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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

RECOMBINANT DNA ADVISORY COMMITTEE
WORKING GROUP ON RELEASE INTO THE ENVIRONMENT
MINUTES OF MEETING¹

FEBRUARY 11, 1985

The Working Group on Release into the Environment of the Recombinant DNA Advisory Committee was convened at 9:00 a.m. on February 11, 1985, at the National Institutes of Health, Stone House, 9000 Rockville Pike, Bethesda, Maryland 20205. The meeting was open to the public. Dr. Gerard McGarrity was the Chair. The following people were present for all or part of the meeting:

Working Group Members:

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| Charles Arntzen | David Pramer |
| Royston Clowes | Thomas Pirone |
| Nina Fedoroff | Frances Sharples |
| Susan Gottesman | Anne Vidaver |
| George Lacy | Elizabeth Milewski |
| Gerard McGarrity | (Executive Secretary) |
| David Pimentel | |

A working group roster is attached (Attachment I).

Ad Hoc Consultants:

Robert Colwell, University of California, Berkeley
Susan Hirano, University of Wisconsin

Liaison Representatives:

Morris Levin, Environmental Protection Agency
Henry Miller, Food and Drug Administration
Sue Tolin, U.S. Department of Agriculture

Other National Institutes of Health Staff:

Kenneth Cremer, NIDR
William Gartland, NIAID

¹The working group is advisory to the RAC, and its recommendations should not be considered as final or accepted.

Others:

Fred Betz, Environmental Protection Agency
Irene Brandt, Eli Lilly and Company
Marie A. Dray, Pharmaceutical Manufacturers Association
Charles J. Eby, Monsanto Company
Joseph R. Fiksel, Arthur D. Little, Inc.
Richard Fink, Massachusetts Institute of Technology
Alan Goldhammer, Industrial Biotechnology Association
Robert Lee Hotz, Atlanta Journal
Carl Mazza, Environmental Protection Agency
Elliott A. Norse, Ecological Society of America
Jane Rissler, Environmental Protection Agency
J. David Sakura, Arthur D. Little, Inc.
Mark C. Segal, Environmental Protection Agency
Smita Sidhanti, University of Pittsburgh
Zigfridas Vaituzis, Environmental Protection Agency
Patricia Williams, F-D-C Reports, Inc.
Judith Wortman, American Institute of Biological Sciences

Dr. McGarrity called the meeting of the Working Group on Release into the Environment to order at 9:00 a.m. He asked the participants to identify themselves.

Dr. McGarrity said four agenda items would be addressed during the meeting: (1) updates on agency activities related to field testing of genetically modified organisms from the National Institutes of Health (NIH), Environmental Protection Agency (EPA), U.S. Department of Agriculture (USDA), National Science Foundation (NSF), and the Food and Drug Administration (FDA); (2) the guidance document entitled "Points to Consider for Submissions Involving Testing in the Environment of Microorganisms Derived by Recombinant DNA Techniques" (Attachments II and III); (3) an update on the conference being organized by the American Society for Microbiology (ASM) on the effects of releases of modified organisms into the environment; and (4) B11 testing conditions for modified microorganisms in greenhouses (Attachment IV).

UPDATES ON AGENCY ACTIVITIES

Dr. Gartland said the Federal Register of December 31, 1984, contains a proposal for a coordinated framework for regulation of biotechnology. This Federal Register attempts to provide a concise index of U.S. laws related to biotechnology, to clarify the policies of the major regulatory agencies involved in reviewing products and processes of biotechnology, to describe a scientific advisory mechanism for assessment of biotechnology issues, and to explain how the activities of the Federal agencies will be coordinated.

Dr. Gartland said the Recombinant DNA Advisory Committee (RAC) was instituted in 1974 to oversee the NIH Guidelines for Research Involving Recombinant DNA Molecules. Review of biomedical research applications has been and will probably continue to be RAC's major emphasis.

Dr. Gartland said the NIH had given approval for field testing of three different proposals involving organisms modified using recombinant DNA. These proposed tests are currently enjoined under the lawsuit brought against the NIH and Department of Health and Human Services (DHHS) by the Foundation on Economic Trends. The NIH has recently completed an Environmental Assessment (EA) on one of these cases (the proposal by Drs. Stephen Lindow and Nickolas Rancopoulos of the University of California, Berkeley, to field test modified ice nucleating bacteria). This EA has been filed by the NIH with the U.S. Court of Appeals; the NIH is requesting the injunction be lifted and field testing be allowed to proceed while the court is considering the lawsuit filed by the Foundation on Economic Trends.

Dr. Gartland said no NSF representative is attending the February 11, 1985, meeting of the Working Group on Release into the Environment; he could report, however, that NSF is attempting to institute a committee to deal with ecology issues in biotechnology.

Dr. Morris Levin of the EPA said EPA is assembling a risk assessment program on environmental impacts of introductions of modified organisms. The EPA is

also beginning to constitute a committee to review proposals involving environmental release of modified organisms.

Dr. Jane Rissler of the EPA added that the December 31, 1984, Federal Register contained EPA's policy position; EPA is awaiting comment on this announcement.

Dr. Tolin of the USDA said USDA is awaiting comments on USDA's policy statement published in the December 31, 1984, Federal Register. She said USDA is evaluating whether it will establish a RAC-like review body.

Dr. Miller of FDA said the FDA position statement in the December 31, 1984, Federal Register is self-explanatory. The FDA is considering several alternative methods of obtaining scientific input in FDA decisions. An FDA review committee which resembles the RAC may be instituted or the review committee may resemble other FDA advisory committees. Alternatively, the FDA review committee may have a structure somewhat like RAC and somewhat like other FDA advisory committees.

Dr. Sharples asked if an interagency coordinating committee would also be instituted. Dr. Gartland replied that the December 31, 1984, Federal Register proposes the establishment of a Biotechnology Science Board; however, the Cabinet Council Working Group is currently filling the function of an interagency coordinating committee.

POINTS TO CONSIDER FOR SUBMISSIONS INVOLVING TESTING IN THE ENVIRONMENT OF MICROORGANISMS DERIVED BY RECOMBINANT DNA TECHNIQUES

Dr. Gartland said in the future, proposals involving field testing of modified microorganisms may be reviewed by agencies other than the NIH. The working group should, however, continue developing this points to consider document for several reasons: (1) the document the working group develops may be useful to any other agency reviewing field tests of genetically modified microorganisms; and (2) a system of dual review in which a proposal may be submitted to more than one committee for review is being proposed. The RAC may be asked to review proposals involving field testing of modified microorganisms, and this document would be useful in such reviews.

