Based on the following considerations, EPA has decided that inter-generic combinations (combinations from source organisms of different genera) but not intra-generic combinations (source organisms from the same genus) are sufficiently likely to result in new combinations of traits that they should be given special attention. First, combinations of genetic material from microorganisms from different genera are more likely to result in new traits than combinations of genes from microorganisms within the same genus. Also, while genetic exchange occurs naturally and somewhat commonly among many microorganisms, it is more likely to occur in nature within a single genus than across many different genera (Refs. 2, 12, 13). Finally, genus designations provide a practical criterion for administrative and regulatory purposes.

The Agency has decided to exclude certain combinations from special consideration as inter-generic organisms. Excluded are inter-generic combinations in which the genetic material added to the recipient microorganism consists only of well-characterized, non-coding regulatory regions. The resulting organisms do not possess new combinations of traits; rather, they exhibit quantitative changes in preexisting traits. In addition, if experience or data indicate that certain other inter-generic combinations warrant exclusion, the Agency will use the appropriate statutory or policy mechanisms under FIFRA and TSCA

to waive certain requirements for reviewing them. For example, EPA is considering exempting from PMN review under TSCA those inter-generic combinations used only in physically contained systems.

Although EPA considers intra-generic combinations to be less likely to produce new combinations of traits than inter-generic combinations, the Agency realizes that science provides no absolute standard for such distinctions. Nevertheless, EPA believes the approach it has adopted is practical and facilitates the identification of those microorganisms that should be subject to special attention and also that should be considered "new" under TSCA. If experience reveals that intra-generic combinations that could cause adverse effects will be developed, the Agency will modify its policies to require review of these products.

Unit IV contains more detailed guidance for determining if a given microorganism is the result of an inter-generic combination. The determinations are based on taxonomic designations of organisms. The Agency is aware that microbial taxonomy is a dynamic and often controversial science (Refs. 4, 18) and that new information concerning microorganisms' properties and interrelationships will alter taxonomic designations. However, the Agency believes that its procedures can be sufficiently flexible to accommodate the developments that

will occur, and that there are many significant advantages to using taxonomic standards. These advantages are discussed in more detail in Unit IV.

b. Nonindigenous microorganisms. Another category of organisms that are likely to exhibit traits new to an environment is nonindigenous microorganisms. Application of nonindigenous microorganisms in the environment could pose a high degree of uncertainty with respect to their behavior. Experience shows that scientists cannot always accurately predict how such organisms will behave in their new environment (Ref. 15, 16). It can be difficult to predict whether a nonindigenous microorganism will be subject to the physical and biological control factors present in the environment where it is to be introduced. In a small number of cases, nonindigenous pathogens such as the chestnut blight fungus and the Dutch elm disease fungus have caused significant adverse effects. As a result, there exist today regulations that govern the intentional movement of some, but not all, nonindigenous species (e.g., the Plant Pest Act administered by USDA). EPA believes that nonindigenous microorganisms whose uses are covered by FIFRA should be subject to Agency review and evaluation before they are released in the environment, to minimize the uncertainties with respect to their behavior. However, EPA does recognize that small-scale use of certain nonindigenous microbial pesticides (i.e., pathogens) may

pose greater potential risk than others, and has accordingly adopted abbreviated review procedures for small-scale use of nonpathogenic nonindigenous microbial pesticides. Unit II addresses these issues, and Unit IV provides guidance on determining whether a microorganism is nonindigenous.

E. EXPLANATION OF JURISDICTION -- EPA AND USDA

Both EPA and USDA seek to assure the safety of microbial products and yet minimize impediments to intellectual and economic advances in biotechnology. Because some of the statutes the agencies administer entail overlapping responsibilities, the two agencies are eliminating duplicative requirements wherever possible and coordinating their reviews.

Where allowed by statute, EPA and USDA have sought to eliminate overlapping reviews altogether. This notice reflects many instances where this has been done. Where overlaps could not be avoided, the agencies have established mechanisms for coordinating their reviews. EPA and USDA will identify principal liaisons who will have the responsibility to share information, coordinate data requests, and keep one another informed of communications with submitters. Also, the agencies will form a coordinating committee to meet periodically and work out general coordination problems that may transcend specific reviews. Finally, the National Biological Impact Assessment Program that

has been established within USDA will provide a common resource of scientists available to both agencies to review procedures, protocols, and projects on an advisory basis.

Submitters are encouraged to contact either agency if they have jurisdictional questions, but general guidelines are described below.

First, inter-generic microorganisms containing genetic material from a pathogenic source organism must be reported to both agencies (definitions of "inter-generic" and "pathogen" may be found in Unit IV). In this case, statutory constraints make it necessary for both EPA and USDA to review the products because the microbes are potential "pests" subject to the Plant Pest Act, and they are "new" and therefore subject to TSCA premanufacture notification (or they are pesticides and subject to FIFRA notification). However, the agency reviews have somewhat different purposes, in that the EPA review is for a general use of an organism under TSCA or for use as a pesticide under FIFRA, while the USDA review is for a specific permit application. The agencies will coordinate these reviews as explained earlier.

Second, persons developing inter-generic organisms that contain no genetic material from a pathogen and that do not meet the USDA definition of a "plant pest" will be expected to report only to EPA; they will not report to USDA at all. EPA will inform USDA and the submitter if any data suggest that the organism has pest qualities which may require a permit from

USDA. This avoids unnecessary duplication of effort and is consistent with the non-discretionary responsibility under TSCA to review new organisms and under FIFRA to review pesticides.

Third, in the case of intra-generic engineered organisms that contain genetic material from a pathogen, the use of the organism will determine which agency reviews it. When used solely for non-pesticidal agricultural purposes, such organisms must be reported only to USDA under the Plant Pest Act. When used for non-agricultural purposes, such organisms should be reported to EPA, either voluntarily under the TSCA section 5(a)(2) rule EPA will be developing or, if the organisms is a pesticide, under FIFRA. In both cases, the microorganisms should also be reported to USDA as potential plant or animal pathogens. When such dual reporting is necessary, the agencies will assist the submitter by coordinating through the mechanisms described above.

In the case of intra-generic microbes containing no genetic material from pathogens and nonenginered microorganisms, EPA will gather general information under section 8(a) of TSCA and conduct abbreviated reviews under FIFRA (see Units II and III of the EPA notice). Both agencies agree that members of this category of microbes, in general, present the lowest risk and therefore do not need a high level of scrutiny before any release into the environment. However, the FIFRA abbreviated reviews and the TSCA section 8(a) reporting will ensure that both agencies are aware

of environmental releases of these organisms and can take appropriate action when necessary.

F. EPA BIOTECHNOLOGY SCIENCE ADVISORY COMMITTEE

EPA is establishing a Science Advisory Committee for biotechnology. The formation of this committee is consistent with intentions stated in two FEDERAL REGISTER notices issued by the Office of Science and Technology Policy (50 FR 47174, November 14, 1985 and 49 FR 50904 December 31, 1984). The committee's primary functions will be to provide peer review of specific product submissions under TSCA, FIFRA, and other EPA statutes and scientific oversight of the Agency's biotechnology programs.

The committee will consist of independent scientists and members of the lay public. It will be of sufficient size and diversity to provide the range of expertise required to assess the scientific and technical issues pertinent to its responsibilities. The committee will be supplemented by consultants when they are needed to extend the range of expertise of the standing committee, and will be authorized to form subcommittees or panels for any purpose consistent with its charter.

Scientific members of the committee will be selected on the basis of their professional qualifications to examine the questions of hazard, exposure, and risk to humans, other non-target organisms, and ecosystems. Some committee members

will serve as liaisons (holding joint membership) with the FIFRA Scientific Advisory Panel (SAP) and with the EPA Science Advisory Board (SAB). The SAC will also include nonvoting representatives from other Federal agencies that are involved in regulating products of biotechnology.

The Agency intends for meetings of the SAC to be open to the public. Meetings may be closed by the Chairperson when necessary, such as during discussion of issues subject to statutory confidentiality requirements, but EPA will encourage open public discussion of issues to the greatest extent possible (see unit I.G. below).

G. CONFIDENTIAL BUSINESS INFORMATION

Both FIFRA and TSCA generally prohibit the Agency from releasing certain confidential business information (CBI). These prohibitions apply to information on products of biotechnology, and the Agency will meet its obligations to protect information claimed confidential by applicants and other data submitters. However, the Agency also recognizes that there is strong public interest in many aspects of biotechnology, particularly in the possibility of adverse effects resulting from the environmental release of genetically engineered organisms. Accordingly, it is the Agency's policy to carry out as much of its review as possible in the open, in order to provide an opportunity for public participation and to increase public confidence in the review process. The Agency is encouraged by the extent to which

industry and other submitters have been willing to authorize the release of relevant information to date and urges future data submitters to limit confidentiality claims as much as possible in order to foster an open review process.

H. INTERNATIONAL ASPECTS

EPA is committed to the policy described in the section entitled "International Aspects" in the Office of Science and Technology Policy Preamble, published in this FEDERAL REGISTER. This section is herein incorporated by reference.

SUMMARY TABLE: PRIOR NOTIFICATION AND REVIEW OF MICROORGANISMS APPLIED IN THE ENVIRONMENT

TYPE OF MICROBIAL PRODUCT	COVERAGE BY NOTIFICATION AND REVIEW POLICY 1/			
	FIFRA		TSCA	
	≤10 acres	>10 acres	≤10 acres	>10 acres
1. Genetically engineered microorganisms				
a. Formed by deliberate combinations of genetic material from dissimilar source organisms (inter-generic combinations)	X	X	X	X
b. Formed by genetic engineering other than inter-generic combinations				
i. pathogenic source organisms 2/	X	X	X	X
ii. nonpathogenic source organisms	O	X	O	O
2. Nonengineered microorganisms				
a. Nonindigenous pathogens 2/	X	X	O	X
b. Nonindigenous nonpathogens	O	X	O	O
c. Indigenous pathogens 2/		X	O	X
d. Indigenous nonpathogens		X	O	O

1/ "X" designates that the microorganism will be subject to EPA review prior to small-scale (10 acres or less) or large scale (greater than 10 acres) environmental applications, as indicated. Under TSCA, submitters would only notify the Agency once (at the first appropriate time), unless during the original review EPA specifies that further reporting is required.

"O" designates that the microorganism will be subject to abbreviated review prior to small-scale (10 acres or less) or large scale (greater than 10 acres) environmental applications, as indicated. Under FIFRA, this provision is effective immediately. Under TSCA, the abbreviated notification will be implemented through rule-making.

2/ Pathogens in this category used solely for non-pesticidal agricultural purposes will not be subject to EPA notification requirements. They will be subject only to USDA review. See Unit IV for a definition of "agricultural uses" and "pathogens."

II. APPLICABILITY OF THE FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA) TO MICROBIAL PRODUCTS

A. BACKGROUND

Biological agents, including microorganisms, may be used as pesticides, and as such they are subject to regulation under FIFRA unless specifically exempted by regulation. FIFRA establishes EPA's authority over the distribution, sale, and use of pesticide products. Before EPA can register a pesticide, it must have sufficient data to determine that the product, when used in accordance with widespread and commonly recognized practice, will not cause (or significantly increase the risk of) unreasonable adverse effects to humans or the environment. In recent years, the Agency has put in place policies, procedures, and regulations to address the human health and environmental concerns raised by the application of biological pesticides (including genetically engineered and nonindigenous microbial products) in the environment. This unit outlines EPA's regulatory mechanism for these products and updates its policy on small-scale field testing of microbial pesticides.

Regulations promulgated under FIFRA and appearing at 40 CFR 162.5(c)(4) specify that microorganisms, when used as pesticides, are regulated under FIFRA. The specific kinds of data and information that are required to support the registration of each microbial pesticide under FIFRA are detailed in 40 CFR 158.65, 158.170, and 162.163. The Agency has also

published guidance for developing these data in the Pesticide Assessment Guidelines: Subdivision M--Biorational Pesticides (Ref. 20).

The Agency must conduct a complete evaluation and review of the data submitted to support any pesticide registration before determining whether the pesticide should be registered. This evaluation is conducted with respect to the general criteria set forth in 40 CFR 162.7(d) and (e) and 162.167. Prior to registration, producers may test their pesticide products under an experimental use permit (EUP), issued pursuant to section 5 of FIFRA and 40 CFR Part 172. The data and information needed to support the issuance of an EUP for microbial pesticides are specified at 40 CFR 158.170.

