DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Recombinant DNA Research: Actions Under the Guidelines

AGENCY: National Institutes of Health, PHS, DHHS.

ACTION: Notice of Actions under the NIH Guidelines for Research Involving Recombinant DNA Molecules (59 FR 34496, 59 FR 40170, 60 FR 20726).

SUMMARY: This notice sets forth an action to be taken by the Director, National Institutes of Health (NIH), under the NIH Guidelines for Research Involving Recombinant DNA Molecules.

FOR FURTHER INFORMATION CONTACT: Additional information can be obtained from Dr. Nelson A. Wivel, Director, Office of Recombinant DNA Activities (ORDA), Office of Science Policy and Technology Transfer, National Institutes of Health, Suite 302, 6000 Executive Boulevard, MSC 7010, Bethesda, Maryland 20892–7010, (301) 496–9838.

SUPPLEMENTARY INFORMATION: Today's action is being promulgated under the NIH Guidelines for Research Involving Recombinant DNA Molecules. This proposed action was published for comment in the Federal Register of August 18, 1994 (58 FR 44098), November 8, 1994 (59 FR 55796), February 8, 1995 (60 FR 7630), and May 22, 1995 (60 FR 27207), and reviewed and recommended for approval by the NIH Recombinant DNA Advisory Committee (RAC) at its meeting on June 8–9, 1995.

I. Background Information and Decisions on Actions Under the NIH Guidelines

A. Amendments to Sections II, III, IV, V, Appendices B, C, H, and Q of the NIH Guidelines Regarding Updating the Classification of Microorganisms

In a letter dated June 24, 1993, Dr. Diane Fleming, President of the Mid-Atlantic Biological Safety Association requested the revision and updating of Appendix B, Classification of Microorganisms on the Basis of Hazard. The Mid-Atlantic Biological Safety Association submitted an updated list of the classification of microorganisms for the Recombinant DNA Advisory Committee to review which included the latest taxonomy and agent risk group classifications as defined by the Centers for Disease Control and Prevention.

During the September 9–10, 1993, meeting, the Recombinant DNA Advisory Committee recommended by consensus that the current classification of etiological agents described in the Biosafety in Microbiological and Biomedical Laboratories, 3rd edition, May 1993, U.S. Department of Health and Human Services, should be endorsed by the Committee. The Committee retained the option to adopt any modifications to the Centers for Disease Control and Prevention listing. The Committee recommended that the revised Appendix B, Classification of Microorganisms on the Basis of Hazard, submitted by Dr. Fleming should not be adopted until the Committee received letters of concurrence from both the Centers for Disease Control and Prevention and the NIH Division of Safety.

In a telephone call on October 20, 1994, Dr. Fleming stated that Appendix B, Classification of Microorganisms on the Basis of Hazard, would be reviewed by experts from the Centers for Disease Control and Prevention and the American Society for Microbiology. The revised Appendix B was submitted to the Recombinant DNA Advisory Committee December 1–2, 1994, meeting for review and discussion. During the December 1994 meeting, the Committee recommended publishing the revised Appendix B in the Federal Register for public comment, with further review of this proposal and possible approval during the March 6–7, 1995, meeting.

During the March 6–7, 1995 meeting, the Recombinant DNA Advisory Committee deferred approval of the proposed amendments to Appendix B pending additional revisions to the remaining sections and appendices of the NIH Guidelines that are required to adequately accommodate the revised Appendix B (Sections II, III, IV, V, Appendices C, H, and Q). The motion for deferral included a recommendation that a subcommittee consisting of Dr. Stephen Straus (Chair of the Subcommittee), ad hoc experts, and Office of Recombinant DNA Activities staff would meet to develop the required modifications. The motion passed by a vote of 17 in favor, 0 opposed, and no abstentions.

On May 5, 1995, the Appendix B Subcommittee met to finalize the document in terms of its listing of pathogens and the text of the NIH Guidelines related to Appendix B in other sections and appendices (Sections II, III, IV, V, Appendices C, H, and Q). During the June 8–9, 1995 meeting, the Recombinant DNA Advisory Committee reviewed the document. There was a concurrence that the Risk Group classification serves as an initial guidance to assign an appropriate containment level for a particular experiment by the Institutional Biosafety Committees and the investigators. Since the new Appendix B is primarily concerned with human pathogenicity, it addresses only the human etiologic agents and omits all animal agents. The Committee observed that this omission created a problem because some of the animal agents, particularly the group of viruses known as oncogenic viruses are frequently used as vectors for gene transfer in the laboratories or in human studies. The Recombinant DNA Advisory Committee approved a motion to: (1) establish a working group to recommend exemption of additional vector systems in Appendix C (exempt host-vector systems), and (2) accept the proposed amendments to Appendix B with the provision to develop a new Appendix B–V relating to animal viruses relevant to human studies, and to list specific examples of agents under Appendix B–I, Risk Group 1 (RG1) Agents. The motion was approved by a vote of 17 in favor, 0 opposed, and no abstentions.

On June 13, 1995, the Office of Recombinant DNA Activities forwarded two versions of the Appendix B–V, Animal Viral Etiologic Agents in Common Use to the Appendix B Subcommittee. Most of these agents were previously listed as Class 2 oncogenic viruses in two separate categories of low and moderate risk agents in the original Appendix B. Since none of these animal etiologic agents are associated with disease in healthy human adults, one version of Appendix B–V listed these agents as a single group recommended for Biosafety Level 1 containment and another version listed them in a two-tier system for either Biosafety Level 1 or Biosafety Level 2 containment. Subsequent discussion with the members of the Appendix B Subcommittee concluded that while there was no reason to have a separate group of ''moderate'' risk agents in this list, it was prudent to recommend conducting experiments under a Biosafety Level 2 containment with several agents that are capable of infecting human cells, e.g., amphotropic and xenotropic murine leukemia virus.

During the September 11–12, 1995, meeting, the Recombinant DNA Advisory Committee reviewed the updated Appendix B along with other sections and appendices of the NIH Guidelines (Sections II, III, IV, V, Appendices C, H, and Q) relating to classification of microorganisms. It was observed that some viruses in the moderate risk group could infect human cells but their replication was largely restricted to their animal hosts. Some Committee members pointed out that

some viruses with oncogenes such as SV40 have been treated more cautiously than viruses without oncogenes; therefore, a two-tier list should be used. Dr. Wivel explained that listing a group of animal viruses as ''moderate risk'' agents introduces an inconsistency into Appendix B. Some strains of these viruses, although capable of infecting human cells, have not been shown to be associated with any disease in healthy human adults. They fall within the definition of Risk Group 1 agents, i.e., agents that are not associated with disease in healthy adult humans. Two committee members inquired why several viruses in the original Appendix B are not listed in the new version. Dr. Thomas Shih (Executive Secretary, Appendix B Subcommittee) explained that several rarely used viruses such as chick embryo lethal orphan virus are deleted from the new list. The list includes commonly used organisms, and it is not intended to be inclusive since many other animal agents are not listed. Dr. Walters (Chair, Recombinant DNA Advisory Committee) stated that the consensus of the committee is to accept the list of animal viruses in Appendix B–V as a reasonable modification of Appendix B.