Dr. McGarrity reviewed the history of the development of the points to consider document. At the October 5, 1984, meeting of the Working Group on Release into the Environment, the working group constructed a draft document based on portions of a subgroup document developed by Drs. Lacy, Milewski, Pirone, Tolin, and Vidaver and portions of the EPA document entitled Points to Consider in the Preparation of TSCA Premanufacturing Notices for Genetically-Engineered Microorganisms which the EPA had sent to the working group to elicit comment and to provide information. Dr. McGarrity said the working group had subsequently met on October 30, 1984, to continue to develop the document. The document (Attachments II and III) the working group will discuss at the February 11, 1985, meeting is the current draft version of the points to consider.

Dr. McGarrity said this draft document contains a Section V (Attachment III) dealing with risk analysis written by Drs. Tolin and Lacy. He suggested the working group begin by discussing this portion of the document.

Dr. Tolin said Section V, Risk Analysis, attempts to offer guidance on synthesizing and analyzing the information requested in Sections II, III, and IV of the document. The nature of the modified organism and the nature of the proposed tests are emphasized as major considerations. Part A, The Nature of the Organism, of Section V poses a question for each of the major sections of the working group document. Part B, The Nature of the Test, of Section V requests a summary of testing protocol information. Section V does not indicate how the proposal will be reviewed.

Dr. Robert Colwell of the University of California, Berkeley, felt proposed Section V was a good primer. He was troubled, however, by the section's declarative format. He suggested the language of proposed Section V be softened by adding the phrases "proper and appropriate" and "if necessary."

Dr. Pimentel agreed proposed Section V was well thought out. He suggested the committee consider substituting the word "predicted" for the word "probability" in Section V.

Dr. McGarrity suggested the working group begin by considering the first two sentences of Section V. These sentences read as follows:

"Small-scale field testing is a necessary part of risk analysis since artificial environments are not adequate simulations of natural environments. However, field testing must not be undertaken until results of field testing in artificial contained environments, together with careful consideration of the genetics, biology, and ecology of the nonmodified and the modified organisms, enable a reasonable prediction that no environmental risk will result from the release of the modified organism in the small-scale test."

Dr. Gottesman said the language in the second sentence suggesting test results should permit a reasonable prediction of "no environmental risk" is too absolute. She pointed out that some risk of adverse environmental effects might be acceptable in certain cases in view of potential benefits. In addition, RAC might recognize some cases as "trivial" and require less stringent review.

Dr. Pimentel said the document should not allude to "trivial cases," as it is currently impossible to determine which proposals would require less stringent review. Dr. Sharples agreed; she said even if the organism is familiar, it should be evaluated in the context of the proposed field test.

Dr. Pimentel suggested the first sentence should indicate artificial environments are "not fully" adequate simulations. Dr. Vidaver suggested the sentence should state artificial environments are "not necessarily" adequate simulations. Dr. Colwell suggested artificial environments are "not always" adequate simulations.

Dr. Carl Mazza of the EPA suggested the first two sentences in Section V be deleted. He felt these sentences did not discuss any new concepts; the document's preamble states the reasons field testing is necessary. The second sentence could be interpreted as categorically stating that field testing must not be undertaken until closed system testing indicates no environmental risk will occur.

Dr. Miller agreed with Dr. Mazza. He suggested the tone of the second sentence, if this sentence is retained in the section, should be less imperative.

Drs. Vidaver and Tolin felt the concept that artificial environments are not necessarily simulants of natural environments should be reiterated in Section V since this section is the most important section of the document.

Dr. Gottesman suggested the first sentence of Section V be deleted. The clause, "However, field testing must not be undertaken" of the second sentence should also be deleted. Dr. Gottesman reiterated that in some cases some risk might be acceptable in view of large benefits. If the working group concludes some risk exists, the working group might impose additional controls in the field test.

Dr. Sharples said the working group wishes to know whether or not the proposed field test might present a risk; the language of the second sentence should reflect this desire.

Dr. Fedoroff suggested the words "risk of environmental damage" should be substituted for the words "environmental risk."

Dr. Gottesman suggested the word "risks" in the third sentence be modified by the word "possible."

Dr. Colwell suggested the fourth sentence read as follows:

"The issues addressed might include, but not be limited to, the following:"

Dr. Gottesman moved that the working group accept three sentences modified as follows:

"Results of testing in artificial contained environments together with careful consideration of the genetics, biology, and ecology of the nonmodified and the modified organisms will enable a reasonable prediction of whether or not significant risk of environmental damage will result from the release of the modified organism in the small-scale field test. In this section, the information requested in Sections II, III and IV should be summarized to present an analysis of possible risks to the environment in the test as it is proposed. The issues addressed might include but not be limited to the following items:"

By a vote of eleven in favor, none opposed, and one abstention, the working group accepted the proposed language.

Dr. McGarrity called the attention of the working group to Section V-A-1 of Section V-A, The Nature of the Organism. Section V-A-1 reads as follows:

"The role of the nonmodified organism in the environment of the test site is essentially understood, including any adverse effects on other organisms."

Dr. Fedoroff thought the declarative format would not elicit the desired information. Dr. Sharples suggested these items should be in the form of "points for consideration" rather in the form of declarative statements. The working group agreed to this format change. Dr. Colwell suggested the words "is essentially understood" should be deleted from this section. The working group agreed to these proposed modifications.

Dr. McGarrity then drew the attention of the working group to Section V-A-2 which reads as follows:

"Analysis of the genetic modification (e.g., deletion, insertion, modification of specific DNA sequences) would predict that the probability of adverse effects on the environment is low."

Dr. Fedoroff questioned the intended purpose of Section V-A-2. She suggested this section as written asks investigators to give their best guess.

Dr. Gottesman suggested Sections V-A-2 and V-A-3 might be combined into a single section addressing both the genetic modification and an evaluation of the predicted effect.

Dr. Pirone did not feel these sections should be combined. He felt Section V-A-2 requests distinctly different information than Section V-A-3.

Dr. Pimentel said Section V-A-2 requests information on the genetic modification; Section V-A-3 should request information on the potential effects of the modified organism on the environment. Dr. Colwell thought Section V-A-2 requested information on the construction of the organism. He felt this section should also elicit information on whether the introduced genetic information might be transferred to other organisms. Drs. Colwell and Pimentel felt combining Sections V-A-2 and V-A-3 would create a very complex information request.

Dr. Fedoroff thought the document should ask for an evaluation of the possibility the introduced genetic modification might result in adverse effects on the environment. Dr. Arntzen thought Dr. Fedoroff's proposed information request would be too global. Section V-A-2 should simply request information about the organism's stability.

Dr. Hirano suggested Section V-A-2 should request "an evaluation of the risk associated with the procedures used to modify the organism."

Dr. Pramer thought Section V-A-2 should address the concept that the genetic modification either poses no risk or presents a quantifiable risk to the environment. Dr. Fedoroff said the genetic modification does not affect the environment; rather the modified organism affects the environment.