The regulations governing EUPs include a generally applicable presumption that EUPs will not be required for certain small-scale experimental uses of new pesticides (or new uses of previously registered pesticides). Recently, however, the Agency issued a statement of interim policy on small-scale field testing of nonindigenous and genetically altered microbial pesticides, published in the FEDERAL REGISTER of (October 17, 1984, 49 FR 40659) see also 49 FR 50882, December 31, 1984. Briefly, the policy statement announced that the small-scale field test provision of 40 CFR 172.3 would not automatically apply to, and that the Agency should be notified before the initiation of, any

field testing of genetically altered or nonindigenous microbial pesticides to determine if EUPs are required. This policy is being revised by this notice and is discussed in detail in Unit II.D of this unit.

B. SCOPE OF FIFRA

1. Pesticides addressed by this notice. All pesticides whose active ingredient(s) consist of microorganism(s) (i.e., all microbial pesticides) are addressed by this notice. Microbial pesticides may include bacteria and blue-green algae, fungi, viruses, and protozoa used as pest control agents.

2. Pesticides not addressed by this notice. The Agency has determined that certain nonmicrobial organisms which fall within the definition of biological control agents are already addressed by other agencies, specifically USDA and the Department of the Interior. Examples of these biological control agents are vertebrates, insect predators, nematodes, and macroscopic parasites. Therefore, pursuant to section 25(b) of FIFRA and 40 CFR 162.5(c)(4), these nonmicrobial biological control agents have been exempted from regulation under FIFRA. However, if EPA, in cooperation with other agencies, determines that certain biological control agents exempted by § 162.5(c)(4) are not being adequately regulated, these organisms will be referred to the attention of the appropriate agency or added to the exceptions in

§ 162.5(c)(4) by amendment. In the latter case, those organisms would no longer be considered exempt from the provisions of FIFRA.

This unit of the notice does not address any chemical pesticide product or byproduct produced by microorganisms. Such chemicals are covered under current pesticide regulations, registration procedures, data requirements, and testing guidelines (see 40 CFR Parts 158 through 180; and Subdivisions D through O of the Pesticide Assessment Guidelines).

3. Information-gathering policy. In order to expand its level of knowledge and expertise, monitor the industry, and determine whether its current policy needs modification, the Agency needs as complete a data base as possible. Accordingly, those developing microbial products intended for use as pesticides that are not otherwise subject to FIFRA review are encouraged to keep the Agency apprised of their activities. In addition, registrants of microbial pesticides are reminded that, pursuant to FIFRA section 6(a)(2), they must report any information regarding unreasonable adverse effects of the pesticide on the environment.

C. MICROBIAL PESTICIDES -- HISTORY AND LONG-TERM REGULATORY STRATEGY

1. History. Microbial pesticides have been in use for many years. In 1948, the Federal Government registered the first such product, Bacillus popilliae, to control Japanese beetle larvae in

turf. However, it was not until the late 1960s and early 1970s that interest in microbial pesticides began to increase. At that time, EPA began to develop policies and procedures to specifically address microbial pesticide products. In 1983, EPA's Office of Pesticide Programs published testing guidelines for microbial pesticides (Ref. 20). A year later, EPA issued a final regulation (40 CFR Part 158) specifying the data requirements for pesticide registration (including genetically engineered microbial pesticides). As of 1985, there were 14 microbial pesticides used in several hundred separate products registered for use in agriculture, forestry, mosquito control, and homes.

As indicated in Unit II.A above, EPA issued an interim policy on small-scale field testing of genetically altered and nonindigenous microbial pesticides in October 1984 (49 FR 40659). To date, under this policy, EPA has received and reviewed five notifications for genetically engineered microbial pesticides and two notifications for nonindigenous microbial pesticides. Three EUP applications, required in part to address unresolved issues identified in the review of these notifications, have since been received. These applications were for genetically engineered microbial pesticides.

2. Long-term regulatory strategy. Although EPA has an established regulatory mechanism for microbial pesticides, the Agency envisions some further modifications in the future to specify certain policies in more detail, keep the assessment process current with existing scientific knowledge, and ensure an efficient review mechanism. Some of these anticipated modifications are discussed here.

As noted in Unit I, EPA intends to revise the EUP regulations (40 CFR Part 172) to incorporate the concepts embodied in the interim policy on small-scale field testing. Specifically, Part 172 will be revised to specify more clearly which applicants must notify EPA before conducting small-scale field tests with microbial pesticides and the content of notification.

As noted in the overview to this EPA notice (Unit I.F), EPA is forming a Science Advisory Committee. The Scientific Advisory Panel, an advisory group mandated by FIFRA, will continue to serve in its advisory capacity on specific submissions under FIFRA, until the SAC is formed.

FIFRA requires EPA to review and periodically update its guidelines, and OPP has begun this process for the Subdivision M Pesticide Assessment Guidelines. The Guidelines are currently being revised to reflect current testing methodology and advances in risk assessment capabilities resulting from OPP's recent experience in evaluating genetically engineered microbial

pesticides. In addition, as the Agency gains risk assessment experience and assembles a larger body of risk assessment data, it may be appropriate to amend the Part 158 data requirements regulation to add to or modify the data requirements that apply to genetically engineered and nonindigenous microbial pesticides.

D. REGULATORY REVIEW OF MICROBIAL PESTICIDES

This unit describes EPA's data requirements and review procedures for microbial pesticides. In particular, Unit II.D.1 describes the requirements and review plan for those microbial pesticides subject to review under FIFRA before they may be used in any application in the environment (i.e., small-scale field testing). Unit II.D.2 outlines the regulatory review for those microbial pesticides subject to the FIFRA requirements for an experimental use permit or registration. In most instances, microbial pesticides subject to the provisions in Unit II.D.1 will also be subject to the provisions in Unit II.D.2 when they are to be used for larger scale or commercial purposes in the environment.

1. Small-scale field testing. Prior to obtaining a registration for a pesticide product, applicants generally need to conduct field studies in order to gather product performance, use, and other types of data necessary to support the registration of their product. The regulations governing field studies (40 CFR Part 172) include a generally applicable presumption that EUPs will not be required for certain

small-scale uses of new pesticides (or new uses of previously registered pesticides). The Agency issued a statement of interim policy addressing small-scale field testing of microbial pesticides in 1984. The interim policy announced that the Agency should be notified before initiation of any field testing of genetically altered or nonindigenous microbial pesticides. The purpose of this policy is to provide a mechanism for the Agency to evaluate these proposed small-scale field tests for possible risk to human health or the environment and determine whether EUPs are required before the tests can be initiated.

Small-scale field studies are (1) terrestrial field studies that involve 10 acres or less of land; and (2) aquatic field studies that involve 1 surface acre or less of water.

To minimize the regulatory burden on producers of genetically engineered and nonindigenous microbial pesticides, and more closely correlate the level of Agency review with potential risk of the microorganism, the Agency has adopted a two-level review system based on its evaluation of the potential risks posed by various types of microorganisms. The two-level system will allow the Agency to receive some basic information on small-scale testing of genetically engineered and nonindigenous microorganisms that are less likely to pose significant risks to humans or the environment (Level I reporting), while reserving full notification and review procedures for microorganisms about which there is more concern (Level II notification). The review

system is designed so that producers of microbial pesticides may proceed with their small-scale field tests without Agency approval, unless they are notified within a specified time that additional information or an EUP is required. In the case of level I reporting, producers need only provide a limited amount of information, and are assured of an expedited response from the Agency if it is determined that additional information is required.

The two-level system is based on the analysis set forth at Unit I.D. in which the Agency has defined groups of microorganisms that raise more concerns about their likelihood to pose risks to humans or the environment when released into the environment than other microorganisms. Specifically, these include microbial pesticides formed by deliberately combining genetic material from organisms of different genera and genetically engineered or nonindigenous microbial pesticides derived from pathogenic source organisms. However, other genetically engineered and nonindigenous microbial pesticides are less likely to pose significant risks to humans or the environment when applied in small-scale field tests. Accordingly, the Agency has determined that this second category of microbial pesticides will be subjected to a reporting requirement and will be reviewed as described in Unit II.D.1 a through c below. The Agency will have up to 30 days to review the reported information. The kind of information needed to

fulfill the reporting requirement is typically already available to an applicant as an essential part of product research and development, and is not generally expected to require generation of new data.

All microbial pesticides formed by deliberately combining genetic material from organisms of different genera, and all genetically engineered or nonindigenous microbial pesticides derived from pathogenic source organisms will be subject to the full notification requirements (Level II) as described in Unit II.D.1.e below. The Agency has determined that these organisms should continue to be subjected to the full notification and review procedures set out in the original interim policy published on October 17, 1984. The Agency will have up to 90 days to review a Level II notification.

The scope and requirements for Level I reporting and Level II notification are detailed below. The interim policy as revised by this notice does not apply to studies conducted under enclosed, contained conditions, as defined in Unit IV.

a. Level I reporting. Level I reporting for small-scale field testing applies to all genetically engineered or nonindigenous microbial pesticides not otherwise covered by Level II notification as detailed in II.D.1.d below. Small-scale field tests of additional groups of genetically engineered and nonindigenous microbial pesticides now covered by Level II

notification may also be determined to warrant only abbreviated review in the future. The Agency will make these determinations on a case-by-case basis.

b. Level I information. Each report should include the following information, or, where specific information is not submitted, documentation of why it is not practicable or necessary to provide the information.

(1) Identity of the microorganism, including characteristics, and means and limits of detection.

(2) Description of the natural habitat of the microorganism or its parental strains, including information on natural predators, parasites, and competitors.

(3) Information on the host range of the parental strain(s) or nonindigenous microorganism.

(4) Information on the relative environmental competitiveness of the microorganism, if available.

(5) If the microorganism is genetically engineered, information should be provided on the methods used to genetically engineer the microorganism(s); the identity and location of the rearranged or inserted/deleted gene segment(s) in question; a description of the new trait(s) or characteristic(s) that are expressed; information on potential for genetic transfer and exchange with other organisms, and on genetic stability of any inserted sequence.

(6) A description of the proposed testing program,

including site location, crop to be treated, target pest, amount of test material to be applied, and method of application.

c. Level I reporting process. EPA will have up to 30 days to review the above information to make a preliminary determination of the need for an EUP. If the Agency does not notify the applicant of the need for an EUP within the 30 days, the applicant may proceed with the proposed field test. If, on preliminary assessment, the test raises sufficient concerns such that the Agency determines that additional information or monitoring is warranted, then an EUP will be required (e.g., microorganisms for which there is limited scientific information or regulatory experience, or that raise significant questions concerning genetic stability, competitiveness, or mode of action, or that warrant specific environmental monitoring during the test). In this case, the applicant has two options. First, the applicant may apply for a permit, providing the necessary data and information required to support the application. Alternatively, the applicant may provide all additional data and information required under Level II notification as outlined in Unit II.D.1.e below. If the latter option is chosen, the Agency will have an additional 60 days to review the full notification package and make a final determination as to whether an EUP is required.

d. Level II notification. Level II notification for small-scale field testing applies to microbial pesticides: microbial

pesticides formed by deliberately combining genetic material from organisms of different genera, genetically engineered microbial pesticides derived from source organisms that are pathogens (as defined in Unit IV), and nonindigenous pathogenic microbial pesticides (as defined in Unit IV).

e. Level II requirements. Notification should include adequate information to allow the Agency to evaluate the small-scale field testing program. Each notification should include the following information, or, where specific information is not submitted, documentation of why it is not practicable or necessary to provide the information.

(1) Background information on the microorganism.

(a) Identity of the microorganism, including tables of characteristics, and means and limit of detection using the most sensitive and specific methods available.

(b) Description of the natural habitat of the microorganism or its parental strains, including information on natural predators, parasites, and competitors.

(c) Information on host range, especially infectivity and pathogenicity to nontarget organisms.

(d) Information on survival and ability of the microorganism to increase in numbers (biomass) in the environment (e.g., laboratory or containment facility test data).

(e) If the microorganism is genetically altered, the following information should be provided in addition to the information listed in (a) through (d) above:

i. Information on the methods used to genetically alter the microorganism.

ii. The identity and location of the rearranged or inserted/deleted gene segment(s) in question (host source, nature, base sequence data, or restriction enzyme map of the gene(s)).

iii. Information on the control region of the gene(s), and a description of the new trait(s) or characteristic(s) that are expressed.

iv. Information on potential for genetic transfer and exchange with other organisms, and on genetic stability of any inserted sequence.

v. Information on relative environmental competitiveness compared to the parental strains.

