counts. The Pass or Fail message will indicate whether or not the test was successful. If the test was a Pass, the fit test is over.

(2) A record of the test needs to be kept on file assuming the fit test was successful. The record must contain the test subject's name; overall fit factor; make, model and size of respirator used, and date tested.

BILLING CODE 4510–26–P

APPENDIX F. MEDICAL QUESTIONNAIRES, (Non-mandatory)

1,3 -Butadiene (BD) Initial Health Questionnaire

DIRECTIONS:

You have been asked to answer the questions on this form because you work with BD (butadiene). These questions are about your work, medical history, and health concerns. Please do your best to answer all of the questions. If you need help, please tell the doctor or health care professional who reviews this form.

This form is a confidential medical record. Only information directly related to your health and safety on the job may be given to your employer. Personal health information will not be given to anyone without your consent.

Date:_____

Name:_____ _____ ___ SSN_____/____/_____
Last First MI

Job Title:_____

Company's Name:_____

Supervisor's Name:_____ Supervisor's Phone No.:( )_____-_____

Work History

1. Please list all jobs you have had in the past, starting with the job you have now and moving back in time to your first job. (For more space, write on the back of this page.)

Main Job Duty	Years	Company Name City, State	Chemicals
1			
2			
3			
4			
5			
6			
7			
8			

2. Please describe what you do during a typical work day. Be sure to tell about your work with BD.

_____

_____

_____

3. Please check any of these chemicals that you work with now or have worked with in the past:

benzene	___	carbon tetrachloride ("carbon tet")	___
glues	___	arsine	___
toluene	___	carbon disulfide	___
inks, dyes	___	lead	___
other solvents, grease cutters	___	cement	___
insecticides (like DDT, lindane, etc.)	___	petroleum products	___
paints, varnishes, thinners, strippers	___	nitrites	___
dusts	___		

4. Please check the protective clothing or equipment you use at the job you have now:

gloves	___
coveralls	___
respirator	___
dust mask	___
safety glasses, goggles	___

Please circle your answer of yes or no.

5. Does your protective clothing or equipment fit you properly? yes no

6. Have you ever made changes in your protective clothing or equipment to make it fit better? yes no

7. Have you been exposed to BD when you were not wearing protective clothing or equipment? yes no

8. Where do you eat, drink and/or smoke when you are at work? (Please check all that apply.)

Cafeteria/restaurant/snack bar	___
Break room/employee lounge	___
Smoking lounge	___
At my work station	___

Please circle your answer.

9. Have you been exposed to radiation (like x-rays or nuclear material) at the job you have now or at past jobs? yes no

10. Do you have any hobbies that expose you to dusts or chemicals (including paints, glues, etc.)? yes no

11. Do you have any second or side jobs? yes no

If yes, what are your duties there?_____

_____

_____

_____

12. Where you in the military? yes no

If yes, what did you do in the military?_____

_____

_____

_____

Family Health History

1. In the FAMILY MEMBER column, across from the disease name, write which family member, if any, had the disease.

DISEASE	FAMILY MEMBER
Cancer	
Lymphoma	
Sickle Cell Disease or Trait	
Immune Disease	
Leukemia	
Anemia	

2. Please fill in the following information about family health:

Relative	Alive?	Age at death?	Cause of death?
Father			
Mother			
Brother/Sister			
Brother/Sister			
Brother/Sister			

Personal Health History

Birth Date____/____/____ Age_____ Sex____ Height____ Weight_____

Please circle your answer.