Dr. Gottesman suggested Section V-A-2 should request an evaluation of the predicted effect of the genetic modification on the properties of the nonmodified parent organism in the environment. Dr. Colwell pointed out that Dr. Gottesman's proposed language did not contain the concept of risk.

Dr. Tolin suggested and Dr. Pimentel moved the following language:

"Evaluation of whether or not the specific genetic modification (e.g., deletion, insertion, modification of species DNA sequences) would alter the potential for risk."

Dr. Colwell suggested the words "significant adverse effects" can be substituted for the word "risk." Dr. Pimentel agreed to Dr. Colwell's suggestion. Dr. Pramer seconded the motion.

By a vote of eleven in favor, none opposed, and no abstentions, the working group agreed to this proposed language for Section V-A-2.

Dr. McGarrity drew the attention of the working group to Section V-A-3 which reads as follows:

"Analysis of the tests conducted under contained environments would predict that the modified organism would behave no differently, except for the known genetic modification, from the nonmodified organism in the environment of the test site."

Dr. Colwell suggested this section should request an analysis of the behavior of the modified organism in contained environments in relation to the behavior of the nonmodified parental organism in the test site.

Dr. Fedoroff said Section V-A-3 should request an analysis of the evidence the modified organism will not behave differently, except for the proposed modification, than the parent organism in the test site. Dr. Pramer suggested for most proposals such an analysis would be conjecture or opinion.

Dr. Miller proposed and moved acceptance of the following language:

"Evaluation of results of tests conducted in contained environments to predict the behavior of the modified organism relative to its unmodified precursor."

Dr. Pimentel suggested the word "behavior" be modified by the word "ecological." Dr. Tolin suggested the words "nonmodified parent" be substituted for the words "unmodified precursor." She emphasized the contained systems used to test the organism should be similar to the field test site: e.g., if the organism is to be field tested in the desert, the working group wants information generated in contained systems similar to deserts and not data generated in hothouses.

By a vote of eleven in favor, none opposed, and no abstentions, the working group accepted the modified language.

Dr. McGarrity drew the attention of the working group to Section V-A-4 which reads as follows:

"A worst-case scenario (e.g., increased survival, reproductive capacity, dispersal, transfer of the genetic modification to other organisms, etc.) would predict that no risks greater than those caused by the normodified organism will occur."

Dr. Fedoroff said she did not understand the logic of requesting a worst case scenario; would the investigator construct such a hypothetical situation to prove it would not occur. She thought this requirement would bias investigators' responses.

Dr. Colwell said Section V-A-4 should request an evaluation of the possibility of adverse effect rather than an attempt to concoct a worst case scenario.

Dr. Gottesman thought requesting a worst case evaluation would create problems; someone will always conceive of a different worst case scenario than the investigator or the working group.

Dr. Pimentel pointed out that the EPA uses worst case analysis in evaluating pesticides or toxic substances. He said this exercise provides useful information and perspective.

Dr. Pramer pointed out that evaluating field tests of modified organisms differs from evaluating the effects of pesticides or toxic chemicals. Pesticides generally present real risk; field testing of modified organisms presents an evaluation of hypothetical risk. He thought using the words "worst case scenario" would create anxiety and invite individuals to engage in creative imagery attempts to discuss risk.

Dr. Miller said worst case scenarios provided useful information in some risk evaluations. He gave as an example the calculations performed at the Pasadena, California, conference in 1980 on maximum potential foreign protein production by an engineered microorganism. [Executive Secretary's Note: The Workshop on Recombinant DNA Risk Assessment was held on April 11-12, 1980, and sponsored by the National Institute of Allergy and Infectious Diseases.] Dr. McGarrity said many additional factors must be considered in evaluating environmental releases of engineered organisms than were considered by the participants at the Pasadena meeting.

Drs. Fedoroff and Gottesman suggested the section referring to the worst case scenario be deleted from the document. Dr. Fedoroff moved that Section V-A-4 be deleted. Dr. Pirone seconded the motion. By a vote of seven in favor, three opposed, and one abstention, the working group agreed to delete Section V-A-4.

Dr. McGarrity called the attention of the working group to the section entitled The Nature of the Test. Dr. Tolin said the construction of this section parallels the construction of the section The Nature of the Organism. Dr. Tolin said Section B of Section V requests information on the conditions

of the trial. It asks how the test site was chosen and designed and how these considerations will minimize risk. She said Section V-B-1 reads as follows:

"The test site is of limited size or area and is reasonably isolated from potentially adversely affected ecosystems."

Dr. Fedoroff suggested this section of the document should ask the investigator to defend the choice of site. Dr. Miller suggested the language of Section V-B-1 should read as follows:

"Justify the selection of the test site with respect to its size, location, isolation, etc."

Dr. Alan Goldhammer of the Industrial Biotechnology Association (IBA) asked if the working group would impose a geographical restriction on test sites. He thought EPA documents do not specify this type of restriction. Dr. Rissler said the location of the test site will be of concern to EPA.

Dr. Colwell said the working group would like to know the location of the test site. Dr. Sharples said the working group would evaluate how site selection factors contribute to minimizing risk. Dr. Pramer said Section V-B-1 should ask the investigator how risk management considerations will influence test site selection.

Dr. Pimentel moved that the working group accept Dr. Miller's proposed language for Section V-B-1.

Dr. Fedoroff suggested the abbreviation "etc." be replaced by the words "other relevant factors." Dr. Colwell suggested the "etc." be replaced by the phrase "other factors relevant to risk." The working group agreed to the proposed language by a vote of nine in favor, none opposed, and two abstentions.

Dr. Tolin said Section V-B-2 addresses points of particular importance in introducing the test material. She felt three important issues were: (1) the application method; (2) the time of application; and (3) the introduction protocols. Section V-B-2 reads as follows:

"Introduction protocols are designed to decrease any potential non-target effects of the modified organism."

Dr. Fedoroff said this section solicits information on the features of the introduction protocols that would minimize or eliminate adverse effects. Dr. Pimentel thought Section V-B-2 should discuss the design of the introduction protocols and request a justification of why the design of the introduction protocols would reduce risk to the environment.

Dr. Gottesman asked whether Sections V-B-2 and V-B-3 could be combined.

Dr. Fedoroff did not think Dr. Gottesman's proposed approach would simplify the language of the request.

Dr. Miller suggested Section V-B-2 might read as follows:

"Justify the selection of introduction protocols with respect to potential environmental effects."

Dr. Colwell suggested the words "adverse effects" be substituted for the words "environmental effects."

Dr. Gottesman agreed with Dr. Fedoroff's suggestion that Section V-B-2 should attempt to determine how the introduction protocols would reduce risk; she moved such language. Dr. Pramer seconded the motion.