(2) Description of proposed field test.

(a) The purpose or objectives of the proposed testing.

(b) A detailed description of the proposed testing program, including test parameters.

(c) A designation of the pest organism(s) involved (common and scientific names).

(d) A statement of composition for the formulation to be tested, giving the name and percentage by weight of each ingredient, active and inert, production methods, contamination with extraneous microorganisms, potency and amount of any toxins present, and where applicable the number of viable microorganisms per unit weight or volume of the product (or other appropriate system for designating the quantity of active ingredient).

(e) The amount of pesticide product proposed for use and the method of application.

(f) The State(s) in which the proposed program will be conducted, and specific identification of the exact location of the test site(s) (including proximity to residences and human activities, surface water, etc.).

(g) The crops, fauna, flora, geographical description of sites, modes, dosage rates, frequency, and situation of application on or in which the pesticide is to be used.

(h) A comparison of the natural habitat of the microorganism with the proposed test site.

(i) The number of acres, number of structural sites, or number of animals/plants, by State, to be treated or included in the area of experimental use, and the procedures to be used to protect the test area from intrusion by unauthorized individuals.

(j) The proposed dates or period(s) during which the testing program is to be conducted, and the manner in which supervision of the program will be accomplished.

(k) A description of procedures for monitoring the microorganism within and adjacent to the test site during the field test.

(l) The method of disposal or sanitation of plants, animals, soils, etc., that were exposed during or after the field test.

(m) Means of evaluating potential adverse effects and methods of controlling the microorganism if detected beyond the test area.

In addition, the following references should be consulted for further guidance on the kinds of data and information that may be relevant to the evaluation of genetically engineered microorganisms: "Proposed Points to Consider for Environmental Testing of Microorganisms" developed by the National Institutes of Health Recombinant DNA Advisory Committee Working Group on Release into the Environment (Ref. 11); Subdivision M: Biorational Pesticides" (Ref. 20); a report by the Cornell Ecosystems Reserch Center titled "Potential Impacts of Environmental Release of Biotechnology Products: Assessment, Regulation, and Research Needs (Ref. 9); a National Science Foundation Report titled "The Suitability for Environmental Applications of Biotechnology" (Ref. 3); and EPA "Points to Consider in the Microorganisms" [available from TSCA Assistance Office (address at beginning of this notice)].

f. Level II review process. Once the supporting data have been submitted, EPA has up to 90 days to review each notification of intent to conduct small-scale field testing and to determine whether an EUP is required. The Agency encourages prospective applicants to meet with EPA prior to submission of their notification to discuss their field test and determine what specific data would be necessary to evaluate the product.

EPA's review process will include some or all of the elements described in the following paragraphs. As the Agency builds a baseline of risk assessment data and gains more experience in evaluating these products, certain steps may no longer be necessary. In addition, an abbreviated review process may be appropriate in some situations (e.g., review of a proposal that is similar to an already reviewed case). Such a determination will be made on a case-by-case basis.

Once a notification is received, OPP reviews each proposal and assesses potential risks associated with the proposed experiment. OPP develops a written scientific position for each proposal which identifies potential problems or significant unanswered questions and sets forth a statement of the overall likelihood of significant risk from the proposed field testing. As the review process proceeds, it may be necessary for OPP to request supplemental information.

OPP obtains comments on its assessment from a workgroup within EPA and from other Federal agencies as appropriate (e.g., USDA, National Institutes of Health, Food and Drug Administration, and National Science Foundation). Their comments are incorporated into the scientific position, as appropriate.

OPP contacts the appropriate State pesticides regulatory authorities to ensure that they are aware of the proposal and to discuss EPA's assessment. These contacts ensure that the actions of EPA and the State agencies are as consistent as possible. OPP also notifies the Animal and Plant Health Inspection Service (APHIS) of the USDA so that they can determine whether any aspect of the proposed experiment falls within APHIS jurisdiction and, if so, to avoid duplicative or conflicting assessments.

Thus far, reviews of small-scale field testing proposals for genetically engineered microbial pesticides have emphasized some questions that have not been as significant in the assessments of naturally occurring microbial pesticides. For example, OPP has identified potential risks associated with the transfer of inserted genetic material to other organisms, the competitiveness of the engineered organism compared with the parental organisms in the environment, and the ability of the engineered organism to become established in a new ecological niche and thereby pose a potential adverse environmental impact.

OPP has addressed these and similar questions on a case-by-case basis in its risk assessments. In some cases, applicants have addressed questions by redesigning the proposed application or test microorganism to minimize the potential risk. In other instances, EPA has established data requirements and test methods as a baseline, and has designed specific laboratory test(s) (or tiered series of tests) to establish whether the effect of concern is likely to materialize under field conditions.

If the notification raises complex or controversial scientific questions, OPP provides the notification package and its scientific evaluation to a group of independent scientists constituted as a subpanel of FIFRA's Scientific Advisory Panel. Separate subpanels may be formed to review each proposal since each microorganism and its proposed use may differ and raise questions that require the analysis of individuals with different expertise. The purpose of the SAP subpanel is to obtain an independent peer review of the OPP scientific position, to address specific scientific questions raised by OPP, and to identify any additional points, questions, or problems. As noted previously in Unit I.F, the Agency is forming a Science Advisory Committee which will assume these responsibilities in the future.

At the conclusion of the review, the Agency then decides whether an EUP is required. The decision document sets forth OPP's conclusions with respect to potential risks associated with the proposal, identifies any remaining questions or additional data that may be needed to complete the risk assessment, and, if an EUP is required, may recommend restrictions, limitations, or modifications of the proposal to address areas of concern. If an EUP is not required, the applicant may proceed with the proposed field test. If an EUP is required, the applicant must apply for a permit, providing the necessary data and information required to support the application. The Agency may decide to require an EUP to ensure that the experiment is conducted within certain defined limitations, the necessary data are developed to assess the proposal, or certain kinds of data are developed during the test and reported to the Agency.

2. EUPs, large-scale testing, and registration. Before a pesticide may be marketed as a commercial product, it must first be registered as provided for in section 3 of FIFRA. Large-scale field testing of a microbial pesticide is often necessary to evaluate a potential product and obtain data needed to support registration of the product. This testing, like small-scale field testing under an EUP, is subject to section 5 of FIFRA which authorizes EPA to approve applications for EUPs for limited use of an unregistered product or use of a registered product for an unregistered use. Data requirements for registration are

specified in 40 CFR 158.170 and a subset of these requirements applies to large-scale field testing proposals to be performed under EUPs. The regulatory review process consists of the same basic elements in both situations and is described in this unit.

a. Scope. All microbial pesticides to be used in large-scale field tests are subject to review under FIFRA EUP regulations. The conditions under which an EUP is required are specified at 40 CFR Part 172, which also provides guidance on how to determine whether an EUP must be obtained. Likewise, all microbial pesticides are subject to the FIFRA registration requirements.

b. General requirements for microbial pesticides. The existing pesticide data requirements and regulations governing large-scale field testing (40 CFR Parts 158 and 172) and registration (40 CFR Parts 158 and 162) are applicable to all microbial pesticides, both naturally occurring and otherwise.

The Agency believes that these requirements are adequate for the assessment of indigenous microbial pesticides, and provide a basis for evaluating genetically engineered and nonindigenous microbial pesticides as well. However, the Agency believes that additional data and information, determined on a case-by-case basis, may be necessary to evaluate some properties of genetically engineered and nonindigenous microbial pesticides.

Part 158 explicitly provides the necessary flexibility to require additional data (§ 158.65) as well as the flexibility to waive data requirements that are not applicable (§ 158.45).

c. Additional requirements for genetically engineered and nonindigenous microbial pesticides. Any additional data requirements will be determined on a case-by-case basis depending on the particular microorganism, its parent microoganisms, its native habitat, the pesticide use pattern, and the manner and extent to which the microorganism may have been engineered. These additional requirements could include:

(1) Description of the natural habitat of the microorganism or its parental strains, including information on natural predators, parasites, and competitors.

(2) Information on relative ability to survive and increase in number or biomass as compared to the parental strains.

(3) Selected environmental fate tests from 40 CFR 158.170.

(4) Additional toxicology tests from 40 CFR 158.170.

(5) If the microorganism is genetically altered, then information on the genetic modification techniques used, the identity of inserted gene segment(s) (base sequence data or restriction enzyme map of the gene), the control region of the gene(s), a description of the new traits or characteristics that are intended to be expressed, and tests to evaluate genetic stability and exchange, may be required as specified previously at Unit II.D.1.b above.

d. Review process for genetically engineered and nonindigenous microbial pesticides. EUP applications will be reviewed in compliance with the EUP regulations under 40 CFR Part 172. The registration, reregistration, and classification procedures of 40 CFR Part 162 will be followed for registration applications. The review process will contain the same major elements as those outlined previously for small-scale field testing notifications (see Unit II.D.1.c). Briefly, this process involves scientific review and risk assessment by EPA scientists and, if appropriate, review and comment from other Federal agencies and independent expert consultants.

Once the supporting data have been submitted, EPA has up to 120 days to review an EUP application and determine whether to grant a permit. Past experience indicates that the registration process for a new microbial pesticide may vary from 9 months to several years depending upon the particular product, its use pattern, and the completeness of the registration package submitted to EPA.

Both the EUP and registration process may provide an opportunity for public comment. For example, § 172.11 of the EUP regulations specifies that if an application may be of regional or national significance the Agency will announce receipt of the application in the FEDERAL REGISTER. The announcement is accompanied by a description of the experimental program and public comments are solicited. Similarly, § 162.6 of the

registration regulations specifies that if a registration application relates to a new active ingredient or a new use, notice of receipt of that application shall be published in the FEDERAL REGISTER with a request for public comment. Information on the submission is made available for public inspection.

EPA has several regulatory options for responding to either an EUP or registration application. For example, after completing its review, the Agency may determine that the field test or registration poses no unreasonable risks to humans or the environment and may grant the application. Alternatively, EPA may conclude that some additional information or data are needed to assess the potential risks adequately. In this case, the applicant would be asked to provide the necessary data before EPA would decide whether to grant the application. In other cases, the Agency may impose additional limitations or restrictions on the field test or registration to address a potential risk. Finally, EPA will deny those applications where it has determined that it has all the necessary data to complete a risk assessment and that the field test or registration would pose an unreasonable risk to humans or the environment, even if additional limits or restrictions are imposed.

III. APPLICABILITY OF THE TOXIC SUBSTANCES CONTROL ACT (TSCA) TO MICROBIAL PRODUCTS

A. OVERVIEW OF THIS UNIT

As discussed in the December 84 notice (49 FR 50886), EPA will review certain microorganisms and uses of microorganisms under TSCA. Microorganisms and their DNA molecules are "chemical substances" under section 3 of TSCA, and thus are subject to all the provisions of TSCA, except to the extent they are manufactured, processed, or distributed in commerce for use as pesticides, foods, food additives, drugs, cosmetics, and medical devices. For purposes of analysis and convenience of administering TSCA, EPA has chosen to focus on the microorganism as the "chemical substance."

This unit explains the statutory requirements of TSCA as they apply to microorganisms. It begins by describing which microorganisms are within the scope of TSCA and which are not. Following that are units describing five categories of microorganisms or uses of microorganisms that are or will be subject to reporting requirements under TSCA.

B. SCOPE OF TSCA

Many organisms are not subject to TSCA requirements because of statutory exemptions; others will be exempt from certain TSCA requirements as a matter of regulatory policy. In general, the use of a microorganism determines whether it is subject to TSCA or to other laws.

Many of the comments received by OTS indicated misunderstandings of TSCA's scope. Therefore, those organisms which are and are not subject to TSCA are described in this Unit.

1. Organisms not subject to TSCA -- a. Microbes used as foods, food additives, drugs, cosmetics, medical devices, and pesticides. Microorganisms are sometimes used directly as foods, food additives, drugs (including both human and animal vaccines), cosmetics, medical devices, and pesticides. When microorganisms are used for these purposes, they are explicitly excluded from TSCA and from the policies described in the TSCA portions of this notice (TSCA section 3(2)(B), 15 U.S.C. 2602(2)(B)).