The actions are detailed in Section II—Summary of Actions. I accept these recommendations, and the NIH Guidelines will be amended accordingly.

II. Summary of Actions

A. Amendments to Section II, Safety Considerations (Previously the Entire Section II was Entitled Containment)

Section II is amended to read:

Section II. Safety Considerations

Section II–A. Risk Assessment

Section II–A–1. Risk Groups

Risk assessment requires the exercise of sound judgment by the investigator. The investigator must make an initial risk assessment based on the Risk Group (RG) of an agent (see Appendix B, Classification of Human Etiologic Agents on the Basis of Hazard). Agents are classified into four Risk Groups (RGs) according to their relative pathogenicity for healthy adult humans by the following criteria: (1) Risk Group 1 (RG1) agents are not associated with disease in healthy adult humans. (2) Risk Group 2 (RG2) agents are associated with human disease which is rarely serious and for which preventive or therapeutic interventions are often available. (3) Risk Group 3 (RG3) agents are associated with serious or lethal human disease for which preventive or therapeutic interventions may be available. (4) Risk Group 4 (RG4) agents are likely to cause serious or lethal human disease for which preventive or therapeutic interventions are not usually available.

Section II–A–2. Criteria for Risk Groups

Classification of agents is based on the potential effect of a biological agent on a healthy human adult and does not account for instances in which an individual may have increased susceptibility to such agents, e.g., preexisting diseases, medications, compromised immunity, pregnancy or breast feeding (which may increase exposure of infants to some agents) (see Appendix B, Classification of Human Etiologic Agents on the Basis of Hazard).

Personnel may need periodic medical surveillance to ascertain fitness to perform certain activities; they may also need to be offered prophylactic vaccines and boosters (see Section IV–B–1–f, Responsibilities of the Institution, General Information).

Section II–A–3. Comprehensive Risk Assessment

In deciding on the appropriate containment for an experiment, the initial risk assessment from Appendix B, Classification of Human Etiologic Agents on the Basis of Hazard, should be followed by a thorough consideration of the agent itself and how it is to be manipulated. Factors to be considered in determining the level of containment include agent factors such as: virulence, pathogenicity, infectious dose, environmental stability, route of spread, communicability, operations, quantity, availability of vaccine or treatment, and gene product effects such as toxicity, physiological activity, and allergenicity. Any strain that is known to be more hazardous than the parent (wild-type) strain should be considered for handling at a higher containment level. Certain attenuated strains or strains that have been demonstrated to have irreversibly lost known virulence factors may qualify for a reduction of the containment level compared to the Risk Group assigned to the parent strain (see Section V–B, Footnotes and References of Sections I through IV).

A final assessment of risk based on these considerations is then used to set the appropriate containment conditions for the experiment (see Section II–B, Containment). The containment level required may be equivalent to the Risk Group classification of the agent or it may be raised or lowered as a result of the above considerations. The Institutional Biosafety Committee must approve the risk assessment and the biosafety containment level for recombinant DNA experiments described in Sections III–A, Experiments that Require Institutional Biosafety Committee Approval, RAC Review, and NIH Director Approval Before Initiation, III–B, Experiments that Require NIH/ORDA and Institutional Biosafety Committee Approval Before Initiation, and III–C, Experiments that Require Institutional Biosafety Committee Approval Before Initiation.

Careful consideration should be given to the types of manipulation planned for some higher Risk Group agents. For example, the RG2 dengue viruses may be cultured under the Biosafety Level (BL) 2 containment (see Section II–B); however, when such agents are used for animal inoculation or transmission studies, a higher containment level is recommended. Similarly, RG3 agents such as Venezuelan equine encephalomyelitis and yellow fever viruses should be handled at a higher containment level for animal inoculation and transmission experiments.

Individuals working with human immunodeficiency virus (HIV), hepatitis B virus (HBV) or other bloodborne pathogens should consult Occupational Exposure to Bloodborne Pathogens; Final Rule (56 FR 64175–64182). BL2 containment is recommended for activities involving all blood-contaminated clinical specimens, body fluids, and tissues from all humans, or from HIV- or HBV-infected or inoculated laboratory animals. Activities such as the production of research-laboratory scale quantities of HIV or other bloodborne pathogens, manipulating concentrated virus preparations, or conducting procedures that may produce droplets or aerosols, are performed in a BL2 facility using the additional practices and containment equipment recommended for BL3. Activities involving industrial scale volumes or preparations of concentrated HIV are conducted in a BL3 facility, or BL3 Large Scale if appropriate, using BL3 practices and containment equipment.

Exotic plant pathogens and animal pathogens of domestic livestock and poultry are restricted and may require special laboratory design, operation and containment features not addressed in Biosafety in Microbiological and Biomedical Laboratories (see Section V–C, Footnotes and References of Sections I through IV). For information regarding the importation, possession, or use of these agents see Sections V–G and V–H, Footnotes and References of Sections I through IV.

Section II–B. Containment

Effective biological safety programs * * *

[Rest of Section II remains unchanged.]

B. Amendments to Section III, Experiments Covered by the NIH Guidelines

Section III–C is amended to read:

Section III–C. Experiments That Require Institutional Biosafety Committee Approval Before Initiation

Prior to the initiation of an experiment that falls into this category, the Principal Investigator must submit a registration document to the Institutional Biosafety Committee which contains the following information: (i) the source(s) of DNA; (ii) the nature of the inserted DNA sequences; (iii) the host(s) and vector(s) to be used; (iv) an indication of what protein will be produced if an attempt is to be made to obtain expression of a foreign gene; and (v) the containment conditions that will be implemented as specified in the NIH Guidelines. For experiments in this category, the registration document shall be dated, signed by the Principal Investigator, and filed with the Institutional Biosafety Committee. The Institutional Biosafety Committee shall review and approve all experiments in this category prior to their initiation. Requests to decrease the level of containment specified for experiments in this category will be considered by NIH (see Section IV–C–1–b–(2)–(c), Minor Actions).