Dr. Joseph Fiksel of Arthur D. Little, Inc., asked if this section addresses whether the nature of the test limits undesired consequences.

Dr. Elliott Norse of the Ecological Society of America pointed out that organisms are not the only targets that might be affected by released substances; ground water or soil, for example, might be exposed.

Dr. Rissler pointed out that Dr. Fedoroff's language did not imply introduction protocols would deal with exposure.

Dr. Fedoroff said maximizing exposure of modified organisms in field tests will not necessarily maximize hazard.

Dr. Susan Hirano suggested the best format for this section is a short preamble followed by points of consideration. She suggested Section V-B should read as follows:

"Discuss the following specific features of the experiment that are designed to minimize potential adverse effects of the modified organism:

- "1. Test site, location and size;
- "2. Introduction protocols;
- "3. Population size and reproductive capacity;
- "4. Emergency procedure for aborting the experiment;
- "5. Procedures conducted at the termination of the experiment.

The working group agreed with this suggestion; Dr. Gottesman withdrew her earlier motion.

Dr. Tolin suggested the point referring to population size attempts to elicit information on the effect of the initial inoculum. She said the size and area of the test plot and the number of plants or other target organisms in the test plot are also important considerations. The proposed language should read as follows:

"The Nature of the Test

Discuss the following specific features of the experiment that are designed to minimize potential adverse effects of the modified organism:

- "1. Test site, location and area;
- "2. Introduction protocols;
- "3. Numbers of organisms and their expected reproductive capacity;
- "4. Emergency procedures for aborting the experiment;
- "5. Procedures conducted at the termination of the experiment."

By a vote of thirteen in favor, none opposed, and no abstentions, the working group accepted this proposed language.

Dr. McGarrity then asked the working group to comment on Parts I, II, III, and IV of the document.

Dr. Colwell wished to expand Section IV-B-3 of the document (Attachment II) to indicate the modified organism could be disseminated by biological organisms as well as by physical means. He suggested Section IV-B-3 might read as follows:

"Dissemination routes of the modified organism including physical transport (air, wind, water, soil) as well as incidental dispersal by herbivores predators, pollinators, and other mobile organisms."

Dr. Fedoroff moved acceptance of this language. Dr. Sharples seconded the motion. Dr. Fedoroff felt, however, that the language was long and complicated; she questioned whether the examples could be deleted in order to shorten the section.

Dr. Tolin felt the examples should be deleted; she pointed out that soil includes both biotic and abiotic means of transporting the modified organisms. Some of these biotic means of transport are not, however, "mobile organisms."

Dr. Clowes suggested the investigators be permitted to determine what information should be supplied in response to a specific information request. He suggested the phrase "where appropriate" be added in the document. Dr. Colwell questioned whether the review process might be delayed if the investigator did not initially supply information crucial to the review.

Dr. Fedoroff called the question. By a vote of twelve in favor, none opposed, and no abstentions, the question was called.

By a vote of six in favor, five opposed, and one abstention, the working group accepted the following substitute language for Section IV-B-3:

"Dissemination of the modified organism by wind, water, soil, mobile organisms, and other means."

Dr. Pimentel suggested some examples of immediate surroundings such as "crop, pasture and natural environments" be added to the language of Section IV-A-2 which reads as follows:

"Provide information including diagrams of the experimental location and the immediate surroundings. Describe characteristics of the site that would influence containment or dispersal."

Dr. Tolin disagreed; she felt offering examples of possible immediate surroundings predisposes investigators to overlook important facts such as the location of dwellings and superhighways. She suggested the language as written is adequate. Dr. Pramer agreed with Dr. Tolin; he felt the more specific the language of the working group document, the more likely the information provided by the investigator will be biased and limited. Dr. Arntzen agreed; he felt too specific a working group document will restrict the investigator's view of the proposal. Dr. Pimentel agreed with these arguments and withdrew his proposal.

Dr. Vidaver suggested the word "strain" be deleted from Section IV-A-3. She felt in most cases the investigator would be doing well to simply identify the target organism. Dr. Fedoroff moved the word "strain" be deleted from Section IV-A-3.

By a vote of twelve in favor, none opposed, and no abstentions, the working group agreed to strike the word "strain" from Section IV-A-3.

Dr. Hirano suggested Section IV-B should be moved to another section of the document. As Section IV-B deals with contained system testing, it should either be under Section III or should be the first topic in Section IV. Dr. Clowes agreed; he said the position of Section IV-B and the words "that simulate field conditions" predispose to confusion. He also thought this section should address detection and monitoring sensitivity issues.

Dr. McGarrity pointed out that Section IV-D requests information on monitoring in the field.

- : Dr. Miller suggested the title of Section IV should be "Proposed Field Trials;" he agreed current Section IV-B should be moved to Section III.

Dr. Tolin moved that Section IV-B be the first topic in Section IV; this section should be entitled Prefield Trial Considerations. Dr. Miller seconded the motion.

Dr. Colwell suggested Section C of Section IV-C should have a title such as Containment. Dr. Tolin accepted this proposal as an amendment to her motion.

The working group then voted on the motion to change the position and title of Section IV-B and to add the title Containment to Section IV-C. By a vote of eleven in favor, none opposed, and no abstentions, the working group accepted this motion.

Dr. Colwell suggested the word "numbers" be substituted for the word "amounts" in Section IV-A-1. Dr. Pramer moved Dr. Colwell's suggestion. By a vote of twelve in favor, none opposed, and no abstentions, the working group accepted this motion.

Dr. Vidaver suggested a reporting period be included in Section IV-D, Monitoring. She thought appropriate a requirement that the investigator report to the working group or to RAC 120 days after termination of the experiment.

Dr. Sharples suggested the working group document might state RAC would set reporting periods on a case-by-case basis. She suggested the phrase "according to a schedule attached with the approval" might be added to Section IV-D.

Dr. Tolin moved that the phrase "according to a schedule specified by RAC at the time of approval" be added to Section IV-D. Dr. Miller seconded the motion.

By a vote of twelve in favor, none opposed, and no abstentions, the working group approved the motion.

Dr. Colwell asked whether Section II-C-1 might be expanded to read as follows:

"Host range, including native as well as cultivated or domesticated hosts."

Dr. Vidaver felt including such language would bias the investigator's thinking and limit the types of information the investigator would submit; the term "host range" includes plants, animals and other microorganisms. Dr. Miller thought the investigator should be aware of the host range of the modified organism. Dr. Colwell dropped his suggestion.

Dr. Pramer wondered whether Section I, Summary, should ask if alternative methods of achieving the experimental objectives exist. Dr. McGarrity said traditionally the RAC has not considered whether alternative means might be employed to attain the objective. Dr. Gartland said in field testing cases, however, the working group and RAC might wish to consider risk management tradeoffs.