Microorganisms that are used as foods, food additives, drugs, cosmetics, medical devices, and pesticides are regulated by the Food and Drug Administration (FDA), USDA, or the EPA Office of Pesticide Programs. Applicable requirements for pesticides are described in Unit II of this notice. Requirements for foods, food additives, drugs, cosmetics, and medical devices are described in the FDA and USDA notices in this FEDERAL REGISTER.

b. Microbes used to produce foods, food additives, drugs, cosmetics, and medical devices. In addition to being used themselves for food, drug, and other purposes, microorganisms are often used to produce chemicals that are in turn used for such purposes. For reasons explained in the December 84 Notice, microorganisms will not be reviewed under TSCA when used to produce foods, food additives, drugs (including vaccines), cosmetics, or medical devices. Further information on these uses

may be found in the FDA and USDA notices in this FEDERAL REGISTER.

Microorganisms used in the production of chemical end products other than foods, food additives, drugs (including vaccines), cosmetics, and medical devices are subject to TSCA. They are described in Unit III.B.3 below.

2. Plants and animals not subject to these policies. Plants and animals are not subject to the TSCA policies in this notice, either as whole organisms or as in vitro cultures for the reasons set forth in the December 84 Notice. (Definitions of plants and animals for regulatory purposes are provided in Unit IV of this EPA notice.) There are two exceptions to this general rule. First, if plant or animal gene segments are intentionally incorporated into microorganisms, the microorganisms that contain those plant or animal genes may be subject to TSCA, depending on how they are used (see above). Second, a chemical extracted from a plant or animal may be subject to TSCA, again depending on how it is used. The USDA and FDA notices in this FEDERAL REGISTER contain information about regulations that apply to plants and animals.

3. Organisms subject to TSCA -- microorganisms used for purposes not excluded by law. With the exceptions described above, all microorganisms produced for environmental, industrial, or consumer uses are potentially regulable under TSCA. It is not possible to list all the applications that could be subject to TSCA because many are yet to be developed. Some of the microorganisms that are expected in the near future and that

would be subject to TSCA include microorganisms used in conversion of biomass for energy, pollutant degradation, enhanced oil recovery, metal extraction and concentration, and certain non-food and non-pesticidal agricultural applications, such as nitrogen fixation.

Microorganisms used in the production of a chemical end product will be subject to TSCA if the end product is any chemical substance used for a purpose other than as a food, food additive, drug, cosmetic, or medical device. For example, microorganisms are subject to TSCA if they are used in the production of pesticides, fuels, solvents, dyes, cleansing agents, etc. TSCA jurisdiction over such microorganisms, which may be used entirely in closed manufacturing systems, is consistent with TSCA coverage of conventional chemicals. For example, chemical intermediates -- even those used in closed systems -- fall under TSCA authority and are subject to PMN requirements if new (40 CFR Part 720). Similarly, as described in Unit III.C.1 of this notice, "new" microorganisms used in chemical production are subject to PMN requirements.

4. Chemicals produced by microorganisms -- Status under TSCA. Although the purpose of this notice is to provide information on the applicability of TSCA to microorganisms, some readers may wish to obtain information on requirements that apply to chemicals produced by microorganisms. For example, various proteins and polysaccharide gums are produced by microorganisms and may be subject to TSCA, depending on how they are used (see Unit III.B.1). These chemicals produced by microorganisms are

subject to the same requirements and procedures as chemicals produced by other means. Any special concerns pertaining to the microbial production method, such as the possibility of contaminants, will be considered during the review of the microorganisms used in producing the chemicals. This approach is explained in the December 84 Notice at page 50890.

C. SPECIFIC REQUIREMENTS UNDER TSCA

The fact that an organism is potentially subject to TSCA does not necessarily mean that it will be regulated under TSCA. The rest of this unit explains the specific provisions that apply or will apply to various types of microorganisms falling within TSCA's jurisdiction.

In overview, microorganisms are (or will be) subject to TSCA requirements in the following manner:

(1) As of the date of this notice, microorganisms that are subject to TSCA and contain genetic material from dissimilar source organisms (i.e., organisms from different genera) are subject to PMN requirements.

(2) Microorganisms other than inter-generic combinations that are subject to TSCA and are pathogenic or contain genetic material from pathogens, will in the future, if released into the environment, be subject to "significant new use" reporting requirements under TSCA section 5(a)(2). One exception is that agricultural uses of such organisms will be reviewed by USDA

rather than EPA. EPA expects voluntary notification to begin immediately for uses that will be subject to significant new use reporting requirements.

(3) The research and development exemption from PMN and significant new use notification requirements will be amended so that it no longer applies to microorganisms released to the environment. EPA expects voluntary notification of such uses to begin immediately.

(4) EPA will issue a rule requiring manufacturers and importers to submit general information on environmental uses of microorganisms that are subject to TSCA but not otherwise subject to notification requirements, so that EPA can monitor environmental releases.

(5) All manufacturers, processors, and distributors of microorganisms subject to TSCA are reminded of the requirement to report any information on substantial risks under TSCA section 8(e).

(6) EPA is considering initiating rulemaking that would exempt from PMN requirements inter-generic microorganisms used solely in contained systems and never intentionally released to the environment.

1. Premanufacture notification requirements --

a. Overview. EPA has determined that any microorganisms that are subject to TSCA (described in Unit III.B), and that through deliberate human intervention contain genetic material from dissimilar source organisms, are "new" and therefore subject to PMN requirements of TSCA. This interpretation is effective as of

the date of publication of this notice.

Organisms are considered dissimilar for the purposes of this policy if they are from different genera. In the case of chemically synthesized genes, the Agency will follow the same principle, as clarified below in Unit IV. Detailed guidance on how to determine if organisms are from different genera is also provided in Unit IV.

The Agency is excluding certain inter-generic combinations from PMN requirements, i.e., those inter-generic combinations in which the genetic material added to the recipient microorganism consists only of well-characterized, non-coding regulatory regions (see Unit IV). The resulting organisms do not possess new combinations of traits but rather exhibit quantitative changes in preexisting traits.

EPA is leaving unanswered, for now, the question of whether organisms containing genetic material from other organisms in the same genus (i.e., products of deliberate intra-generic combinations) and those which are developed from a single source organism (e.g., products of undirected mutagenesis, organisms with deletions) should also be considered "new." In the future, it is possible that EPA will decide that such organisms are "new," but for now they are not subject to PMN requirements.

b. Background. For purposes of administering TSCA, EPA must decide what constitutes a "new" microorganism which is subject to PMN requirements. As mentioned in the introduction to the EPA portion of this notice, EPA originally proposed a "process-based" approach to determining whether an organism is

new. This approach stated that an organism would be considered new if significant human intervention had been used in developing it. For example, microorganisms altered by certain techniques -- such as recombinant DNA and cell fusion -- were presumed to be new because they involved significant human intervention. The question of which other techniques should be considered to produce new organisms was left open and comments were solicited.

After reviewing the comments, EPA considered a number of alternative ways to define "new" organisms. These are described in the "Response to Comments" document available as background to this FEDERAL REGISTER notice. In choosing among the alternatives, EPA carefully considered the TSCA mandate to review "new" substances. The Agency also considered related issues, for example, how well the options approximated risk (there was uncertainty with all the options in this respect) and how readily they could be implemented and enforced.

c. Rationale. Having reviewed the TSCA section 5 PMN requirements, the PMN regulations, the public comments, and the current state of science regarding genetic engineering, EPA has concluded that microorganisms resulting from intentional, inter-generic combinations of genetic material, except those in which the transferred material is only a well-characterized, non-coding regulatory region, constitute new organisms for purposes of PMN reporting. The reasons for this are set forth below.

First, the Agency considered the regulatory precedents established in compiling the inventory of existing chemical substances under section 8(b) of TSCA. Any chemical substance not on this inventory is "new" under section 5(a) of TSCA and is therefore subject to PMN requirements. Naturally occurring substances and substances derived from nature with limited human intervention are not explicitly listed on the inventory but are considered implicitly to be on it, and thus are not "new" (see 40 CFR 710.4(b)). A more detailed explanation of the TSCA inventory and related issues is found in the December 84 Notice at pages 50887-50888.

Second, the Agency evaluated these regulatory precedents in the light of scientific knowledge about genetic engineering and microorganisms found in nature. On this basis, EPA concluded that microorganisms found in nature and developed without any deliberate combination of genetic material are not new, because they occur naturally and are derived through limited human intervention. Furthermore, from a scientific standpoint, these microorganisms have a very low probability of exhibiting new combinations of traits. Therefore, the Agency considers that from a legal and scientific standpoint they must be considered naturally occurring (not new). Because such organisms are naturally occurring, they are, as explained above, implicitly listed on the TSCA chemical substances inventory and not subject to PMN requirements.

Third, where genetic material has been combined among source organisms from different genera (inter-generic), the resulting microorganisms should be considered "new" because of the degree of human intervention involved, the significant likelihood of creating new combinations of traits, and the greater uncertainty regarding the potential risks of such microorganisms. However, transfer of genetic material consisting solely of well-characterized, non-coding regulatory regions is a special case. Where only regulatory material is transferred, no distinctly new combinations of traits are introduced; instead, existing traits in the receiving organism are amplified or changed quantitatively. For this reason, EPA believes that microorganisms formed only through inter-generic transfer of well-characterized, non-coding regulatory regions should not be considered "new" under section 5 of TSCA. This is reflected in the definition of "inter-generic" found in Unit IV.

It is possible to argue that some microorganisms formed through intra-generic combinations are products of significant human intervention and may exhibit new combinations of traits, and therefore that they should also be considered new. However, the Agency at this time believes that it is appropriate to exclude such organisms from its definition of "new" because distinctly new combinations of traits are unlikely to occur through transfers of genetic material among closely related organisms, because transfers among closely related organisms are more likely to occur in nature, and because the current state of taxonomy with regard to species designations is sufficiently

unstable that it makes it difficult to include such organisms in a definition of "new" (the rationale is found in Unit I). As explained previously, however, the Agency will continue to review the status of such organisms and may, in the future, determine that certain combinations among similar organisms should be considered new.

In summary, EPA considers organisms deliberately formed to contain genetic material from different genera to be new, except where only well-characterized, non-coding regulatory regions are transferred. Conversely, intra-generic and non-engineered microbes are considered naturally occurring. These conclusions are based on the TSCA section 5 mandate to review "new" substances, and they also reflect a number of scientific considerations. Among these are (1) the Agency's concern that organisms formed with genetic material from different genera warrant regulatory review, because of the inherent uncertainty about the characteristics and behavior of such organisms, (2) the observation that organisms from different genera are less likely to exchange genetic material in nature than organisms that are more closely related, (3) the regulatory precedent that significant human intervention creates new substances for purposes of PMN under TSCA section 5, and (4) the necessity of having a definition of "new" that can be readily interpreted and enforced given the current state of science. These scientific and legal issues are more fully described in Unit II.1.

c. <u>How to comply with the PMN requirements for new microorganisms.</u> The following requirements apply to "new"

microorganisms produced for uses subject to TSCA authority (see Unit III.B.3). Detailed criteria for determining whether a microbe meets the definition of "new" microorganism (i.e., whether it contains genetic material from organisms from different genera) may be found in Unit IV.

Certain PMN policies in this notice are immediately effective. As of the date of publication of this notice, microorganisms that are being manufactured or imported for any TSCA commercial purposes other than research and development (R&D) are subject to PMN requirements 90 days prior to manufacture or import. This requirement applies to both contained and environmental uses that have gone beyond R&D. The requirement is based on the current provisions of 40 CFR Part 720. The definition of R&D under these regulations is clarified in the FEDERAL REGISTER of April 22, 1986 (51 FR 15096).

In addition, new microorganisms that are being manufactured or imported for R&D that involves environmental release will have to be reported to EPA at least 90 days before such activities begin. This policy will be implemented through amendments to 40 CFR 720 (explained fully in Unit III.C.3); in the meantime, persons manufacturing or importing new organisms for R&D activities involving environmental release are expected to comply with this policy voluntarily.

EPA believes that there are no manufacturers who are presently beyond the research and development stage with new microorganisms subject to TSCA. However, if any companies are

now engaged in such activities, they should contact EPA and determine whether a PMN is necessary. If a company in this position contacts EPA promptly, it will not be considered out of compliance with policy. Further information on TSCA PMN requirements may be obtained from the TSCA Assistance Office (address provided at the beginning of the EPA portion of this notice).