Section III–C–1. Experiments Using Risk Group 2, Risk Group 3, Risk Group 4, or Restricted Agents as Host-Vector Systems (see Section II–A, Risk Assessment).

Section III–C–1–a. Experiments involving the introduction of recombinant DNA into Risk Group 2 agents will usually be conducted at Biosafety Level (BL) 2 containment. Experiments with such agents will usually be conducted with whole animals at BL2 or BL2–N (Animals) containment.

Section III–C–1–b. Experiments involving the introduction of recombinant DNA into Risk Group 3 agents will usually be conducted at BL3 containment. Experiments with such agents will usually be conducted with whole animals at BL3 or BL3–N containment.

Section III–C–1–c. Experiments involving the introduction of recombinant DNA into Risk Group 4 agents shall be conducted at BL4 containment. Experiments with such agents will usually be conducted with whole animals at BL4 or BL4–N containment.

Section III–C–1–d. Containment conditions for experiments involving the introduction of recombinant DNA into restricted agents shall be set on a case-by-case basis following NIH/ORDA review. A U.S. Department of Agriculture permit is required for work with plant or animal pathogens (see Section V–G and V–L, Footnotes and References of Sections I through IV). Experiments with such agents shall be conducted with whole animals at BL4 or BL4–N containment.

Section III–C–2. Experiments in which DNA From Risk Group 2, Risk Group 3, Risk Group 4, or Restricted Agents (see Section V–A, Footnotes and References of Sections I through IV) is Cloned into Nonpathogenic Prokaryotic or Lower Eukaryotic Host-Vector Systems.

Section III–C–2–a. Experiments in which DNA from Risk Group 2 or Risk Group 3 agents (see Section II–A, Risk Assessment) is transferred into nonpathogenic prokaryotes or lower eukaryotes may be performed under BL2 containment. Experiments in which DNA from Risk Group 4 agents is transferred into nonpathogenic prokaryotes or lower eukaryotes may be performed under BL2 containment after demonstration that only a totally and irreversibly defective fraction of the agent's genome is present in a given recombinant. In the absence of such a demonstration, BL4 containment shall be used. The Institutional Biosafety Committee may approve the specific lowering of containment for particular experiments to BL1. Many experiments in this category are exempt from the NIH Guidelines (see Section III–E, Exempt Experiments). Experiments involving the formation of recombinant DNA for certain genes coding for molecules toxic for vertebrates require NIH/ORDA approval (see Section III–B–1, Experiments Involving the Cloning of Toxin Molecules With LD_{50} of Less than 100 Nanograms Per Kilogram Body Weight) or shall be conducted under NIH specified conditions as described in Appendix F, Containment Conditions for Cloning of Genes Coding for the Biosynthesis of Molecules Toxic for Vertebrates.

Section III–C–2–b. Containment conditions for experiments in which DNA from restricted agents is transferred into nonpathogenic prokaryotes or lower eukaryotes shall be determined by NIH/ORDA following a case-by-case review (see Section V–L, Footnotes and References of Sections I through IV). A U.S. Department of Agriculture permit is required for work with plant or animal pathogens (see Section V–G, Footnotes and References of Sections I through IV).

Section III–C–3. Experiments Involving the Use of Infectious DNA or RNA Viruses or Defective DNA or RNA Viruses in the Presence of Helper Virus in Tissue Culture Systems.

Caution: Special care should be used in the evaluation of containment levels for experiments which are likely to either enhance the pathogenicity (e.g., insertion of a host oncogene) or to extend the host range (e.g., introduction of novel control elements) of viral vectors under conditions that permit a productive infection. In such cases, serious consideration should be given to increasing physical containment by at least one level.

Note: Recombinant DNA or RNA molecules derived therefrom, which contain less than two-thirds of the genome of any eukaryotic virus (all viruses from a single Family) (See Section V–J, Footnotes and References of Sections I through IV) being considered identical (see Section V–K, Footnotes and References of Sections I through IV), are considered defective and may be used in the absence of helper virus under the conditions specified in Section III–D–1, Experiments Involving the Formation of Recombinant DNA Molecules Containing No More than Two-Thirds of the Genome of any Eukaryotic Virus.

Section III–C–3–a. Experiments involving the use of infectious or defective Risk Group 2 viruses (see Section V–A, Footnotes and References of Sections I through IV, and Appendix B–II, Risk Group 2 Agents) in the presence of helper virus may be conducted at BL2.

Section III–C–3–b. Experiments involving the use of infectious or defective Risk Group 3 viruses (see Section V–A, Footnotes and References of Sections I through IV, and Appendix B–III–D, Risk Group 3 (RG3)—Viruses and Prions) in the presence of helper virus may be conducted at BL3.

Section III–C–3–c. Experiments involving the use of infectious or defective Risk Group 4 viruses (see Section V–A, Footnotes and References of Sections I through IV, and Appendix B–IV–D, Risk Group 4 (RG4)—Viral Agents) in the presence of helper virus may be conducted at BL4.

Section III–C–3–d. Experiments involving the use of infectious or defective restricted poxviruses (see Section V–A and V–L, Footnotes and References of Sections I through IV) in the presence of helper virus shall be determined on a case-by-case basis following NIH/ORDA review. A U.S.

Department of Agriculture permit is required for work with plant or animal pathogens (see Section V–G, Footnotes and References of Sections I through IV).

Section III–C–3–e. Experiments involving the use of infectious or defective viruses in the presence of helper virus which are not covered in Sections III–E–3–a through III–C–3–d may be conducted at BL1.

Section III–C–4. Experiments Involving Whole Animals.

This section covers experiments involving whole animals in which the animal's genome has been altered by stable introduction of recombinant DNA, or DNA derived therefrom, into the germ-like (transgenic animals) and experiments involving viable recombinant DNA-modified microorganisms tested on whole animals. For the latter, other than viruses which are only vertically transmitted, the experiments may not be conducted at BL1–N containment. A minimum containment of BL2 or BL2–N is required.

Caution—Special care should be used in the evaluation of containment conditions for some experiments with transgenic animals. For example, such experiments might lead to the creation of novel mechanisms or increased transmission of a recombinant pathogen or production of undesirable traits in the host animal. In such cases, serious consideration should be given to increasing the containment conditions.