Dr. Sharples asked Dr. Gartland whether this type of information would be useful if the NIH were required to file EAs under the National Environmental Policy Act (NEPA). Dr. Gartland said alternative methods of achieving the experimental goal are not required in EAs.

Dr. Tolin suggested the phrase "including potential benefits" be included in the language of Section I.

Dr. Miller suggested italicizing the following sentence in the document's preamble:

"Information on all these points will not be necessary in all cases but will depend on the properties of the parental organism and the effect of the modification on these properties."

Dr. Clowes said Section III-C-5 is not clear; he asked which ecological characteristics are being referred to in the statement "...such as those listed in Section III above." He suggested Section III-C-5 should read as follows:

"Frequency with which populations undergo shifts in important ecological characteristics such as those listed in Section III-C-1 through Section III-C-4 above."

Dr. Clowes asked what "carriers of pathogens" refers to in Section III-C-3. That section reads as follows:

"Pathogenicity, infectivity, toxicity, virulence, or carrier of pathogens."

Dr. Vidaver suggested the word "vector" should be added to Section III-C-3. "Vector" has a specific meaning in pathogenicity and that meaning should be included in this section. Dr. Tolin explained that a vector might be either the plasmid or virus carrying the recombinant DNA, or the carrier of a pathogen. She suggested the word "vector" used as a carrier of a pathogen be included in this section. Dr. Arntzen moved the four different suggestions by Drs. Tolin, Miller, and Clowes. Dr. Pramer seconded the motion.

By a vote of eleven in favor, none opposed, and no abstentions, the working group accepted the motion.

Dr. Vidaver suggested Section II-B-2-b be modified to read as follows:

"Describe the method of introduction of the vector carrying the insert into the organism to be modified and the procedure for selection of the modified organism."

Dr. Sharples moved the proposed language. Dr. Fedoroff seconded the motion. By a vote of eleven in favor, none opposed, and no abstentions, the working group accepted the motion.

Dr. Miller said he wished to add an asterisk to the working group document; the asterisk would indicate the working group document would not apply to protocols which are being reviewed by other agencies. He felt working group reviews would be duplicative and unnecessary if the protocols are already being adequately reviewed by another agency.

Dr. Sharples did not think the working group should discuss this issue. Such an issue might be discussed by the RAC, but would ultimately be decided by the Director, NIH.

Dr. Miller suggested the working group could recommend his proposal to the Director, NIH.

Dr. Gartland said the NIH is intending to propose in a Federal Register announcement that the NIH will not review proposals being reviewed by other agencies. He pointed out, however, that the Cabinet Council in its proposal for coordinating review of biotechnology proposals has indicated a proposal may be reviewed by more than one review group. He thought Dr. Miller's concerns would be addressed by these activities.

Dr. Miller said he wanted his proposal on the record.

Dr. Levin felt Dr. Miller's proposal was outside of the purview of the Working Group on Release into the Environment. He also questioned how RAC would determine the review being conducted by another agency was adequate.

Dr. McGarrity said Dr. Miller's proposal would require a revision of the NIH Guidelines. He said RAC procedures for amending the Guidelines would have to be followed; therefore, the language proposed by Dr. Miller could not at this time be added to the working group points to consider document.

Dr. Miller said the working group could indicate support for the concept that working group reviews should not duplicate reviews performed by another agency.

Dr. Gartland pointed out that the FDA supports the December 31, 1984, Federal Register. He questioned why Dr. Miller was proposing an action which might contravene that Federal Register notice.

Dr. Mazza agreed the Working Group on Release into the Environment was not the appropriate forum to discuss this issue. He felt the Cabinet Council Working Group was reviewing such issues; and he did not think the working group should attempt to bias that process.

Dr. Tolin noted the points to consider document is an attempt to offer guidance to investigators who wish to submit proposals for review. All the considerations included in the document are of a scientific nature. This document will be useful to any group in any agency reviewing field testing of modified microorganisms.

Dr. McGarrity noted that two more items remained on the working group agenda. He suggested the working group follow one of two alternatives: (1) the working group could vote on Dr. Miller's proposal; or (2) the working group could suggest Dr. Miller officially notify ORDA by letter of his concerns.

The working group voted on the proposal offered by Dr. Miller. By a vote of three in favor, five opposed, and four abstentions, the working group refused the motion offered by Dr. Miller.

Dr. McGarrity said the points to consider document would be published in the Federal Register for thirty days of public comment and presented to the RAC at the May 3, 1985, meeting.

[Executive Secretary's Note: The document "Points to Consider for Submissions Involving Testing in the Environment of Microorganisms Derived by Recombinant DNA Techniques" as adopted at the February 11, 1985, meeting is appended to these minutes as Attachment V.]

UPDATE ON THE ASM CONFERENCE

Dr. Pramer said nine scientific societies and seven federal agencies were cooperating with the ASM in organizing a conference to examine the impact of deliberate releases of genetically modified organisms. He said the meeting will be held June 10-13, 1985, in Philadelphia, Pennsylvania. Participation will be limited to 150 individuals.

The meeting will produce a summary for a non-technical audience; the steering committee has employed a professional science writer to produce this summary.

BLI CONDITIONS FOR GREENHOUSE TESTING OF MICROBES

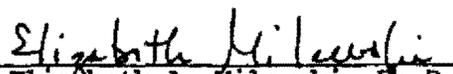
Dr. McGarrity asked Dr. Mazza to present his request (Attachment IV). Dr. Mazza said guidelines for BLI growth conditions for plants in greenhouses had been developed and adopted by RAC. He asked the working group if these guidelines could be applied to greenhouse testing of genetically modified microbes.

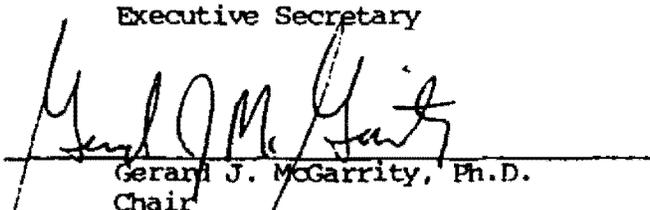
Dr. Tolin said she and Dr. Milewski had generated the guidelines for BLI conditions for testing plants in greenhouses by utilizing information on greenhouse conditions from previous Federal Registers notices dealing with recombinant DNA. This language was subsequently offered to RAC and accepted by that committee. This language, however, only applies to plants. It does not cover greenhouse considerations for testing microbes.

Dr. McGarrity suggested a subgroup of the working group might attempt to address this issue. The working group agreed. Dr. McGarrity asked Drs. Tolin, Vidaver, Pirone, Lacy, and Milewski if they would attempt to deal with this issue. Dr. Milewski said she would contact these individuals at a later date.