(1) How to know if a microorganism is subject to PMN. As stated above, all microorganisms containing deliberate combinations of genetic material from organisms from different genera are new and subject to PMN. An exception to this policy is an inter-generic combination in which the genetic material added to the recipient microorganism consists only of well-characterized, non-coding regulatory regions. Unit IV of this notice contains detailed guidance that manufacturers should use to determine if their microorganisms meet this definition.

Submitters should consult the Agency if they have any questions about how to determine if a microorganism contains genetic material from different genera.

(2) PMN exemptions. EPA considers it a priority to exempt from PMN requirements new organisms that can be shown to meet the findings for exemption under TSCA section 5(h)(4). Further information on exemptions the Agency is considering may be found in Unit III.6 of this notice.

(3) Submitting the PMN. EPA expects manufacturers and importers to contact EPA well in advance of PMN submission, to allow sufficient time for prenotice consultation. These

consultations will help the Agency and the submitter anticipate potential problems and expedite the review.

Information regarding new microorganisms should not be submitted on the standard PMN form, as this form is not applicable to microbial products. Instead, EPA and the submitter will discuss the level and types of information appropriate for the notice during prenotice consultations. The general kinds of information EPA expects to see in most submissions for microorganisms are described in the next unit below.

(4) What information to submit. Section 5(d)(1)(A) of TSCA specifies the information PMN submitters must provide in their notices, including information on production, workplace exposure, and release. In addition, under section 5(d)(1)(B) submitters must provide all test data related to the health and environmental effects of the new chemical substance in their possession or control. For more information on PMN requirements, persons should consult EPA's PMN rule (40 CFR Part 720).

In general, information to assess a substance's potential risk should be developed in a step-wise fashion. PMN submitters should begin with published literature on the source organisms, then move through laboratory, microcosm, growth chamber, and/or greenhouse studies that simulate as closely as possible the conditions of the eventual use or environmental application.

The remainder of this unit describes the types of information EPA expects submitters to provide in PMNs on new

microorganisms.

(a) Identifying the microorganism. PMN submitters must provide information that identifies microorganisms well enough to be listed on the TSCA chemical substance inventory, as discussed below. If the identity and/or use of the microorganism are claimed as confidential business information by the submitter, the PMN must also include a generic description of these items so that the information can be published in the FEDERAL REGISTER. Confidential submissions will be considered incomplete unless this generic information is included (see 40 CFR 720.65, 720.85, and 720.87).

Once a new organism is actually manufactured or imported, it will be listed on the inventory and will be no longer subject to PMN requirements. (See 40 CFR 720.102 concerning submission of a Notice of Commencement of Manufacture or Import.) EPA proposed an approach to inventory listings in a background document to the December 84 Notice. The Agency received very few comments on this document, but those who commented stated that a general method for listing all microbes does not seem possible at this time. The Agency agrees and therefore intends to list microorganisms on the inventory on a case-by-case basis while developing more general procedures for different classes of organisms, and gaining experience that will help in developing standard listings. For now, the inventory definition will usually include the genus and species designations of source

organisms and of the organism being reported, and other relevant phenotypic information such as nutritional and substrate requirements, proteins expressed, primary characteristics for which the microbe was engineered, and characteristics that are atypical for the species.

To identify the microorganism, EPA is likely to require information on:

i. Source organisms (e.g., taxonomy, source, reproductive cycle, and capacity for genetic transfer).

ii. Methods used to manipulate source organisms genetically to obtain the resulting product (e.g., source and function of genetic material to be combined; description of methods for vector construction and introduction, fusion of cells, injection of DNA, etc.).

iii. The special functions obtained (e.g., new traits intended to be expressed; selection method; nature and amount of source genetic material remaining in the product organism; genetic stability of new trait).

(b) Risk assessment information. Data required for conducting the risk assessment will vary according to the specifics of each case, but in general will fall into several major categories: information on exposure, environmental fate, and human health and environmental effects.

If the organism will be produced in enclosed, commercial-scale facilities, or used solely in physically contained systems,

the notice should include the following information:

i. Production processes (e.g., culture conditions and requirements; sites, methods, and amounts of manufacture, processing, storage, and shipment; volume, composition, and disposal of wastes).

ii. Workplace exposure and worker practices (e.g., potential for exposure, worker protection practices, and equipment).

iii. Containment and possible releases (e.g., potential sources and characteristics of releases, physical containment methods, emergency back-up systems, monitoring, and detection methods in event of a release).

In the case of small-scale field tests and other environmental releases, EPA expects that the submitter will provide information on:

(A) Purpose and intended effect of application.

(B) Site of application and surroundings, including geographic, physical, chemical, and biological features.

(C) Numbers of microorganisms and methods of application.

(D) Containment and mitigation measures (e.g., procedures in event of accidental release, for emergency termination of the application, and to reduce dispersal beyond the site).

(E) Monitoring (e.g., detection procedures including their limits, sampling procedures).

For field tests and other environmental releases, data on environmental fate and effects will be essential. In such cases, manufacturers should assume, in the absence of data to the contrary, that the microorganisms may present a risk because of their potential to reproduce and exhibit new traits. Therefore, EPA will expect manufacturers to provide test and other data demonstrating the microorganisms' safety. These data should include:

(i) General background information on the source organisms (e.g., habitat and geographic distribution, interactions with other organisms, involvement in biological cycling processes, potential for genetic exchange in nature).

(ii) Test data on the new organism itself, indicating its potential for survival, replication, dissemination, and genetic exchange with other organisms.

For further guidance, manufacturers should refer to the "Proposed Points to Consider for Environmental Testing of Microorganisms" developed by the National Institutes of Health Recombinant DNA Advisory Committee Working Group on Release into the Environment (Ref. 11). This document is particularly useful in developing data and information for submissions on small-scale field tests. While some points in this document relate solely to recombinant DNA techniques, most of the considerations are relevant to environmental tests of microorganisms regardless of the techniques involved in their production.

In addition, the Agency has prepared a more detailed guidance document entitled "Points to Consider in the Preparation and Submission of PMNs for Microorganisms." This document provides guidance on both environmental and industrial applications of microorganisms and is available from the TSCA Assistance Office (see address at the beginning of this notice).

At least three other documents will be useful to submitters. These are the "EPA Pesticide Assessment Guidelines: Subdivision M -- Biorational Pesticides" (Ref. 20), a National Science Foundation report titled "The Suitability and Applicability of Risk Assessment Methods for Environmental Applications of Biotechnology" (Ref. 3), and a report by the Cornell Ecosystems Research Center titled "Potential Impacts of Environmental Release of Biotechnology Products: Assessment, Regulation, and Research Needs (Ref. 9).

e. The PMN review. All reviews of microorganisms will follow established administrative steps that are the same for all substances subject to PMN review. First, within 5 days of receiving the PMN, EPA will issue an announcement in the FEDERAL REGISTER describing the submission. The announcement will include information on the identity of the new microorganism, the type of use, occupational exposure, production volume, a summary of test data submitted in the notice, and the submitter's identity. It will have confidential business information deleted according to the manufacturer's instructions,

although EPA will strongly encourage manufacturers to release as much information as possible. If identity and use are claimed confidential, the Agency will include a generic description provided by the submitter. EPA will have 90 days to review the PMN (extendable to 180 days), during which time the microorganism cannot be manufactured or processed for purposes other than research and development. Within the review period, the Agency may take action under section 5(e) of TSCA to prohibit or limit the activities, pending receipt of more data, or under section 5(f) or 6 to prohibit or limit the activities if there is sufficient information to make an unreasonable risk finding. Alternatively, EPA may take no action. In this case, manufacture and use may begin without restriction.

(1) Case-by-case assessments. Because of the very recent development of genetically engineered microorganisms for environmental use, there is little direct experience for conducting risk assessments on environmental releases of engineered microorganisms. In the absence of such experience, the Agency will conduct case-by-case reviews by using information from various scientific disciplines and by directly considering the features of specific genetically engineered organisms and their uses.

Many existing risk assessment approaches that are used for non-engineered organisms will contribute to the analysis of risks of engineered microbes in the environment. Some of these will be

adopted with few if any changes, while others will require modifications to address special problems.

EPA believes that standardized protocols and procedures should be gradually blended with the case-by-case approach. As experience is gained, increasingly detailed guidance on routine testing and procedures can and will be developed.

(2) Use of experts. Expert judgment will be critical in determining information needs, evaluating protocols for testing, and reviewing potential risks. Because of the range of expertise that may be required in any given case, EPA intends to supplement its staff expertise by using experts from other government agencies, academia, and other independent sources. Persons will be specifically chosen for their knowledge and experience with organisms and uses related to the PMN under review.

As announced in the December 84 Notice (and further described in Unit I of this notice), EPA is forming a biotechnology Science Advisory Committee to provide scientific advice and promote consistent review procedures.

Many academic experts may have financial or contractual relationships with biotechnology companies. Using non-Agency experts to assist in PMN reviews may therefore raise two potentially sensitive issues: conflicts of interest and access by non-Agency experts to confidential business information. To address these issues, the EPA Office of Toxic Substances has developed special procedures to ensure that scientists

contributing to biotechnology PMN reviews will not have conflicts of interest, and will have the necessary access to CBI to review the PMN without compromising trade secrets or violating TSCA CBI procedures. A document describing these procedures will be placed in the public record for this policy statement.

(3) Major parts of the review process. As stated earlier, EPA expects persons developing biotechnology products to engage in prenotice consultations with the Agency. During these discussions, EPA and the consulting company can identify preliminary concerns by considering the source organisms and intended uses of the microorganism subject to PMN. Significant time may be saved later in the PMN process if these concerns are addressed before the PMN is submitted.

Once the PMN is submitted, EPA will develop hazard and exposure assessments based on information submitted in the PMN, other available information, and consultation with non-Agency experts. Reviewers will consider the types of issues and questions described here and in the various guidance documents on risk assessments for organisms. As appropriate, they may also consult with external scientific experts, and their analyses may be peer reviewed by the Agency's biotechnology Science Advisory Committee.

As a risk/benefit statute, TSCA requires that benefits be estimated and considered in judging whether the risk may be unreasonable. While the risk assessments are being developed, Agency economists will estimate the benefits of the product based on information from the submitter, independent economic research, and consultation with non-Agency experts.

Finally, EPA staff will prepare a summary of the risks and benefits to use in reaching regulatory decisions.

(4) Public involvement in the review. EPA will issue for publication a section 5(d)(2) notice after receipt of a PMN for a new microorganism (see above). EPA will also maintain a copy of the PMN, from which CBI has been deleted, in the OTS Public Information Office at the address listed in Unit VI of the EPA notice. EPA will welcome comments from interested members of the public on the PMN. The public is generally given 30 days to comment on a PMN after publication of the section 5(d)(2) notice.

In addition to the normal procedures for public comment on PMNs, EPA intends that meetings of its biotechnology Science Advisory Committee will be open to the public, although certain portions of meetings may have to be closed to discuss CBI. EPA also intends to charter its committee to include representatives from the lay public. These features will help to ensure that the public has access to information about EPA biotechnology policies and decisions.

(5) Possible regulatory decisions. The Agency may come to one of three decisions at the conclusion of a particular PMN review: (a) there is sufficient information to determine that the risks are reasonable, (b) there is sufficient information to determine that the risks are unreasonable, or (c) there is insufficient information to make a reasoned evaluation of risk, and the substance may present an unreasonable risk or there may be significant or substantial exposure to it.

Where the first decision is made, the Agency will notify the PMN submitter that the manufacture and use may proceed without restriction. In any event, unless the Agency notifies the company to the contrary before the end of the 90-day review period (with a possible 90-day extension), the submitter may begin to manufacture and use the organism.

A decision that risks will be unreasonable leads to two regulatory options. The Agency may require measures to reduce the risks to an acceptable level as a condition of manufacture and use. Alternatively, the Agency may prohibit manufacture or use of the microorganism if there are no alternatives available or practical to reduce the risk sufficiently. Such actions can be taken under TSCA section 5(f).

If the information submitted with the PMN is insufficient for a reasoned evaluation, and EPA finds that the microorganism may present an unreasonable risk or that there may be significant or substantial human exposure to it, or substantial environmental

release, EPA may, under TSCA section 5(e), limit or prohibit the manufacture or use of the microorganism until sufficient data are submitted to the Agency to evaluate the risks.