1. Do you smoke any tobacco products? yes no

2. Have you ever had any kind of surgery or operation? yes no

If yes, what type of surgery:_____

_____

_____

3. Have you ever been in the hospital for any other reasons? yes no

If yes, please describe the reason:_____

_____

_____

4. Do you have any on-going or current medical problems or conditions? yes no

If yes, please describe:_____

_____

_____

5. Do you now have or have you ever had any of the following? Please check all that apply to you.

unexplained fever	___	bruising easily	___	still birth	___
anemia ("low blood")	___	lupus	___	eye redness	___
HIV/AIDS	___	weight loss	___	lumps you can feel	___
weakness	___	kidney problems	___	child with birth defect	___
sickle cell	___	enlarged lymph nodes	___	autoimmune disease	___
miscarriage	___	liver disease	___	overly tired	___
skin rash	___	cancer	___	lung problems	___
bloody stools	___	infertility	___	rheumatoid arthritis	___
leukemia/lymphoma	___	drinking problems	___	mononucleosis ("mono")	___
neck mass/swelling	___	thyroid problems	___	nagging cough	___
wheezing	___	night sweats	___		
yellowing of skin	___	chest pain	___		

Please circle your answer.

6. Do you have any symptoms or health problems that you think may be related to your work with BD? yes no

If yes, please describe:_____

_____

7. Have any of your co-workers had similar symptoms or problems?
yes no don't know

If yes, please describe:_____

_____

8. Do you notice any irritation of your eyes, nose, throat, lungs, or skin when working with BD? yes no

9. Do you notice any blurred vision, coughing, drowsiness, nausea or headache when working with BD? yes no

10. Do you take any medications (including birth control or over-the-counter)? yes no

If yes, please list:_____

_____

11. Are you allergic to any medication, food, or chemicals? yes no

If yes, please list:_____

_____

12. Do you have any health conditions not covered by this questionnaire that you think are affected by your work with BD? yes no

If yes, please explain:_____

_____

13. Did you understand all the questions? yes no

_____

Signature

1,3 -Butadiene (BD) Update Health Questionnaire

DIRECTIONS:

You have been asked to answer the questions on this form because you work with BD (butadiene). These questions ask about changes in your work, medical history, and health concerns since the last time you were evaluated. Please do your best to answer all of the questions. If you need help, please tell the doctor or health care professional who reviews this form.

This form is a confidential medical record. Only information directly related to your health and safety on the job may be given to your employer. Personal health information will not be given to anyone without your consent.

Date:_____

Name:_____ _____ ___ SSN____/___/_____
Last First MI

Job title:_____

Company's Name:_____

Supervisor's Name:_____ Supervisor's Phone No.( )____-_____

Present Work History

1. Please describe any NEW duties that you have at your job:_____
_____
_____
_____
_____

2 Please list any additional job titles you have:

_____ _____
_____ _____
_____ _____

Please circle your answer.

3. Are you exposed to any other chemicals in your work since the last time you were evaluated for exposure to BD? yes no

   If yes, please list what they are:_____
   _____

4. Does your personal protective equipment and clothing fit you properly? yes no

5. Have you made changes in this equipment or clothing to make it fit better? yes no

6. Have you been exposed to BD when you were not wearing protective equipment or clothing?
yes no

7. Are you exposed to any NEW chemicals at home or while working on hobbies?
yes no

If yes, please list what they are:_____
_____

8. Since your last BD health evaluation, have you started working any new second or side jobs?
yes no

If yes, what are your duties there?_____
_____
_____

Personal Health History

1. What is your current weight?_____ pounds

2. Have you been diagnosed with any new medical conditions or illness since your last evaluation?
yes no

If yes, please tell what they are:_____
_____

3. Since your last evaluation, have you been in the hospital for any illnesses, injuries, or surgery?
yes no

If yes, please describe: _____
_____
_____

4. Do you have any of the following? Please place a check for all that apply to you.

unexplained fever	____	bruising easily	____	still birth	____
anemia ("low blood")	____	lupus	____	eye redness	____
HIV/AIDS	____	weight loss	____	lumps you can feel	____
weakness	____	kidney problems	____	child with birth defect	____
sickle cell	____	enlarged lymph nodes	____	autoimmune disease	____
miscarriage	____	liver disease	____	overly tired	____
skin rash	____	cancer	____	lung problems	____
bloody rash	____	infertility	____	rheumatoid arthritis	____
leukemia/lymphoma	____	drinking problems	____	mononucleosis "mono"	____
neck mass/swelling	____	thyroid problems	____	nagging cough	____
wheezing	____	night sweats	____	yellowing of skin	____

chest pain ____

Please circle your answer.