Dr. McGarrity adjourned the meeting at 4:05 p.m. on February 11, 1985.

Respectfully submitted,


 Elizabeth A. Milewski, Ph.D.
 Executive Secretary


 Gerard J. McGarrity, Ph.D.
 Chair

4/16/85
 Date

RECOMBINANT DNA ADVISORY COMMITTEE

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POINTS TO CONSIDER FOR SUBMISSIONS INVOLVING TESTING IN THE ENVIRONMENT
OF MICROORGANISMS DERIVED BY RECOMBINANT DNA TECHNIQUES

Experiments in this category require specific review by the Recombinant DNA Advisory Committee (RAC) and approvals by the National Institutes of Health (NIH) and the Institutional Biosafety Committee (IBC) before initiation. The IBC is expected to make an independent evaluation although this evaluation need not occur before consideration of an experiment by the RAC. Relevant information on the proposed experiments should be submitted to the Office of Recombinant DNA Activities (ORDA). The objective of this review procedure is to evaluate the potential environmental effects of testing of microorganisms that have been modified by recombinant DNA techniques.

These following points to consider have been developed by the RAC Working Group on Release into the Environment as a suggested list for scientists preparing proposals on environmental testing of microorganisms, including viruses, that have been modified using recombinant DNA techniques. The review of proposals for environmental testing of modified organisms is being done on a case-by-case basis because the range of possible organisms, applications, and environments indicate that no standard set of procedures is likely to be appropriate in all circumstances. However, some common considerations allow the construction of points to consider such as those below. Information on all these points will not be necessary in all cases but will depend on the properties of the parental organism and the effect of the modification on these properties.

Approval of small-scale field tests will depend upon the results of laboratory and greenhouse testing of the properties of the modified organism. We anticipate that monitoring of small-scale field tests will provide data on environmental effects of the modified organism. Such data may be a necessary part of the consideration of requests for approval of large-scale tests and commercial applications.

I. Summary

Present a summary of the proposed trial including objectives, significance, and justification for the request.

II. Genetic Considerations of Modified Organism to be Tested

A. Characteristics of the Normodified Parental Organism

1. Information on identification, taxonomy, source, and strain.
2. Information on organism's reproductive cycle and capacity for genetic transfer.

B. Molecular Biology of the Modified Organism

1. Introduced Genes

- a. Source and function of the DNA sequences used to modify the organism to be tested in the environment.
- b. Identification, taxonomy, source, and strain of organism donating the DNA.

2. Construction of the Modified Organism

- a. Describe the method(s) by which the vector with insert(s) has been constructed. Include diagrams as appropriate.
- b. Describe the method of introduction of the vector carrying the insert into organism to be modified; describe the procedure for selection of organisms.
- c. Specify the amount and nature of any vector and/or donor DNA remaining in the modified organism.
- d. Give the laboratory containment conditions specified by the NIH Guidelines for the modified organism.

3. Genetic Stability and Expression

Present results and interpretation of preliminary tests designed to measure genetic stability and expression of the introduced DNA in the modified organism.

III. Environmental Considerations

The intent of gathering ecological information is to assess the effects of survival, reproduction, and/or dispersal of the modified organism.

For this purpose, information should be provided where possible and appropriate on: (i) relevant ecological characteristics of the nonmodified organism; (ii) the corresponding characteristics of the modified organism; and (iii) the physiological and ecological role of donated genetic sequences

in the donor and in the modified organism(s). For the following points, provide information where possible and appropriate on the nonmodified organism and a prediction of any change that may be elicited by the modification.

- A. Habitat and Geographic Distribution
- B. Physical and Chemical Factors which can Affect Survival, Reproduction, and Dispersal
- C. Biological Interactions
 1. Host range.
 2. Interactions with and effects on other organisms in the environment including effects on competitors, prey, hosts, symbionts, predators, parasites, and pathogens.
 3. Pathogenicity, infectivity, toxicity, virulence, or carrier of pathogens.
 4. Involvement in biogeochemical or in biological cycling processes (e.g., mineral cycling, cellulose and lignin degradation, nitrogen fixation, pesticide degradation).
 5. Frequency with which populations undergo shifts in important ecological characteristics such as those listed in Section III above.
 6. Likelihood of exchange of genetic information between the modified organism and other organisms in nature.

IV. Trials to be Conducted

A. Conditions of the Trial

Describe the trial involving release of the modified organism into the environment:

1. Amounts of organisms and methods of application.
2. Provide information including diagrams of the experimental location and the immediate surroundings. Describe characteristics of the site that would influence containment or dispersal.
3. If the modified organism has a target organism, provide the following:
 - a. Identification, taxonomy, and strain;
 - b. The anticipated mechanism and result of the interaction between the released microorganism and the target organism.

B. Provide data related to any anticipated or nonanticipated effects of the modified microorganism on target and nontarget organisms from microcosm, greenhouse, and/or growth chamber experiments that simulate trial conditions. The methods of detection and sensitivity of sampling techniques and periodicity of sampling should be indicated. These studies should include assessment of the following items:

1. Survival of the modified organism.
2. Replication of the modified organism.

3. Dissemination routes of the modified organism.

C. Indicate containment procedures in the event of accidental release as well as intentional release and procedures for emergency termination of the experiment. Specify access and security measures for the area(s) in which the tests will be performed.

D. Monitoring

Describe monitoring procedures and their limits of detection for survival, dissemination, and nontarget interactions of the modified microorganism. Include periodicity of sampling and rationale for monitoring procedures. Collect data to compare the modified organisms with the nonmodified microorganism most similar to the modified organism at the site of the trial. Results of monitoring should be submitted to RAC.

V. Risk Assessment

Summarize risk assessment conclusions and justification for safe conduct of experiment.

IS REMOVED FROM BOTTOM ON PAGE 1, PAGE 2, AND TOP OF PAGE 3 OF 10/5/84 DRAFT:

For the evaluation of the risk associated with the release of a recombinant DNA containing organism into the environment, the probability of an adverse effect will be the product of the probabilities of each of the following three factors.

The special attention given to recombinant DNA containing organisms is based on the assumption that the organism being considered did not exist before in nature and, therefore, may have some unexpected properties. If the organism is essentially identical to one found in nature, then it can be treated in the same way as the natural analog. The Guidelines for Research Involving Recombinant DNA Molecules exempt certain organisms from the requirements of the Guidelines because they represent variants which may arise by natural means (see Sections III-D-2, III-D-3, and III-D-4). Thus, while all experiments involving release of recombinant DNA containing organisms must undergo NIH review (under Section III-A-2), the probability of a unique organism being formed should be relatively low for those organisms which meet the requirements of Sections III-D-2, III-D-3, and III-D-4.