2. Significant new uses of microorganisms -- a. Overview. EPA intends to supplement its PMN requirements by requiring persons to notify the Agency before they introduce pathogenic microorganisms (including microorganisms containing genetic material from pathogens) into the environment. Notification will be required for new environmental applications of genetically engineered pathogens prior to their release in any amounts into the environment, while notification for nonengineered pathogens will be required at a somewhat later stage, prior to their introduction on more than 10 acres of land (or some equivalent measurement standard in cases where acreage is not applicable, e.g. aquatic uses). If a pathogen used for agricultural purposes is subject to USDA review, it will not be subject to this policy. Applicable definitions may be found in Unit IV.

EPA intends to implement these notification requirements through a significant new use rule (SNUR) under TSCA section 5(a)(2). The public will have the opportunity to comment on the proposed rule, including its scope and possible categories that could be excluded from coverage.

Until the rule is final, EPA expects persons introducing pathogens into the environment for non-agricultural new uses to report to EPA voluntarily. In the unlikely event that an

imminent hazard would arise during this interim period, the Agency could use its authority under section 7 of TSCA to immediately limit or prohibit the manufacture, processing, distribution in commerce, use, or disposal of the hazardous product.

b. SNUR background. Section 5(a)(2) of TSCA (15 U.S.C. 2604(a)(2)) authorizes EPA to determine that a use of a chemical substance is a significant new use. The Agency must make this determination by rule, after consideration of all relevant factors, including those listed in section 5(a)(2). Once EPA determines that a use of a chemical substance is a significant new use, section 5(a)(1)(B) of TSCA requires persons to submit a notice to EPA at least 90 days before they manufacture, import, or process the substance for that use.

Persons subject to a SNUR must comply with most of the same notice requirements and regulatory procedures as submitters of PMNs under section 5(a) of TSCA. EPA's review procedures and regulatory authority are the same for SNUR notices as for PMNs. However, if EPA does not take action on a SNUR notice, section 5(g) of TSCA requires the Agency to explain in the FEDERAL REGISTER its reasons for not taking action. Procedures and requirements for PMN review are described above in Unit III.C.1.

c. SNUR rationale. As explained in the December 84 Notice, EPA recognizes that any approach to defining "new" microorganisms, including the one described in Unit III.C.1,

excludes some types of organisms from PMN review and therefore may not address some significant potential risks. EPA believes there is one currently identifiable category of microorganisms that is not being treated as "new" under TSCA at this time but that should be reviewed before environmental release. That category includes pathogens and microorganisms that contain genetic material from pathogens (henceforth, both are referred to collectively as "pathogens"). As explained in more detail in Unit I, the Agency believes it is necessary to review pathogens released to the environment because of their ability to cause disease in microbes, plants, animals, and humans.

EPA intends to take a slightly different regulatory approach with nonengineered pathogens. The Agency will not require SNUR reporting on the use of nonengineered pathogens until they are to be used on more than 10 acres of land, or some equivalent standard (to be determined) for uses where acreage is an inappropriate standard (e.g. aquatic or subterranean uses). The reason for this exception is explained in Unit I.D, "Rationale for Approach."

To avoid duplicative requirements with USDA, EPA will exclude pathogens used solely for agricultural purposes from the scope of its SNUR. USDA permits to use such organisms are mandatory, while EPA review would be discretionary because these are not "new" organisms. However, new environmental applications of pathogens for non-agricultural purposes will be subject to EPA

review as significant new uses, and will in some cases also be subject to USDA oversight (if they are plant or animal pests under the USDA definition). In such cases, USDA's review will primarily be for the purpose of detecting potential adverse agricultural effects, while EPA's review will focus on the potential non-agricultural impacts. See Unit I.E for an explanation of how the agencies will work together to coordinate their reviews.

EPA is considering whether it should also include provisions in the SNUR requiring notification prior to small-scale releases or commercial uses of other categories of organisms besides pathogens. For example, some people have expressed concern over nonindigenous organisms, and others have expressed concern over organisms that degrade structural components of nature such as lignin and cellulose. Members of neither category are subject to PMN when the organisms involved are naturally occurring or intra-generic (not new), and they would not be subject to the provisions for pathogens described above. However, they may present certain risks because they are new to the environment in which they are used or because of their degradative capabilities. The literature contains much documentation of the adverse effects that have occasionally been caused by nonindigenous organisms such as the chestnut blight fungus and Dutch Elm disease fungus. There is, on the other hand, very little known about many degradative organisms and their potential

for adverse effects. The Agency will request comments on these concerns when it issues its proposed SNUR.

d. Guidelines for voluntary compliance. As stated above, EPA intends to propose a SNUR for persons who manufacture, import, or process pathogenic microorganisms for non-agricultural, new environmental uses. The rule will describe, in detail, the persons who will be subject to the rule and the organisms and activities for which significant new use reporting will be required. In the meantime, EPA strongly encourages persons who are planning new environmental uses of pathogens or organisms with genetic material from known pathogens, except those used solely for agricultural purposes, to report their activities to the Agency and to provide information similar to that required for a PMN for a new microorganism.

For purposes of voluntary reporting, persons may use the following definitions and assumptions. These guidelines may be changed in the proposed and final forms of the SNUR.

(1) How to know if a use would be considered a significant new use. For purposes of voluntary reporting, the Agency encourages people to be as comprehensive as possible and to consider that any new, non-agricultural release of a pathogen to the environment is appropriate to report. "Environmental release" is defined in Unit IV; this definition should be used in the interim until the SNUR is final. Cases that may not be entirely clear, e.g., use in waste-water treatment plants and use

in mines or oil wells, should be reported until the Agency provides further guidance.

Many microorganisms that are pathogens or that contain genetic material from pathogens are being used in the environment already. For example, specific naturally occurring pathogens are used for waste treatment purposes and are tested in non-contained experiments. These applications of these specific organisms cannot be considered significant "new" uses because they are ongoing. Therefore, persons now using pathogens in environmental applications will not be expected to notify the Agency of such uses of these pathogens, except for informational purposes (see Unit III.C.4).

In developing the proposed and final rule, the Agency will have to determine exactly which types of uses should be considered significant new uses, taking into account that the purpose of the rule is to ensure the Agency has the opportunity to review releases of pathogens that could entail significant exposure or risk to the environment or the public. Considerations relating to the appropriate scope of the rule will be discussed in the proposed SNUR, and the public will be invited to comment.

(2) How to know if an organism is a pathogen. Unit IV of this notice contains the definition of "pathogen" that the Agency will use for purposes of administering TSCA and FIFRA, and

provides guidance on how to determine if an organism is a pathogen.

(3) How to know if an organism is genetically engineered. As discussed above, EPA will not require nonengineered pathogens to be reported until they are used on more than ten acres of land (or some equivalent standard, not yet determined, for uses where acreage is an inappropriate standard). For now, a pathogen should be considered nonengineered if there has been no deliberate attempt to promote genetic changes. Any human intervention beyond removal from the environment and selection for the desired variant populations should be considered to result in an engineered organism.

(4) Submitting the significant new use notice. Persons subject to the SNUR will have to notify the Agency at least 90 days prior to any new, non-agricultural use involving environmental release of engineered pathogens. The Agency will treat nonengineered pathogens slightly differently; producers of nonengineered pathogens will be subject to significant new use notification 90 days prior to new uses involving environmental applications on more than 10 acres of land. Significant new use notifications for microorganisms should contain the same general types of information as PMN submissions for microorganisms. In all cases, SNUR notice submitters should initiate prenotice consultations with EPA well in advance of the actual submission, to expedite the Agency's review of the notice.

e. Significant new use notice review. EPA reviews of significant new uses of microorganisms will be conducted in a fashion similar to PMN reviews of microorganisms. The review must be completed in 90 days, extendable for good cause to 180 days. In conducting the review, EPA will use Agency and non-Agency scientists selected for their expertise on issues relevant to the specific case.

The Agency recognizes that various environmental uses of different types of pathogens pose very different levels of potential risk to human health and the environment. For example, risks should generally be lower when pathogens are applied in areas distant from host organisms; the manufacturer has used nonpathogenic strains of a pathogenic species; transfered genes are for a trait not directly involved in pathogenicity; the pathogenic source organisms have very narrow host ranges; and pathogenic genes have been deleted.

Because it recognizes these variations in risk, the Agency expects to subject some pathogenic microorganisms to more rigorous regulatory oversight than others.

3. Research and development (R&D) exemption --

a. Overview. TSCA section 5(h)(3) exempts from PMN and SNUR notification requirements chemical substances manufactured in small quantities solely for R&D. However, to ensure adequate review prior to environmental release, EPA intends to require persons developing "new" microorganisms and certain engineered

pathogens to notify EPA prior to any research involving environmental release. This will be accomplished by amending the PMN rule (and possibly the general SNUR rules in 40 CFR Part 721) to specify that field testing of microorganisms does not fall within the definition of "small quantities" for R&D. Until the necessary rule changes implementing this policy are final, EPA expects submitters to comply with this policy voluntarily. Notice submitters are advised to consult the Agency if they are unsure whether a particular test is subject.

b. Background. As explained in the December 84 notice (at page 50891), section 5(h)(3) of TSCA exempts from PMN requirements new chemical substances produced "only in small quantities solely for purposes of research and development." ("Small quantities" must be defined by rule.) The same exemption applies to substances produced for significant new uses. If this exemption as now defined were applied to living microorganisms, many microorganisms would go unreviewed by EPA until perhaps years after their initial testing in the environment. Because microorganisms can reproduce in the environment and have the potential to exhibit new traits, this has raised the question of whether these field tests for R&D purposes could present significant risks that would go unreviewed.

Because of this concern, an important issue for EPA in implementing the biotechnology program has been whether to alter the R&D exemption of TSCA section 5 notice requirements in the case of living organisms. EPA requested and received substantial

public comments on this issue, which it considered carefully in developing this policy. The comments and EPA's response to them are described in the EPA "Response to Comments" document, available as part of the public record of this EPA notice.

c. Rationale. The PMN rule definition of "small quantities" for R&D has been appropriate for most chemicals subject to TSCA because of the assumption that chemical R&D generally involves limited exposure and therefore limited risk. In the case of field tests involving living microorganisms, this assumption will not always apply. Microorganisms that survive may reproduce, potentially leading to significant exposure and risks. Because of their ability to reproduce and therefore increase beyond the amount originally released, living microorganisms used in the environment cannot be considered to meet the commonly understood meaning of "small quantities" for research and development, and thus do not qualify for the exemption.

d. Implementation. To implement the change in the R&D exemption, EPA intends to amend the PMN rule (40 CFR 720.3(cc) and 720.36) and possibly the SNUR general provisions in the 40 CFR Part 720. The amendments will specify when an organism is considered not to qualify for the R&D exemption, and will provide enforceable standards for that determination.

Until the R&D rule amendments are final, EPA expects commercial researchers intending to release new, living

microorganisms and engineered pathogens into the environment to report their activities to the Agency as explained in the units on PMN and SNUR notification (Units III.C.1 and 2). In addition, EPA strongly encourages researchers, prior to the time of reporting, to maintain records regarding containment procedures used in their experiments. Researchers should use the definition of "environmental release" provided in Unit IV as a guide, ask EPA for further guidance if questions arise, and in general be as inclusive as possible in their estimation of what should be reported.

e. Noncommercial R&D. Noncommercial R&D is exempt from section 5 of TSCA under section 5(g) and would therefore be exempt from PMN and SNUR requirements even under the proposed amendments. EPA has defined "noncommercial" for all chemical substances subject to TSCA section 5 in a final rule published in the FEDERAL REGISTER of April 22, 1986 (51 FR 15096). As a general guide, R&D done by a commercial company should be considered commercial, and purely academic R&D should be considered noncommercial. For more specific guidance, the reader should examine the definition of "noncommercial" in the final rule and the discussion of "noncommercial" in the proposed PMN rule revisions published in the FEDERAL REGISTER of December 27, 1984 (49 CFR 50208). Readers should also note that the NIH Recombinant DNA Advisory Committee (RAC) and USDA Agriculture Biotechnology Recombinant DNA Advisory Committee (ABRAC) have

jurisdiction over many noncommercial R&D activities, specifically recombinant DNA experimentation at institutions that receive funds from NIH and USDA. Both of these committees encourage submission of experiments from other sources as well.