Section III–C–4–a. Recombinant DNA, or DNA or RNA molecules derived therefrom, from any source except for greater than two-thirds of eukaryotic viral genome may be transferred to any nonhuman vertebrate or any invertebrate organism and propagated under conditions of physical containment comparable to BL1 or BL1–N and appropriate to the organism under study (see Section V–B, Footnotes and References of Sections I through IV). Animals that contain sequences from viral vectors, which do not lead to transmissible infection either directly or indirectly as a result of complementation or recombination in animals, may be propagated under conditions of physical containment comparable to BL1 or BL1–N and appropriate to the organism under study. Experiments involving the introduction of other sequences from eukaryotic viral genomes into animals are covered under Section III–C–4–b, Experiments Involving Whole Animals. For experiments involving recombinant DNA-modified Risk Groups, 2, 3, 4, or restricted organisms, see Sections V–A, V–G, and V–L, Footnotes and References of Sections I through IV. It is important that the investigator demonstrate that the fraction of the viral genome being utilized does not lead to productive infections. A U.S. Department of Agriculture permit is required for work with plant or animal pathogens (see Section V–G, Footnotes and References of Sections I through IV).

Section III–C–4–b. For experiments involving recombinant DNA, or DNA or RNA derived therefrom, involving whole animals, including transgenic animals, and not covered by Sections III–C–1, Experiments Using Risk Group 2, Risk Group 3, Risk Group 4, or Restricted Agents as Host-Vector Systems, or III–C–4–a, Experiments Involving Whole Animals, the appropriate containment shall be determined by the Institutional Biosafety Committee.

[The rest of the Section III–C remains unchanged.]

C. Amendments to Section IV, Roles and Responsibilities

Section IV–C–1–b–(2)–(e) is amended to read:

Section IV–C–1–b–(2)–(e). Setting containment under Sections III–C–1–d, Experiments Using Risk Group 2, Risk Group 3, Risk Group 4, or Restricted Agents as Host-Vector Systems, and III–C–2–b, Experiments in which DNA from Risk Group 2, Risk Group 3, Risk Group 4, or Restricted Agents is Cloned into Nonpathogenic Prokaryotic or Lower Eukaryotic Host-Vector Systems;

[The rest of the Section IV–C–1–b–(2) remains unchanged.]

D. Amendments to Section V, Footnotes and References of Sections I Through IV

Section V is amended to read:

Section V. Footnotes and References of Sections I through IV

Section V–A. The NIH Director, with advice of the RAC, may revise the classification for the purposes of the NIH Guidelines (see Section IV–C–1–b–(2)–(e), Minor Actions). The revised list of organisms in each risk group is reprinted in Appendix B, Classification of Human Etiologic Agents on the Basis of Hazard.

Section V–B. Section III, Experiments Covered by the NIH Guidelines, describes a number of places where judgments are to be made. In all these cases, the Principal Investigator shall make the judgment on these matters as part of his/her responsibility to ''make the initial determination of the required levels of physical and biological containment in accordance with the NIH Guidelines'' (see Section IV–B–4–c–(1), Principal Investigator). For cases falling under Sections III–A through III–D, Experiments Covered by the NIH Guidelines, this judgment is to be reviewed and approved by the Institutional Biosafety Committee as part of its responsibility to make an ''independent assessment of the containment levels required by the NIH Guidelines for the proposed research'' (see Section IV–B–2–b–(1), Institutional Biosafety Committee). The Institutional Biosafety Committee may refer specific cases to NIH/ORDA as part of NIH/ORDA's functions to ''provide advice to all within and outside NIH'' (see Section IV–C–3, Office of Recombinant DNA Activities). NIH/ORDA may request advice from the RAC as part of the RAC's responsibility for ''interpreting the NIH Guidelines for experiments to which the NIH Guidelines do not specifically assign containment levels'' (see Section IV–C–1–b–(2)–(f), Minor Actions).

Section V–C. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention and the National Institutes of Health. Biosafety in Microbiological and Biomedical Laboratories, 3rd edition, 1993. Copies are available from: Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402 (stock # 017–040–00523–7), Phone (202)–512–2356.

Section V–D. Classification of Etiologic Agents on the Basis of Hazard, 4th Edition, July 1974, U.S. Department of Health, Education, and Welfare, Public Health Service, Centers for Disease Control, Office of Biosafety, Atlanta, Georgia 30333.

Section V–E. Benenson, Abram S. ed., Control of Communicable Diseases in Man, 15th edition. 1990. American Public Health Association, Washington, DC.

Section V–F. World Health Organization Laboratory Biosafety Manual, 2nd edition. 1993. WHO Albany, NY. Copies are available from: WHO Publication Centre, USA, (Q Corp) 49 Sheridan Avenue, Albany, New York 12210; Phone: (518)–436–9686 (Order # 1152213).

Section V–G. A U.S. Department of Agriculture permit, required for import and interstate transport of plant and animal pathogens, may be obtained from the U.S. Department of Agriculture, ATTN: Animal and Plant Health Inspection Service (APHIS), Veterinary Services, National Center for Import-Export, Products Program, 4700 River Road, Unit 40, Riverdale, MD 20737. Phone: (301)–734–8499; Fax: (301)–734–8226.

Section V–H. American Type Culture Collection Catalogues of plant viruses, animal viruses, cells, bacteria, fungi, etc. are available from American Type Culture Collection, 12301 Parklawn Drive, Rockville, Maryland 20852–1776. Phone: (800)–638–6597; Fax: (301)–231–5826.

Section V–I. U.S. Department of Labor, Occupational Safety and Health Administration. 1991. Occupational Exposure to Bloodborne Pathogens, Final Rule (56 FR 64175–64182).

Section V–J. As classified in the 6th Report on the International Committee on Taxonomy of Viruses: Classification and Nomenclature of Viruses, F.A. Murphy et al., Archives of Virology/ Supplement 10, 1995, Springer-Verlag, New York, New York.

Section V–K. i.e., the total of all genomes within a family shall not exceed two-thirds of the genome.

Section V–L. Organisms including alastrim, smallpox (variola) and whitepox may not be studied in the United States except at specified facilities. All activities, including storage of variola and whitepox, are restricted to the single national facility (World Health Organization Collaborating Center for Smallpox Research, Centers for Disease Control and Prevention, Atlanta, Georgia).

Section V–M. In accordance with accepted scientific and regulatory practices of the discipline of plant pathology, an exotic plant pathogen (e.g., virus, bacteria, or fungus) is one that is unknown to occur within the U.S. (see Section V–G, Footnotes and References of Sections I through IV). Determination of whether a pathogen has a potential for serious detrimental impact on managed (agricultural, forest, grassland) or natural ecosystems should be made by the Principal Investigator and the Institutional Biosafety Committee, in consultation with scientists knowledgeable of plant diseases, crops, and ecosystems in the geographic area of the research.