What is the probability of the establishment in the environment of the recombinant organism or the recombinant DNA it contains. Survival of the organism, stability of the inserted DNA, and ability of the organism to grow and compete with other organisms will all be relevant in determining this probability value. In addition, the possible mechanisms for transfer of the recombinant DNA to other organisms and the availability of those organisms at the release site will be important. Finally, the number of organisms to be released will help determine how stability and transfer information should be interpreted.

What is the probability of the organism or a product of the organism causing harm? For this consideration, one should assume that establishment in the environment has occurred. The probability of harm can be estimated from an analysis of the known properties of the parental unmodified organism, and an informed judgement about the role the introduced material is likely to play in changing those properties. Results from laboratory and greenhouse tests will serve as the first tests of a prediction, but results from preliminary field tests will be the best test for unexpected consequences.

POSSIBLE INSERT FOR END OF FIRST ¶, PAGE 1:

The special attention which has been given to organisms derived by recombinant DNA techniques is based on the assumption that the modified organism did not exist before in nature and therefore may have some unexpected properties.



VIRGINIA POLYTECHNIC INSTITUTE AND STATE UNIVERSITY

Blacksburg, Virginia 24061

DEPARTMENT OF PLANT PATHOLOGY, PHYSIOLOGY AND WEED SCIENCE

M E M O R A N D U M

TO: Working Group on Release into the Environment
Recombinant DNA Advisory Committee

FROM: Sue Tolin and George Lacy

SUBJECT: Section V for February 11, 1985 meeting

Attached is a draft of Section V. Risk Analysis prepared at your request for inclusion in the "Points to Consider" guidance document for investigators submitting proposals for experiments involving release of microorganisms into the environment. This is to be included in place of Section V. Risk Assessment on page 6, or Attachment II - page 7 sent to each of you by ORDA in the mailing concerning the February 11 meeting. Please review and make comments accordingly at the meeting.

Attachment

Addressees: Dr. Arntzen Dr. Miller
 Dr. Clowes Dr. Mitchell
 Dr. Colwell Dr. Pimentel
 Dr. Federoff Dr. Pirone
 Dr. Gottesman Dr. Pramer
 Dr. Hirano Dr. Scandalios
 Dr. Levin Dr. Sharples
 Dr. McGarrity Dr. Vidaver
 Dr. Milewski

D R A F T

V. RISK ANALYSIS

Small-scale field testing is a necessary part of risk analysis since artificial environments are not adequate simulations of natural environments. However, field testing must not be undertaken until results of testing in artificial contained environments, together with careful consideration of the genetics, biology, and ecology of the non-modified and the modified organisms, enable a reasonable prediction that no environmental risk will result from the release of the modified organism in the small-scale test. In this section, the information presented in Sections II, III and IV should be summarized to present an analysis of risk to the environment in the test as it is proposed. The issues addressed might include, but not be limited to, the following lines of argument.

A. The nature of the organism

1. The role of the non-modified organism in the environment of the test site is essentially understood, including any adverse effects on other organisms.
2. Analysis of the genetic modification (eg. deletion, insertion, modification of specific DNA sequences) would predict that the probability of adverse effects on the environment is low.
3. Analysis of the tests conducted under contained environments would predict that the modified organism would behave no differently, except for the known genetic modification, from the non-modified organism in the environment of the test site.

4. A worst-case scenario (eg. increased survival, reproductive capacity, dispersal, transfer of the genetic modification to other organisms, etc.) would predict that no risks greater than those caused by the non-modified organism will occur.

B. The nature of the test

1. The test site is of limited size or area and is reasonably isolated from potentially adversely affected ecosystems.
2. Introduction protocols are designed to decrease any potential non-target effects of the modified organism.
3. Numbers of the modified organism released and the expected reproductive capability would predict a low probability of affecting the surrounding environment adversely.
4. Emergency procedures for aborting the experiment are effective.
5. Procedures conducted at the termination of the experiment eliminate the potential for adverse carry-over effects attributable to the modified organism.

DRAFT - February 4, 1985

Sue Tolin and George Lacy



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Working Group on Release into the Environment
Recombinant DNA Advisory Committee (RAC)

FROM: Carl Mazza, Science Advisor
Chemical Control Division (TS-794)

TO: Elizabeth Milewski, Ph.D.
Department of Health and Human Services

Thank you for notifying us of the next meeting of the RAC's Workgroup on release to the environment. We understand that the primary purpose of that meeting is to develop guidelines for investigators submitting proposals involving release of microorganisms into the environment. This discussion is of particular interest to the Environmental Protection Agency because of our own work in developing such guidance both in the Office of Pesticides Programs (OPP) and the Office of Toxic Substances (OTS). In this regard, there are several documents that could be of use in your deliberations:

1. The "Points to Consider" staff document, prepared by OTS, which was distributed at the last meeting of the workgroup.
2. Subpart M, Assessment Guidelines for Microbial Pesticides (Attached), while not specifically developed for genetically engineered organisms, should provide useful information. It has been made available to the workgroup in the past.
3. A list of information elements (attached) developed by OPP that we believe are relevant to the assessment of small scale field tests of genetically engineered microorganisms.

We believe it would be useful to consider two other related items at the October 5th meeting. In developing guidelines for microorganisms in the environment, we think it would be helpful to consider the availability and adequacy of guidelines for the conduct of greenhouse and other experiments with recombinant DNA microorganisms. Guidelines in this area are necessary to distinguish experiments conducted in greenhouses from those conducted in the open environment.

Finally, you may wish to discuss the status of the proposed spring conference on "Risk Assessment" which is to be jointly sponsored by interested Agencies. It is important to make progress in the planning of this conference; it may be useful to involve the workgroup more directly.

RECOMBINANT DNA ADVISORY COMMITTEE

Pl Growth Conditions for Plants

If the IBC requires Pl growth conditions for plants, this can be met by either (1) a limited access greenhouse, or (2) a plant growth chamber, which are insect-restrictive and in which a pest control regime is maintained. Sterilization of run-off water is required only where this is a plausible route for dissemination of viable microorganisms containing recombinant DNA. Soil, plant parts, and unwanted plant material shall be sterilized before disposal. Plant materials which have to be removed from the greenhouse or cabinet for turnover research shall be maintained under good laboratory practices as applied to plants. Plants can be transported locally, e.g., between laboratory, growth chamber, and greenhouse, at physically separated locations provided:

(1) plants are in a vegetative condition, i.e., no reproductive organs or structures (e.g., pollen, flowers, seeds) are present, or the reproductive organs of the plants are covered to prevent dispersal of reproductive cells and spores; (2) plants are kept in an enclosed area or container (i.e., water-proof, insect-restrictive); and (3) plants are essentially "hand-carried" between locations.