5. Do you have any symptoms or health problems that you think may be related to your work with BD? yes no

   If yes, please describe:_____
   _____

6. Have any of your co-workers had similar symptoms or problems?
   yes no don't know

   If yes, please describe:_____
   _____

7. Do you notice any irritation of your eyes, nose, throat, lungs, or skin when working with BD?
   yes no

8. Do you notice any blurred vision, coughing, drowsiness, nausea, or headache when working with BD? yes no

9. Have you been taking any NEW medications (including birth control or over-the-counter)? yes no

   If yes, please list:

   _____ _____ _____

   _____ _____ _____

10. Have you developed any NEW allergies to medications, foods, or chemicals?
    yes no

    If yes, please list:

    _____ _____ _____

    _____ _____ _____

11. Do you have any health conditions not covered by this questionnaire that you think are affected by your work with BD? yes no

    If yes, please explain:_____
    _____

12. Did you understand all the questions? yes no

_____
Signature

BILLING CODE 4510–26–C

PART 1915—[AMENDED]

Part 1915 of 29 CFR is hereby amended as follows:

1. The authority citation for 29 CFR part 1915 continues to read as follows:

Authority: Sec. 41, Longshore and Harbor Workers Compensation Act (33 U.S.C. 941); secs. 4, 6, and 8 of the Occupational Safety and Health Act of 1970 (29 U.S.C. 653, 655, and 657); sec. 4 of the Administrative Procedure Act (5 U.S.C. 553); Secretary of Labor's Order No. 12–71 (36 FR 8754), 8–76 (41 FR 25059), 9–83 (48 FR 35736), or 1–90 (55 FR 9033), as applicable; 29 CFR part 1911.

§ 1915.1000 [Amended]

2. The entry in Table Z–1 of Section 1915.1000, for ''Butadiene (1,3–Butadiene)'' is amended as follows: remove the ''1000'' and ''2200'' from the columns entitled ppm [a]* and mg/m^3 [b]* respectively; add ''1 ppm/5 ppm STEL'' in the ppm [a]* column; and add the following to the butadiene entry: ''; See 29 CFR 1910.1051; 29 CFR 1910.19(l)'' so that the entry reads as follows: ''Butadiene (1,3–Butadiene); See 29 CFR 1910.1051; 29 CFR 1910.19(l).''

PART 1926—[AMENDED]

Part 1926 of 29 CFR is hereby amended as set forth below:

Subpart Z—[Amended]

1. The authority citation for Subpart Z of 29 CFR part 1926 is revised to read as follows:

Authority: Sec. 107, Contract Work Hours and Safety Standards Act (40 U.S.C. 333); secs. 4, 6, 8, Occupational Safety and Health Act of 1970 (29 U.S.C. 653, 655, 657); Secretary of Labor's Order No. 12–71 (36 FR 8754), 8–76 (41 FR 25059) 9–83 (48 FR 35736) or 1–90 (55 FR 9033), as applicable; 29 CFR part 1911.

Appendix A to § 1926.55 [Amended]

2. The entry in Appendix A to § 1926.55 for ''Butadiene (1,3–Butadiene)'' is amended as follows: remove the ''1000'' and ''2200'' from the columns entitled ppma and mg/m^3 [b] respectively; add ''1 ppm/5 ppm STEL'' in the ppm[a] column; and add the following to the butadiene entry; ''; See 29 CFR 1910.1051; 29 CFR 1910.19(l)'' so that the entry reads as follows: ''Butadiene (1,3–Butadiene); See 29 CFR 1910.1051; 29 CFR 1910.19(1).''

[FR Doc. 96–27791 Filed 11–1–96; 8:45 am]

BILLING CODE 4510–26–P