E. Amendments to Appendix B, Classification of Human Etiologic Agents on the Basis of Hazard

Appendix B is amended to read:

Appendix B. Classification of Human Etiologic Agents on the Basis of Hazard

Appendix B includes those biological agents known to infect humans, as well as selected animal agents, that may pose theoretical risks if inoculated into humans. Included in the lists are species known to be pathogenic, mutated, or recombined; non-pathogenic species and strains are not considered. Non-infectious life cycle stages of parasites are excluded.

This appendix reflects the current state of knowledge and should be considered a resource document. The more commonly encountered agents are included; however, this appendix is not meant to be all inclusive. Information on agent risk assessment may be found in the Agent Summary Statements of the Centers for Disease Control and Prevention/National Institutes of Health publications, Biosafety in Microbiological and Biomedical Laboratories (see Sections V–C, V–D, V–E, and V–F, Footnotes and References of Sections I through IV). Further guidance on agents not listed in Appendix B may be obtained through: Centers for Disease Control and Prevention, Biosafety Branch, Atlanta, Georgia 30333, Phone: (404)–639–3883, Fax: (404)–639–2294; National Institutes of Health, Division of Safety, Bethesda, Maryland 20892, Phone: (301)–496–1357; National Animal Disease Center, U.S. Department of Agriculture, Ames, Iowa 50010, Phone: (515)–862–8258.

A special committee of the American Society for Microbiology will conduct an annual review of this appendix and its recommendation for changes will be presented to the Recombinant DNA Advisory Committee as proposed amendments to the NIH Guidelines.

Appendix B—Table 1.—Basis for the Classification of Biohazardous Agents by Risk Group (RG)

Risk Group 1 (RG1).	Agents that are not associated with disease in healthy adult humans.
Risk Group 2 (RG2).	Agents that are associated with human disease which is rarely serious and for which preventive or therapeutic interventions are often available.
Risk Group 3 (RG3).	Agents that are associated with serious or lethal disease for which preventive or therapeutic interventions may be available (high individual risk but low community risk).
Risk Group 4 (RG4).	Agents that are likely to cause serious or lethal human disease for which preventive or therapeutic interventions are not usually available (high individual risk and high community risk).

Appendix B–I. Risk Group 1 (RG1) Agents

RG1 agents are not associated with disease in healthy adult humans. Examples of RG1 agents include asporogenic *Bacillus subtilis* or *Bacillus licheniformis* (see Appendix C–IV–A, *Bacillus subtilis* or *Bacillus licheniformis Host-Vector Systems, Exceptions), Eschenrichia coli*-K12 (see Appendix C–II–A, *Escherichia coli K–12 Host-Vector Systems, Exceptions),* and adeno-associated virus types 1–4.

Those agents not listed in Risk Groups (RGs) 2, 3 and 4 are not automatically or implicitly classified in RG1; a risk assessment must be conducted based on the known and potential properties of the agents and their relationship to agents that are listed.

Appendix B–II. Risk Group 2 (RG2) Agents

RG2 agents are associated with human disease which is rarely serious and for which preventive or therapeutic interventions are often available.

Appendix B–II–A. Risk Group 2 (RG2)—Bacterial Agents Including Chlamydia

—*Acinetobacter baumannii* (formerly *Acinetobacter calcoaceticus*)
—*Actinobacillus*
—*Actinomyces pyogenes* (formerly *Corynebacterium pyogenes*)
—*Aeromonas hydrophila*
—*Amycolata autotrophica*
—*Archanobacterium haemolyticum* (formerly *Corynebacterium haemolyticum*)
—*Arizona hinshawii*—all serotypes
—*Bacillus anthracis*
—*Bartonella henselae, B. quintana, B. vinsonii*
—*Bordetella including B. pertussis*
—*Borrelia recurrentis, B. burgdorferi*
—*Burkholderia* (formerly *Pseudomonas* species) except those listed in Appendix B–III–A (RG3))
—*Campylobacter coli, C. fetus, C. jejuni*
—*Chlamydia psittaci, C. trachomatis, C. pneumoniae*
—*Clostridium botulinum, Cl. chauvoei, Cl. haemolyticum, Cl. histolyticum, Cl. novyi, Cl. septicum, Cl. tetani*
—*Corynebacterium diphtheriae, C. pseudotuberculosis, C. renale*
—*Dermatophilus congolensis*
—*Edwardsiella tarda*
—*Erysipelothrix rhusiopathiae*
—*Escherichia coli*—all enteropathogenic, enterotoxigenic, enteroinvasive and strains bearing K1 antigen, including *E. coli* O157:H7
—*Haemophilus ducreyi, H. influenzae*
—*Helicobacter pylori*
—*Klebsiella*—all species except *K. oxytoca* (RG1)
—*Legionella* including *L. pneumophila*
—*Leptospira interrogans*—all serotypes
—*Listeria*
—*Moraxella*
—*Mycobacterium* (except those listed in Appendix B–III–A (RG3)) including *M. avium* complex, *M. asiaticum, M. bovis* BCG vaccine strain, *M. chelonei,*

M. fortuitum, M. kansasii, M. leprae, M. malmoense, M. marinum, M. paratuberculosis, M. scrofulaceum, M. simiae, M. szulgai, M. ulcerans, M. xenopi
—*Mycoplasma,* except *M. mycoides* and *M. agalactiae* which are restricted animal pathogens
—*Neisseria gonorrhoea, N. meningitidis*
—*Nocardia asteroides, N. brasiliensis, N. otitidiscaviarum, N. transvalensis*
—*Rhodococcus equi*
—*Salmonella* including *S. arizonae, S. cholerasuis, S. enteritidis, S. gallinarum-pullorum, S. meleagridis, S. paratyphi,* A, B, C, *S. typhi, S. typhimurium*
—*Shigella* including *S. boydii, S. dysenteriae,* type 1, *S. flexneri, S. sonnei*
—*Sphaerophorus necrophorus*
—*Staphylococcus aureus*
—*Streptobacillus moniliformis*
—*Streptococcus* including *S. pneumoniae, S. pyogenes*
—*Treponema pallidum, T. carateum*
—*Vibrio cholerae, V. parahemolyticus, V. vulnificus*
—*Yersinia enterocolitica*