February 6, 1984

DRAFT

Attachment V - Page

DRAFT

POINTS TO CONSIDER FOR SUBMISSIONS INVOLVING TESTING IN THE ENVIRONMENT
OF MICROORGANISMS DERIVED BY RECOMBINANT DNA TECHNIQUES

Experiments in this category require specific review by the Recombinant DNA Advisory Committee (RAC) and approvals by the National Institutes of Health (NIH) and the Institutional Biosafety Committee (IBC) before initiation. The IRC is expected to make an independent evaluation although this evaluation need not occur before consideration of an experiment by the RAC. Relevant information on the proposed experiments should be submitted to the Office of Recombinant DNA Activities (ORDA). The objective of this review procedure is to evaluate the potential environmental effects of testing of microorganisms that have been modified by recombinant DNA techniques.

These following points to consider have been developed by the RAC Working Group on Release into the Environment as a suggested list for scientists preparing proposals on environmental testing of microorganisms, including viruses, that have been modified using recombinant DNA techniques. The review of proposals for environmental testing of modified organisms is being done on a case-by-case basis because the range of possible organisms, applications, and environments indicate that no standard set of procedures is likely to be appropriate in all circumstances. However, some common considerations allow the construction of points to consider such as those below. Information on all these points will not be necessary in all cases but will depend on the properties of the parental organism and the effect of the modification on these properties.

RELEASE INTO THE ENVIRONMENT
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Approval of small-scale field tests will depend upon the results of laboratory and greenhouse testing of the properties of the modified organism. We anticipate that monitoring of small-scale field tests will provide data on environmental effects of the modified organism. Such data may be a necessary part of the consideration of requests for approval of large-scale tests and commercial applications.

I. Summary

Present a summary of the proposed trial including objectives, significance, and justification for the request.

II. Genetic Considerations of Modified Organism to be Tested

A. Characteristics of the Nonmodified Parental Organism

1. Information on identification, taxonomy, source, and strain.
2. Information on organism's reproductive cycle and capacity for genetic transfer.

B. Molecular Biology of the Modified Organism

1. Introduced Genes

- a. Source and function of the DNA sequence used to modify the organism to be tested in the environment.
- b. Identification, taxonomy, source, and strain of organism donating the DNA.

2. Construction of the Modified Organism

- a. Describe the method(s) by which the vector with insert(s) has been constructed. Include diagrams as appropriate.
- b. Describe the method of introduction of the vector carrying the insert into the organism to be modified and the procedure for selection of the modified organism.
- c. Specify the amount and nature of any vector and/or donor DNA remaining in the modified organism.
- d. Give the laboratory containment conditions specified by the NIH Guidelines for the modified organism.

3. Genetic Stability and Expression

Present results and interpretation of preliminary tests designed to measure genetic stability and expression of the introduced DNA in the modified organism.

III. Environmental Considerations

The intent of gathering ecological information is to assess the effects of survival, reproduction, and/or dispersal of the modified organism.

For this purpose, information should be provided where possible and appropriate on: (i) relevant ecological characteristics of the nonmodified organism; (ii) the corresponding characteristics of the modified organism; and (iii) the physiological and ecological role of donated genetic sequences in the donor and in the modified organism(s). For the following points, provide information where possible and appropriate on the nonmodified

organism and a prediction of any change that may be elicited by the modification.

A. Habitat and Geographic Distribution

B. Physical and Chemical Factors which can Affect Survival, Reproduction, and Dispersal

C. Biological Interactions

1. Host range.
2. Interactions with and effects on other organisms in the environment including effects on competitors, prey, hosts, symbionts, predators, parasites, and pathogens.
3. Pathogenicity, infectivity, toxicity, virulence, or as a carrier (vector) of pathogens.
4. Involvement in biogeochemical or in biological cycling processes (e.g., mineral cycling, cellulose and lignin degradation, nitrogen fixation, pesticide degradation).
5. Frequency with which populations undergo shifts in important ecological characteristics such as those listed in III-C points 1 through 4 above.
6. Likelihood of exchange of genetic information between the modified organism and other organisms in nature.

IV. Proposed Field Trials

A. Pre-Field Trial Considerations

Provide data related to any anticipated effects of the modified microorganism on target and nontarget organisms from microcosm, greenhouse, and/or growth chamber experiments that simulate trial conditions. The methods of detection and sensitivity of sampling techniques and periodicity of sampling should be indicated. These studies should include, where relevant, assessment of the following items:

1. Survival of the modified organism.
2. Replication of the modified organism.
3. Dissemination of the modified organism by wind, water, soil, mobile organisms, and other means.

B. Conditions of the Trial

Describe the trial involving release of the modified organism into the environment:

1. Numbers of organisms and methods of application.
2. Provide information including diagrams of the experimental location and the immediate surroundings. Describe characteristics of the site that would influence containment or dispersal.

3. If the modified organism has a target organism, provide the following:
 - a. Identification and taxonomy.
 - b. The anticipated mechanism and result of the interaction between the released microorganism and the target organism.

C. Containment

Indicate containment procedures in the event of accidental release as well as intentional release and procedures for emergency termination of the experiment. Specify access and security measures for the area(s) in which the tests will be performed.

D. Monitoring

Describe monitoring procedures and their limits of detection for survival, dissemination, and nontarget interactions of the modified microorganism. Include periodicity of sampling and rationale for monitoring procedures. Collect data to compare the modified organisms with the nonmodified microorganism most similar to the modified organism at the site of the trial. Results of monitoring should be submitted to the RAC according to a schedule specified at the time of approval.

V. Risk Analysis

Results of testing in artificial contained environments together with careful consideration of the genetics, biology, and ecology of the nonmodified and the modified organisms will enable a reasonable prediction of whether or not significant risk of environmental damage will result from the release of the modified organism in the small-scale field test. In this section,

the information requested in Sections II, III, and IV should be summarized to present an analysis of possible risks to the environment in the test as it is proposed. The issues addressed might include but not be limited to the following items:

A. The Nature of the Organism

1. The role of the nonmodified organism in the environment of the test site, including any adverse effects on other organisms.
2. Evaluation of whether or not the specific genetic modification (e.g., deletion, insertion, modification of specific DNA sequences) would alter the potential for significant adverse effects.
3. Evaluation of results of tests conducted in contained environments to predict the ecological behavior of the modified organism relative to that of its nonmodified parent.

B. The Nature of the Test

Discuss the following specific features of the experiment that are designed to minimize potential adverse effects of the modified organism:

1. Test site location and area.
2. Introduction protocols.
3. Numbers of organisms and their expected reproductive capacity.
4. Emergency procedures for aborting the experiment.
5. Procedures conducted at the termination of the experiment.