4. General information reporting requirements --

a. Overview. EPA intends to collect general information prior to the environmental use of microorganisms that are subject to TSCA, but that are not the subject of premanufacture or significant new use notification requirements. EPA will gather such information by means of a section 8(a) reporting rule. The information EPA collects will primarily be used to monitor environmental uses of microorganisms, thus making the Agency aware of cases that may require special regulatory action under other TSCA authorities. It will also be used to help the Agency evaluate and modify the scope of its biotechnology programs over time.

b. Section 8(a) background. Section 8(a) of TSCA authorizes EPA to issue rules requiring manufacturers, importers and processors of specified chemical substances to submit information to the Agency. TSCA section 8(a)(2) authorizes the Agency to obtain a broad range of data, including information on chemical identity and structure, production, use, exposure, disposal, and health and environmental effects. Small manufacturers, importers, and processors, as defined by EPA, are exempt from section 8(a) reporting and recordkeeping

requirements, with certain statutory exceptions.

c. Rationale for section 8(a) rule. As explained in the overview to the EPA portion of this notice, the biotechnology review procedures described in this notice are intended to focus on the current areas of highest priority based on considerations of risk and on determinations about what makes an organism "new." However, there is a relatively high degree of scientific uncertainty involved in establishing these priorities at this early stage in the development of the biotechnology industry. The Agency cannot say definitively that all the microorganisms and uses that are not at this time subject to notification requirements will never need to be regulated or should never be subject to notification requirements in the future.

EPA believes that TSCA section 8(a) is the best mechanism available for determining whether specific microorganisms or categories of microorganisms not subject to PMN or SNUR notice requirements may need to be regulated. The Agency must be aware of how microorganisms are being used in the environment to fulfill its responsibility to identify and prevent important or immediate hazards that might unexpectedly arise with specific uses. The section 8(a) reporting will also provide EPA with necessary information to assess whether its overall priorities with regard to biotechnology regulation have been, in fact, appropriately set and whether they should change over time. As was pointed out by many comments on the Agency's first proposed

statement on biotechnology, flexibility and incorporation of new information should be major components of any regulatory scheme.

d. Implementation -- (1) Who will have to report under section 8(a)? When promulgated, EPA intends for this rule to apply to manufacturers, importers, and processors of microorganisms that are subject to TSCA and to be released in the environment, but are not otherwise reviewed under the PMN and SNUR policies described earlier. In other words, general information will be required prior to environmental releases of all microorganisms that are subject to TSCA and that are non-engineered pathogens, or that are intra-generic or naturally occurring non-pathogens.

Although the rule will apply in general to the above groups, small manufacturers, importers, and processors are usually exempt from section 8(a) reporting and recordkeeping requirements. EPA has established general exemption standards for small manufacturers (40 CFR Part 704). The Agency will consider whether these standards should be retained or altered in some way to reflect considerations particular to the biotechnology industry.

When EPA issues its notice of proposed rulemaking, the public will have an opportunity to comment on the question of who will have to report under the rule.

(2) What information will have to be reported under section 8(a)? EPA is in the process of considering exactly what

information it will propose to require on microbial products and uses under the section 8(a) reporting rule. In deciding what information should be reported on microorganisms, EPA will consider what information is necessary for the Agency to assess the safety of planned environmental releases, and to assess its biotechnology regulations over time and consider necessary and appropriate improvements. The Agency will also consider the economic impact of special information and whether the information is generally "known to or reasonably ascertainable by" potential respondents to the rule.

5. Reporting of information on substantial risks. All manufacturers, processors, and distributors of microbial products subject to TSCA, including those involved in research and development, are reminded of their responsibility to notify EPA immediately of any new information which "reasonably supports the conclusion that such substance or mixture presents a substantial risk of injury to health or the environment" (TSCA section 8(e)).

Guidance on the section 8(e) requirement was published in the FEDERAL REGISTER of March 16, 1978 (43 FR 11110). Manufacturers, processors, and distributors will find that this policy statement provides general guidance on TSCA section 8(e) reporting, but it should not be considered exhaustive in terms of the types of information that would reasonably support a conclusion of substantial risk. Specifically with regard to microorganisms, the types of information that should be reported

include but are not limited to (1) pathogenicity to humans, plants, animals, or microbes, (2) significant ability to displace other organisms in the intended use area, (3) significant potential to transfer genetic material to other organisms, and (4) any other significant potential to cause harm to human health or the environment.

Manufacturers, processors, and distributors should be vigilant and immediately report substantial risk information concerning microorganisms subject to TSCA.

6. Exemptions from Premanufacture Notification Requirements. Section 5(h)(4) of TSCA allows EPA, by rule, to exempt from PMN requirements chemical substances that it finds will not present unreasonable risks. EPA expects to use this authority, where appropriate, to reduce the burden of PMN reporting requirements.

In its December 84 notice (at page 50891), EPA asked for comment on the issue of whether certain microorganisms or categories of microorganisms should be exempt from PMN requirements under the authority of section 5(h)(4) of TSCA. Ten respondents stated that organisms used in closed systems should be exempt under the 5(h)(4) provision, although several specifically remarked that appropriate biological and physical containment conditions should first be determined and met. Others suggested modifications to this approach, such as expedited reviews or reduced information requirements rather than

outright exemption, or application of the exemption only to specific organisms or substances (e.g., E. coli. used in contained systems). One commenter believed that an exemption was not appropriate because there is no current Federal authority to determine safety in the event of accidental release.

Under TSCA, the PMN policy described in Unit III.C.1 extends to commercial-scale, closed system uses of microorganisms as well as environmental releases. The statute requires that all manufacturers of "new" substances must submit PMNs, regardless of whether they are used in contained facilities or open environments. Nonetheless, EPA believes that closed-system uses of new microorganisms will often present lower risks than environmental releases of the same organisms. The contained uses may therefore warrant a section 5(h)(4) exemption, and EPA is hereby announcing its intent to pursue that possibility.

Since the Agency does not yet have sufficient information to make the necessary finding under section 5(h)(4) that such activities "will not present an unreasonable risk of injury to human health or the environment," it is soliciting more data to support that finding in the case of closed system uses. The Agency would appreciate receiving data that would support an exemption either for all inter-generic microorganisms used in closed systems, or for specific categories of such microbes. For example, a category that has been suggested for exemption is inter-generic combinations involving organisms that exchange DNA

by known physiologic processes, and that are on the NIH RAC exchanger list. This possible exclusion is mentioned in the OSTP preamble published in this FEDERAL REGISTER.

Information and data relevant to this issue should be sent to EPA at the address listed at the beginning of this notice.

In addition to supporting the use of section 5(h)(4) exemptions, the Agency will try to identify categories of organisms that pose lower risk even though they may not meet the necessary findings for exemption. In such cases, the Agency will consider reducing the burden of PMN reporting by lowering the information requirements associated with the PMN, and by conducting expedited reviews. The Agency requests any data or information that could be used to support exemptions or expedited reviews.

IV. DEFINITIONS OF TERMS FOR REGULATORY PURPOSES

As explained in the previous units of this notice, EPA intends at this time to focus its regulatory programs on microorganisms containing genetic material from dissimilar source organisms (defined as organisms from different genera), pathogenic microorganisms, microorganisms containing genetic material from pathogens, nonindigenous microorganisms, and TSCA nonagricultural environmental applications. Applicable requirements are described in Units II and III of this notice. The purpose of this unit is to provide detailed information on how a person should determine whether a specific product is a

pathogen, contains genetic material from a pathogen, contains genetic material from organisms of different genera (inter-generic combination), is nonindigenous, is released to the environment, or is used for nonagricultural TSCA purposes.

A. HOW TO DETERMINE IF A PRODUCT IS AN INTER-GENERIC COMBINATION

For purposes of implementing its concept of "new" microorganisms, the Agency is defining "new" microorganisms as those formed by deliberate combinations of genetic material from organisms of different genera.

This standard is purposely based on the taxonomic designations of microorganisms. While imperfect in many ways, taxonomy appears to provide the best available standard for "dissimilarity" among organisms, for the following reasons:

1. Although subject to periodic revision within the scientific community, taxonomy is a common language used by scientists to describe how organisms are similar and dissimilar (Refs. 4, 18).

2. Taxonomy reflects the most recent scientific observations about phenotypic and genotypic differences between organisms.

3. Taxonomy provides a universally available point of reference that can be understood by industry and enforced by the Agency.

4. EPA expects microorganisms being used in biotechnology

research and development will have or can be assigned clear taxonomic designations; therefore, the use of taxonomic standards imposes few if any additional requirements on industry.

5. There is a significant administrative advantage to independently established criteria such as taxonomic standards, because EPA will not have to create and maintain a separate set of criteria for regulatory purposes.

The Agency expects all manufacturers to know or determine the currently accepted designations (genus, species) of the source organisms they have used in producing microbial products subject to FIFRA and TSCA. In addition, EPA expects submitters to use taxonomic literature and taxonomic experts, if necessary, to determine the correct identity of their microorganisms. A number of comments on the December 84 Notice stated that organisms manipulated by modern genetic engineering will in most cases already be well characterized. This fact should make implementation of this policy relatively easy in most cases.

Excluded from this policy on inter-generic combinations are organisms that have resulted from the addition of inter-generic material that is well-characterized and contains only non-coding regulatory regions such as operators, promoters, origins of replication, terminators, and ribosome-binding regions.

"Well-characterized, non-coding regulatory regions" means that the producer of the microorganism can document the

following:

a. The exact nucleotide base sequences of the regulatory region and any inserted flanking nucleotides.

b. The regulatory region and any inserted flanking nucleotides do not code for protein, peptide, or functional RNA molecules.

c. The regulatory region solely controls the activity of other regions that code for protein or peptide molecules or act as recognition sites for the initiation of nucleic acid or protein synthesis.

EPA emphasizes that this policy excludes only inter-generic combinations that have resulted solely from the addition of well-characterized, non-coding regulatory regions. If the final organism contains any regions from organisms of other genera that do not meet this restriction, such as coding regulatory regions or any poorly characterized regions, the organism is considered new and does not come under the exclusion for regulatory regions discussed above.

To document these features, EPA expects that companies will use sources such as citations to published scientific literature, copies of unpublished studies relied upon, or data from tests performed to determine the above characteristics.

If persons do not know the genera of particular organisms, they should consult standard sources such as the following:

i. Bacteria

(1) Skerman, V.B.D., V. McGowan, and P.H.A, Sneath. 1980. Approved list of bacterial names. International Journal of Systematic Bacteriology 30:225-420.

(2) Moore, W.E.C., E.P. Cato, and L.V.H. Moore. 1985. Index of the bacterial and yeast nomenclature changes published in the International Journal of Systematic Bacteriology since the 1980 approved list of bacterial names (1 January 1980 to 1 January 1985). International Journal of Systematic Bacteriology 35:382-407.

Manufacturers should consult issues of the International Journal of Systematic Bacteriology for validly published names and for names placed on Validation Lists since January 1985.

ii. Algae

(1) DeToni, 1889. Sylloge Algarum.

(2) Index Kewensis. 1895-present. (Royal Botanical Gardens, Kew.)

iii. Protozoa

(1) Nomenclator Zoologicus. 1758-present. Published in four volumes and two supplements from 1939 onwards. Edited by S.A. Neave. Zoological

Society, London.

(2) Index Zoologicus. 1800-1900. Charles Owen Waterhouse. (Published 1902.) Edited by David Sharpe. Zoological Society, London.

(3) Index Zoologicus. 1902-present. (Zoological Society, London.)

iv. Fungi

(1) Saccardo, P.A. 1882-1921. Sylloge Fungorum. (Pavia, 25 vol.)

(2) Clements, F.E. and C.L. Shear. 1931. The Genera of Fungi (H.W. Wilson and Co., N.Y.)

(3) Index to Fungi. 1940-present. Commonwealth Mycological Institute, Kew, Surrey, England.

(4) Petrak's List of Fungal Names. 1922-1940. Commonwealth Mycological Institute, Kew, Surrey, England.

(5) Hawksworth, D.L., B.C. Sutton, and G.C. Ainsworth. 1983. Ainsworth and Bisby's Dictionary of the Fungi. Commonwealth Mycological Institute, Kew, Surrey, England.

v. Viruses

(1) Mathews, R.E.F. 1979. Classification and nomenclature of viruses, 3rd report of the International Committee on Taxonomy of Viruses.

Intervirology 12(3-5):1-199.