Appendix B–II–B. Risk Group 2 (RG2)—Fungal Agents

—*Blastomyces dematitidis*
—*Cladosporium bantianum, C. (xylohypha) trichoides*
—*Cryptococcus neofomans*
—*Dactylaria galopava (Ochroconis gallopavum)*
—*Epidermophyton*
—*Exophiala (Wangiella) dermatitidis*
—*Fonsecaea pedrosoi*
—*Microsporum*
—*Paracoccidioides braziliensis*
—*Penicillium marneffei*
—*Sporothrix schenckii*
—*Trichophyton*

Appendix B–II–C. Risk Group 2 (RG2)—Parasitic Agents

—*Ancylostoma* human hookworms including *A. duodenale, A. ceylanicum*
—*Ascaris* including *Ascaris lumbricoides suum*
—*Babesia* including *B. divergens, B. microti*
—*Brugia* filaria worms including *B. malayi, B. timori*
—*Coccidia*
—*Cryptosporidium* including *C. parvum*
—*Cysticercus cellulosae* (hydatid cyst, larva of *T. solium*)
—*Echinococcus* including *E. granulosis, E. multilocularis, E. vogeli*
—*Entamoeba histolytica*
—*Enterobius*
—*Fasciola* including *F. gigantica, F. hepatica*
—*Giardia* including *G. lamblia*
—*Heterophyes*
—*Hymenolepis* including *H. diminuta, H. nana*
—*Isospora*
—*Leishmania* including *L. braziliensis, L. donovani, L. ethiopia, L. major, L. mexicana, L. peruvania, L. tropica*
—*Loa loa* filaria worms
—*Microsporidium*
—*Naegleria fowleri*
—*Necator* human hookworms including *N. americanus*
—*Onchoerca* filaria worms including, *O. volvulus*
—*Plasmodium* including simian species, *P. cynomologi, P. falciparum, P. malariae, P. ovale, P. vivax*
—*Sarcocystis* including *S. sui hominis*
—*Schistosoma* including *S. haematobium, S. intercalatum, S. japonicum, S. mansoni, S. mekongi*
—*Strongyloides* including *S. stercoralis*
—*Taenia solium*
—*Toxocara* including *T. canis*
—*Toxoplasma* including *T. gondii*
—*Trichinella spiralis*
—*Trypanosoma* including *T. brucei brucei, T. brucie gambiense, T. brucei rhodesiense, T. cruzi*
—*Wuchereria bancrofti* filaria worms

Appendix B–II–D. Risk Group 2 (RG2)—Viruses

Adenoviruses, Human—All Types

Alphaviruses (Togaviruses)—Group A Arboviruses

—Eastern equine encephalomyelitis virus
—Venezuelan equine encephalomyelitis vaccine strain TC–83
—Western equine encephalomyelitis virus

Arenaviruses

—Lymphocytic choriomeningitis virus (non-neurotropic strains)
—Tacaribe virus complex
—Other viruses as listed in the reference source (see Section V–C, Footnotes and References of Sections I through IV)

Bunyaviruses

—Bunyamwera virus
—Rift Valley fever virus vaccine strain MP–12
—Other viruses as listed in the reference source (see Section V–C, Footnotes and References of Sections I through IV)

Calciviruses

Coronaviruses

Flaviviruses (Togaviruses)—Group B Arboviruses

—Dengue virus serotypes 1, 2, 3, and 4
—Yellow fever virus vaccine strain 17D
—Other viruses as listed in the reference source (see Section V–C, Footnotes and References of Sections I through IV)

Hepatitis A, B, C, D, and E Viruses

—Herpesviruses—except Herpesvirus simiae (Monkey B virus) (see Appendix B–IV–D, Risk Group 4 (RG4)—Viral Agents)
—Cytomegalovirus
—Epstein Barr virus
—*Herpes simplex* types 1 and 2
—*Herpes zoster*
—Human herpesvirus types 6 and 7

Orthomyxoviruses

—Influenza viruses types A, B, and C
—Other tick-borne orthomyxoviruses as listed in the reference source (see Section V–C, Footnotes and References of Sections I through IV)

Papovaviruses

—All human papilloma viruses

Paramyxoviruses

—Newcastle disease virus
—Measles virus
—Mumps virus
—Parainfluenza viruses types 1, 2, 3, and 4
—Respiratory syncytial virus

Parvoviruses

—Human parvovirus (B19)

Picornaviruses

—Coxsackie viruses types A and B
—Echoviruses—all types
—Polioviruses—all types, wild and attenuated
—Rhinoviruses—all types
—Poxviruses—all types except Monkeypox virus (see Appendix B–III–D, Risk Group 3 (RG3)—Viruses and Prions) and restricted poxviruses including Alastrim, Smallpox, and White-pox (see Section V–L, Footnotes and References of Sections I through IV)
—Reoviruses—all types including Coltivirus, human Rotavirus, and Orbivirus (Colorado tick fever virus)

Rhabdoviruses

—Rabies virus—all strains
—Vesicular stomatitis virus—laboratory adapted strains including VSV-Indiana, San Juan, and Glasgow

Togaviruses (see Alphaviruses and Flaviviruses)

—Rubivirus (rubella)

Appendix B–III. Risk Group 3 (RG3) Agents

RG3 agents are associated with serious or lethal human disease for which preventive or therapeutic interventions may be available.

Appendix B–III–A. Risk Group 3 (RG3)—Bacterial Agents Including Rickettsia

—*Bartonella*
—*Brucella* including *B. abortus, B. canis, B. suis*
—*Burkholderia (Pseudomonas) mallei, B. pseudomallei*
—*Coxiella burnetii*
—*Francisella tularensis*
—*Mycobacterium bovis* (except BCG strain, see Appendix B–II–A, Risk Group 2 (RG2)—Bacterial Agents Including *Chlamydia*); M. tuberculosis
—*Pasteurella multocida* type B—''buffalo'' and other virulent strains
—*Rickettsia akari, R. australis, R. canada, R. conorii, R. prowazekii, R. rickettsii, R. siberica, R. tsutsugamushi, R. typhi (R. mooseri)*
—*Yersinia pestis*

Appendix B–III–B. Risk Group 3 (RG3)—Fungal Agents

—*Coccidioides immitis* (sporulating cultures; contaminated soil)
—*Histoplasma capsulatum, H. capsulatum var. duboisii*

Appendix B–III–C. Risk Group 3 (RG3)—Parasitic Agents

None

Appendix B–III–D. Risk Group 3 (RG3)—Viruses and Prions

Alphaviruses (Togaviruses)—Group A Arboviruses

—Semliki Forest virus
—St. Louis encephalitis virus
—Venezuelan equine encephalomyelitis virus (except the vaccine strain TC–83, see Appendix B–II–D, Risk Group 2 (RG2)—Viruses)
—Other viruses as listed in the reference source (see Section V–C, Footnotes and References of Sections I through IV)

Arenaviruses

—Lymphocytic choriomeningitis virus (LCM) (neurotropic strains)

Bunyaviruses

—Hantaviruses including Hantaan virus
—Rift Valley fever virus

Flaviviruses (Togaviruses)—Group B Arboviruses

—Japanese encephalitis virus
—Yellow fever virus
—Other viruses as listed in the reference source (see Section V–C, Footnotes and References of Sections I through IV)

Poxviruses

—Monkeypox virus

Prions

—Transmissible spongioform encephalopathies (TME) agents (Creutzfeldt-Jakob disease and kuru agents) (for containment instruction, see Section V–C, Footnotes and References of Sections I through IV)

Retroviruses

—Human immunodeficiency virus (HIV) types 1 and 2
—Human T cell lymphotropic virus (HTLV) types 1 and 2
—Simian immunodeficiency virus (SIV)

Rhabdoviruses

—Vesicular stomatitis virus

Appendix B–IV. Risk Group 4 (RG4) Agents

RG4 agents are likely to cause serious or lethal human disease for which preventive or therapeutic interventions are not usually available.

Appendix B–IV–A. Risk Group 4 (RG4)—Bacterial Agents

None

Appendix B–IV–B. Risk Group 4 (RG4)—Fungal Agents

None

Appendix B–IV–C. Risk Group 4 (RG4)—Parasitic Agents

None

Appendix B–IV–D. Risk Group 4 (RG4)—Viral Agents

Arenaviruses (Togaviruses)—Group A Arboviruses

—Guanarito virus
—Lassa virus
—Junin virus
—Machupo virus

Bunyaviruses (Nairovirus)

—Crimean-Congo hemorrhagic fever virus

Filoviruses

—Ebola virus
—Marburg virus

Flaviviruses (Togaviruses)—Group B Arboviruses

—Tick-borne encephalitis virus complex including Absetterov, Central European encephalitis, Hanzalova, Hypr, Kumlinge, Kyasanur Forest disease, Omsk hemorrhagic fever, and Russian spring-summer encephalitis viruses

Herpesviruses (alpha)

—Herpesvirus simiae (Herpes B or Monkey B virus)

Hemorrhagic fever agents and viruses as yet undefined.

Appendix B–V. Animal Viral Etiologic Agents in Common Use

The following list of animal etiologic agents is appended to the list of human etiologic agents. None of these agents is associated with disease in healthy adult humans; They are commonly used in laboratory experimental work.

A containment level appropriate for RG1 human agents is recommended for their use. For agents that are infectious to human cells, e.g., amphotropic and xenotropic strains of murine leukemia virus, a containment level appropriate for RG2 human agents is recommended.

Baculoviruses

Herpesviruses

—Herpesvirus ateles
—Herpesvirus saimiri
—Marek's disease virus
—Murine cytomegalovirus

Papovaviruses

—Bovine papilloma virus
—Polyoma virus
—Shope papilloma virus
—Simian virus 40 (SV40)

Retroviruses

—Avian leukosis virus
—Avian sarcoma virus
—Bovine leukemia virus
—Feline leukemia virus
—Feline sarcoma virus
—Gibbon leukemia virus
—Mason-Pfizer monkey virus
—Mouse mammary tumor virus
—Murine leukemia virus
—Murine sarcoma virus
—Rat leukemia virus

F. Amendments to Appendix C, Exemptions Under Section III–E–6

Appendix C–I–A is amended to read:

Appendix C–I–A. Exceptions

The following categories are not exempt from the NIH Guidelines: (i) experiments described in Section III–A which require Institutional Biosafety Committee approval, RAC review, and NIH Director approval before initiation, (ii) experiments described in Section III–B which require NIH/ORDA and Institutional Biosafety Committee approval before initiation, (iii) experiments involving DNA from Risk Groups 3, 4, or restricted organisms (see Appendix B, Classification of Human Etiologic Agents on the Basis of Hazard, and Sections V–G and V–L, Footnotes and References of Sections I through IV) or cells known to be infected with these agents, (iv) experiments involving the deliberate introduction of genes coding for the biosynthesis of molecules that are toxic for vertebrates (see Appendix

F, Containment Conditions for Cloning of Genes Coding for the Biosynthesis of Molecules Toxic for Vertebrates), and (v) whole plants regenerated from plant cells and tissue cultures are covered by the exemption provided they remain axenic cultures even though they differentiate into embryonic tissue and regenerate into plantlets.

Appendix C–II–A is amended to read:

Appendix C–II–A. Exceptions

The following categories are not exempt from the NIH Guidelines: (i) experiments described in Section III–A which require Institutional Biosafety Committee approval, RAC review, and NIH Director approval before initiation, (ii) experiments described in Section III–B which require NIH/ORDA and Institutional Biosafety Committee approval before initiation, (iii) experiments involving DNA from Risk Groups 3, 4, or restricted organisms (see Appendix B, Classification of Human Etiologic Agents on the Basis of Hazard, and Sections V–G and V–L, Footnotes and References of Sections I through IV) or cells known to be infected with these agents, may be conducted under containment conditions specified in Section III–C–2, Experiments in which DNA from Risk Group 2, Risk Group 3, Risk Group 4, or Restricted Agents is Cloned into Nonpathogenic Prokaryotic or Lower Eukaryotic Host-Vector Systems, with prior Institutional Biosafety Committee review and approval, (iv) large scale experiments (e.g., more than 10 liters of culture), and (v) experiments involving the cloning of toxin molecule genes coding for the biosynthesis of molecules toxic for vertebrates (see Appendix F, Containment Conditions for Cloning of Genes Coding for the Biosynthesis of Molecules Toxic for Vertebrates).

Appendix C–III–A is amended to read:

Appendix C–III–A. Exceptions

The following categories are not exempt from the NIH Guidelines: (i) experiments described in Section III–A which require Institutional Biosafety Committee approval, RAC review, and NIH Director approval before initiation, (ii) experiments described in Section III–B which require NIH/ORDA and Institutional Biosafety Committee approval before initiation, (iii) experiments involving DNA from Risk Groups 3, 4, or restricted organisms (see Appendix B, Classification of Human Etiologic Agents on the Basis of Hazard, and Sections V–G and V–L, Footnotes and References of Sections I through IV) or cells known to be infected with these agents, may be conducted under containment conditions specified in Section III–C–2, Experiments in which DNA from Risk Group 2, Risk Group 3, Risk Group 4, or Restricted Agents is Cloned into Nonpathogenic Prokaryotic or Lower Eukaryotic Host-Vector Systems, with prior Institutional Biosafety Committee review and approval, (iv) large scale experiments (e.g., more than 10 liters of culture), and (v) experiments involving the deliberate cloning of genes coding for the biosynthesis of molecules toxic for vertebrates (see Appendix F, Containment Conditions for Cloning of Genes Coding for the Biosynthesis of Molecules Toxic for Vertebrates).