If the taxonomic positions of source organisms are ambiguous or if the boundaries of a genus are in dispute, the Agency expects the submitter to be aware of these controversies. Ambiguities at the species level or lower will not affect the FIFRA and TSCA policies. However, if the taxonomy at the genus level is controversial, such that organisms may be considered by some to belong to the same genus and by others to belong to different genera, the submitter must comply with the applicable requirements of FIFRA or TSCA, or come to EPA for a case-specific determination (address provided at the beginning of this notice). In general, submitters should expect that organisms will be considered inter-generic if the taxonomy of either source organism, at the genus level, is controversial.

In the case of chemically synthesized genes, the Agency will follow a similar principle. The genetic sequence of the synthesized gene may be identical to a sequence known to occur in an organism in the same genus as the recipient organism. If so, the resulting organism will be considered intra-generic. However, the producer should be prepared to document how it made this determination. Conversely, the sequence of the synthesized gene may be different or not known to be identical to a sequence in the genus of the recipient organism. In this case, the resulting product will be considered inter-generic.

EPA's definition of inter-generic combinations contains a standard of intent on the part of the manufacturer or producer. Inter-generic combinations that occur as unintentional by-products of microorganisms coming in contact with one another will not be considered subject to the provisions of TSCA and FIFRA that apply to inter-generic combinations. For example, inter-generic combinations may occur at very low frequencies if microorganisms from different genera are applied to the same plot of land, or are sold together as mixtures. Similarly, if manufacturers develop organisms that are naturally infected with viruses, and if the developer did not intend to promote and did not provide conditions actively promoting the infection of the organisms with the naturally occurring viruses, then the microorganisms containing naturally occurring inter-generic combinations would not be considered inter-generic under the FIFRA and TSCA policies.

On the other hand, if the manufacturer or producer intentionally provides conditions to promote genetic transfer, or if inter-generic organisms are primary components of a product or mixture, then the microorganisms will be considered inter-generic and subject to the applicable provisions of FIFRA and TSCA.

Submitters should consult the Agency if they have any questions about these distinctions.

B. HOW TO DETERMINE IF A PRODUCT IS A PATHOGEN

For the purposes of this policy, a pathogen is defined as a virus or organism (including its viruses and plasmids, if any) that has the ability to cause disease in other living organisms (i.e., humans, animals, plants, or microorganisms). A disease is an abnormal physiological function in an organism, occurring as a consequence of the activity of proliferating microorganisms directly associated with or infecting the host organism, or due to biologically active substances such as toxins, antibiotics, or growth regulators produced by a microorganism (Refs. 5, 6, 7, 8, 14, 19).

This policy is not meant to include such organisms as competitors or colonizers of the same substrates, commensalistic or mutualistic microorganisms, or opportunistic pathogens. However, if a microorganism has more than one mechanism for affecting other organisms and one of these is pathogenicity, then the microorganism is considered to be a pathogen.

A microorganism will be subject to EPA policies regarding pathogens if:

1. The organism belongs to a pathogenic species or to a species containing pathogenic strains, according to sources identified by EPA below, or from information known to the producer that suggests that the organism is a pathogen; excepted are organisms belonging to a strain used for laboratory research or commercial purposes and generally recognized as non-pathogenic

according to sources identified by EPA, or information known to the producer and EPA; an example of a nonpathogenic strain of a pathogenic species is Escherichia coli K-12; examples of nonpathogenic species are Bacillus subtilis, Lactobacillus acidophilus, and Saccharomyces species; or,

2. The organism has been derived from a pathogen or has been deliberately engineered such that it contains genetic material from a pathogenic organism as defined in item 1, above. An exception to this requirement is a genetically engineered organism developed by transferring well-characterized, non-coding regulatory regions from a pathogenic donor to a nonpathogenic recipient.

"Well-characterized, non-coding regulatory region" means that the producer of the microorganism can document the following:

a. The exact nucleotide base sequences of the regulatory region and any inserted flanking nucleotides.

b. The regulatory region and any inserted flanking nucleotides do not code for protein, peptide, or functional RNA molecules.

c. The regulatory region solely controls the activity of other regions that code for protein or peptide molecules or act as recognition sites for the initiation of nucleic acid or protein synthesis.

To document these items, EPA expects that companies will use sources such as citations to published scientific literature, copies of unpublished studies, or data from tests performed to determine the above characteristics.

The Agency is excluding genetically engineered organisms containing material from pathogens if the material transferred is from a pathogenic donor to a nonpathogenic recipient, and consists solely of well-characterized, non-coding regulatory regions. In this case, the transferred material does not code for traits directly associated with pathogenicity. The Agency believes that these organisms do not pose significant risks because they do not possess new combinations of traits or pathogenic traits, but instead exhibit quantitative changes in preexisting traits in a nonpathogenic recipient.

The Agency is excluding opportunistic pathogens for two reasons. First, in terms of risk priorities, outright pathogens are of significantly greater concern than organisms that would not act as pathogens except under unusual circumstances. Second, because of the very large number of microorganisms that could be considered to be opportunistic, their inclusion would result in an inappropriately restrictive policy.

There are a number of standard sources that can be used to determine whether a microorganism belongs to a pathogenic species. EPA is compiling a list of such sources, and is

considering developing a list of pathogenic species, as part of future rulemaking activities. As interim guidance, persons should consider sources such as the following:

(1) Anne, W., ed. 1980. Fish Diseases. Springer-Verlag, New York.

(2) Anver, M.R. and C. Pond. 1984. Biology and Diseases of Amphibians. In Laboratory Animal Medicine, J.G. Fox, B.J. Cohen, F.M. Loew, eds. Academic Press, Orlando, FL.

(3) Bliss, D.E., ed. 1982-1985. Biology of Crustaceans (Volume 6 Pathobiology). Academic Press, New York.

(4) Blood, D.C., J.A. Henderson, and O.M. Radostits. 1979. Veterinary Medicine: A Textbook of the Diseases of Cattle, Sheep, Pigs, and Horses. 5th edition. Lea & Febiger, Philadelphia, PA.

(5) Braude, A. 1986. Medical Microbiology and Infectious Diseases. 2nd edition. W.B. Saunders, Philadelphia, PA.

(6) Buchanan, A.M. 1982. Veterinary Microbiology. Elsevier Scientific, Amsterdam.

(7) Buchanan, R.E. and N.E. Gibbons, eds. 1974. Bergey's Manual of Determinative

Bacteriology. 8th edition. Williams and Wilkins Co., Baltimore.

(8) Cantwell, G.E., ed. Insect Diseases, M. Dekker, New York

(9) Commonwealth Mycological Institute. Descriptions of Plant Pathogenic Bacteria, Fungi, and Viruses. Commonwealth Agricultural Bureaux, Kew, Surrey, England.

(10) Davidson, E., ed. 1981. Pathogenesis of Invertebrate Microbial Diseases. Allanheld, Osmum, Totowa, NJ.

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The Agency expects that producers will be sufficiently familiar with the relevant literature and the species of the microorganisms under development that the pathogenicity or lack of it will already be known. Therefore, the Agency does not believe that determining whether an organism belongs to a pathogenic species based on published sources will be burdensome.

Where there is disagreement among sources about whether a strain belongs to a pathogenic species, the submitter must assume that it belongs to a pathogenic species, or come to EPA for a case-specific determination (address provided at the beginning of this notice).

As part of further rulemaking, the Agency plans to develop a list of nonpathogenic strains of pathogenic species, in addition to *E. coli* K-12, that will be exempt from Agency policies for pathogenic microorganisms. In the interim, if a submitter is using a strain that belongs to a pathogenic species, except *E. coli* K-12, the submitter should assume that it is pathogenic.

Because of the pathogenic potential of most, if not all, viruses, and because the species concept does not generally apply

in virus taxonomy, the Agency will consider any product that is or contains genetic material from a virus to be a pathogen.

The Agency intends to update this guidance periodically, particularly the list of publications.

C. HOW TO DETERMINE IF A PRODUCT IS A NONINDIGENOUS MICROORGANISM

A microorganism will be considered nonindigenous to any one of the geographic areas listed below if it is isolated from outside that area:

1. The continental United States, including Alaska, and the immediately adjoining countries (i.e., Canada and Mexico).

2. The Hawaiian Islands.

3. The Caribbean Islands including Puerto Rico and the U.S. Virgin Islands.

For example, a microorganism from Hawaii, developed for use as a microbial pesticide in the continental U.S., will be considered to be nonindigenous to the continental United States. Under FIFRA, the Agency would therefore be notified before initiation of small-scale field testing of the microbial pesticide in the continental U.S.

In normal usage, nonindigenous organisms are generally considered to be naturally occurring organisms placed in environments where they are not native or have not evolved. This concept means that a microorganism could be considered nonindigenous to an ecosystem that is adjacent to the one in

which it evolved, nonindigenous to ecosytems far removed, or even indigenous to nearby or far-removed ecosystems. This happens for a number of reasons such as the widely varying effects of geographic barriers as isolating mechanisms; microbial dispersal mechanisms; and the biological, chemical, and physical features shaping different environments. Given the complexity and impracticality of determining whether a particular microoganism is indigenous to a wide range of habitats that may exist within regions and states, the Agency has selected continental boundaries to describe geographic regions that are clearly isolated and are easily used for administrative purposes. These boundaries will be used to determine whether a microorganism is nonindigenous and hence subject to particular provisions under FIFRA (see Unit II).

D. HOW TO DETERMINE IF A PRODUCT IS RELEASED TO THE ENVIRONMENT

In the future, it is likely that a definition of environmental release will be developed. In the interim, the Agency's approach will focus on when an organism is considered to be contained rather than when it is released.

An organism will be considered environmentally contained if the organism is used in a laboratory that complies with NIH RAC guidelines; or the organism is used in a contained greenhouse, fermenter, or other contained structure. In general, "contained greenhouse, fermenter, or other contained structure" means a

building or structure that has a roof and walls. It should also have a ventilation system to minimize microbial release to the outdoors, a system for sterilizing water runoff and wastes, and a system for restricting insects, if any of these are plausible routes for dissemination of microorganisms. Experimenters should control pests, sterilize soil or other material containing microorganisms before disposal or reuse, and generally limit access only to those persons who must have access for research purposes.

E. HOW TO DETERMINE IF A PRODUCT IS USED FOR NONAGRICULTURAL PURPOSES

An agricultural use of a microorganism is any use or application, the primary purpose of which is to produce, enhance, or cultivate plants or animals. The definition is not meant to include pesticides.

F. DEFINITION OF PLANTS AND ANIMALS

For the purposes of this EPA notice, plants are defined as multicellular organisms characterized by eukaryotic cell walls, photosynthetic ability, and embryonic development. Members include mosses, liverworts, and vascular plants (including most terrestrial crop plants). Animals are defined as multicellular organisms composed of eukaryotic cells with ingestive nutrition and lacking rigid cell walls and photosynthetic ability. Members

include coelenterates, flatworms, molluscs, segmented worms, arthropods, echinoderms, and vertebrates.

V. REFERENCES

The following books, articles, and reports were used in preparing this notice:

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VI. PUBLIC RECORD

EPA has established a public record for this statement of policy (docket number OPTS-00049A) which is available to the public in the OTS Public Information Office, 8 a.m. to 4 p.m., Monday through Friday, except legal holidays.

The Public Information Office is located in Rm. E-107,

401 M. St. S.W., Washington, D.C. 20460. The record includes all information considered by EPA in formulating this policy. The record includes the following categories of information:

1. FEDERAL REGISTER notices.

2. Support documents and reports.

3. Public comments, summaries of comments, and EPA's responses to comments on the EPA December 1984 Notice on biotechnology (49 FR 50860).

4. Communications.

The record also includes, by reference, published literature cited in this policy statement and generally available.

The docket of the record detailing its specific contents is available in the OTS Reading Room.

VII. REGULATORY ASSESSMENT REQUIREMENTS

A. REGULATORY FLEXIBILITY ACT

As required by the Regulatory Flexibility Act (5 U.S.C. 605(b)), EPA has assessed the impact of the immediately effective aspects of this policy on small businesses. EPA has determined that the immediately effective requirements will not create additional impacts on small businesses over those already identified in the final PMN rule, 40 CFR Part 720, and the Interim Policy for small-scale field testing of microbial pesticides (49 FR 40659).

B. PAPERWORK REDUCTION ACT

The information collection requirements contained in this policy have been approved by the Office of Management and Budget (OMB) under provisions of the Paperwork Reduction Act of 1980, 44 U.S.C. 3501 et seq. and have been assigned OMB control numbers 2070-0012 and 2070-0069.

Dated: _____

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Administrator.