Appendix C–IV–A is amended to read:

Appendix C–IV–A. Exceptions

The following categories are not exempt from the NIH Guidelines: (i) experiments described in Section III–A which require Institutional Biosafety Committee approval, RAC review, and NIH Director approval before initiation, (ii) experiments described in Section III–B which require NIH/ORDA and Institutional Biosafety Committee approval before initiation, (iii) experiments involving DNA from Risk Groups 3, 4, or restricted organisms (see Appendix B, Classification of Human Etiologic Agents on the Basis of Hazard, and Sections V–G and V–L, Footnotes and References of Sections I through IV) or cells known to be infected with these agents, may be conducted under containment conditions specified in Section III–C–2, Experiments in which DNA from Risk Group 2, Risk Group 3, Risk Group 4, or Restricted Agents is Cloned into Nonpathogenic Prokaryotic or Lower Eukaryotic Host-Vector Systems, with prior Institutional Biosafety Committee review and approval, (iv) large scale experiments (e.g., more than 10 liters of culture), and (v) experiments involving the deliberate cloning of genes coding for the biosynthesis of molecules toxic for vertebrates (see Appendix F, Containment Conditions for Cloning of Genes Coding for the Biosynthesis of Molecules Toxic for Vertebrates).

Appendix C–V–A is amended to read:

Appendix C–V–A. Exceptions

The following categories are not exempt from the NIH Guidelines: (i) experiments described in Section III–A which require Institutional Biosafety Committee approval, RAC review, and NIH Director approval before initiation, (ii) experiments described in Section III–B which require NIH/ORDA and Institutional Biosafety Committee approval before initiation, (iii) experiments involving DNA from Risk Groups 3, 4, or restricted organisms (see Appendix B, Classification of Human Etiologic Agents on the Basis of Hazard, and Sections V–G and V–L, Footnotes and References of Sections I through IV) or cells known to be infected with these agents, may be conducted under containment conditions specified in Section III–C–2, Experiments in which DNA from Risk Group 2, Risk Group 3, Risk Group 4, or Restricted Agents is Cloned into Nonpathogenic Prokaryotic or Lower Eukaryotic Host-Vector Systems, with prior Institutional Biosafety Committee review and approval, (iv) large scale experiments (e.g., more than 10 liters of culture), and (v) experiments involving the deliberate cloning of genes coding for the biosynthesis of molecules toxic for vertebrates (see Appendix F, Containment Conditions for Cloning of Genes Coding for the Biosynthesis of Molecules Toxic for Vertebrates).

Appendix C–VI is amended to read:

Appendix C–VI. Footnotes and References of Appendix C

Appencix C–VI–A. The NIH Director, with advice of the RAC, may revise the Appendix B classification for the purposes of these NIH Guidelines (see Section IV–C–1–b–(2)–(b), NIH Director-Specific Responsibilities). The revised list of organisms in each Risk Group is reprinted in Appendix B.

G. Amendments to Appendix H, Shipment

Appendix H–III is amended to read:

Appendix H–III. Footnotes and References of Appendix H

For further information on shipping etiologic agents contact: (i) The Centers for Disease Control and Prevention, ATTN: Biohazards Control Office, 1600 Clifton Road, Atlanta, Georgia 30333, (404) 639–3883, FTS 236–3883; (ii) The U.S. Department of Transportation, ATTN: Office of Hazardous Materials Transportation, 400 7th Street SW., Washington, DC 20590, (202) 366–4545; or (iii) U.S. Department of Agriculture, ATTN: Animal and Plant Health Inspection Service (APHIS), Veterinary Services, National Center for Import-Export, Products Program, 4700 River Road, Unit 40, Riverdale, MD 20737. Phone: (301) 734–8499; Fax: (301) 734–8226.

H. Amendments to Appendix Q, Physical and Biological Containment for Recombinant DNA Research Involving Animals

Appendix Q–III–C is amended to read:

Appendix Q–III–C. Risk Group 4 and restricted microorganisms (see Appendix B, Classification of Human Etiologic Agents on the Basis of Hazard, and Sections V–G and V–L, Footnotes and References of Sections I through IV) pose a high level of individual risk for acquiring life-threatening diseases to personnel and/or animals. To import animal or plant pathogens, special approval must be obtained from U.S. Department of Agriculture, Animal and Plant Health Inspection Service (APHIS), Veterinary Services, National Center for Import-Export, Products Program, 4700 River Road, Unit 40, Riverdale, MD 20737. Phone: (301) 734–8499; Fax: (301) 734–8226.

Laboratory staff shall be required to have specific and thorough training in handling extremely hazardous infectious agents, primary and secondary containment, standard and special practices, and laboratory design characteristics. The laboratory staff shall be supervised by knowledgeable scientists who are trained and experienced in working with these agents and in the special containment facilities.

Within work areas of the animal facility, all activities shall be confined to the specially equipped animal rooms or support areas. The maximum animal containment area and support areas shall have special engineering and design features to prevent the dissemination of microorganisms into the environment via exhaust air or waste disposal.

OMB's ''Mandatory Information Requirements for Federal Assistance Program Announcements'' (45 FR 39592, June 11, 1980) requires a statement concerning the official government programs contained in the Catalog of Federal Domestic Assistance. Normally, NIH lists in its announcements the number and title of affected individual programs for the guidance of the public. Because the guidance in this notice covers not only virtually every NIH program but also essentially every Federal research program in which DNA recombinant molecule techniques could be used, it has been determined not to be cost effective or in the public interest to attempt to list these programs. Such a list would likely require several additional pages. In addition, NIH could not be certain that every Federal program would be included as many Federal agencies, as well as private organizations, both national and international, have elected to follow the NIH Guidelines. In lieu of the individual program listing, NIH invites readers to direct questions to the information address above about whether individual programs listed in the Catalog of Federal Domestic Assistance are affected.

Effective Date: December 14, 1995.

Harold Varmus,

Director, National Institutes of Health.

[FR Doc. 96–689 Filed 1–18–96; 8:45 am]

BILLING CODE 4140–01–M