EVALUATION OF THE AGRICULTURAL BIOTECHNOLOGY RISK ASSESSMENT RESEARCH GRANTS PROGRAM: COMMENTS FROM THE SCIENTIFIC COMMUNITY AND RECOMMENDATIONS FOR FUTURE PROGRAMMING

February 1997

Prepared for

BIOTECHNOLOGY RISK ASSESSMENT RESEARCH GRANTS PROGRAM administered jointly by The Cooperative State Research, Education, and Extension Service and The Agricultural Research Service of THE UNITED STATES DEPARTMENT OF AGRICULTURE

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Biotechnology Risk Assessment Research Grants Program
administered jointly by the Cooperative State Research, Education, and Extension Service and the Agricultural Research Service
of the United States Department of Agriculture

Prepared by

An ad hoc Expert Panel
of the
Life Sciences Research Office

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FOREWORD

The Life Sciences Research Office (LSRO), Federation of American Societies for Experimental Biology (FASEB), provides scientific assessments of topics in the biomedical sciences. Comprehensive and quick-response reports are based upon literature reviews and the scientific analyses of knowledgeable investigators active in specific areas of biology and medicine. Proceedings from workshops and symposia include synopses of presentations, references, and opinions provided by participants.

This report was developed by LSRO/FASEB through a cooperative agreement with the Biotechnology Risk Assessment Research Grants Program (BRARGP) administered jointly by the Cooperative State Research, Education, and Extension Service (CSREES) and the Agricultural Research Service (ARS) of the United States Department of Agriculture (USDA). The drafting of the report and recruitment of participating scientists was accomplished through a subcontract with the Agricultural Research Institute (ARI), a private nonprofit research organization. It was edited by Daniel J. Raichen, Ph.D., Senior Staff Scientist/Project Leader, and Richard A. Herrett, Ph.D., Executive Director, ARI. The report is based on a synthesis of solicited comments from 21 scientists with expertise in agricultural biotechnology risk assessment, and the review and comments of the draft document by an ad hoc Expert Panel convened by LSRO. The members of the Expert Panel were chosen for their qualifications, experience, and judgement with due consideration for balance and breadth in the appropriate professional disciplines. Members of the Expert Panel and those scientists who contributed comments used in this report are identified in Chapter V.

This project was divided into two phases. In Phase I, LSRO and ARI staff identified and solicited comments from 21 scientists familiar with the questions raised in the objective and scope of work of the agreement with USDA BRARGP. Phase I culminated in the production of a draft report containing a synthesis of the comments of 18 the 21 scientists. In Phase II, LSRO convened an ad hoc Expert Panel to review the draft document for accuracy in reflecting the comments of the 18 reviewers. Subsequently, the Expert Panel met to discuss their evaluations of the draft report, and offer further comments and suggestions about the USDA BRARGP. The deliberations and subsequent conclusions and recommendations of the Expert Panel were incorporated into the final report presented herein.

The Expert Panel members reviewed the draft and final reports. However, the listing of these individuals in Chapter V does not imply that the individual Panel members specifically endorse all statements in the report. The LSRO and ARI accept responsibility for the study conclusions and accuracy of the report.

The final report was reviewed and approved by the FASEB Committee on Research and Education (which consists of representatives of each constituent Society of FASEB) under authority delegated by the FASEB Board. Upon completion of these review procedures, the report was approved and transmitted to USDA by the Executive Director, FASEB.

While this is a report of the Federation of American Societies for Experimental Biology, it does not necessarily reflect the opinions of the individual members of the FASEB constituent Societies.

February 27, 1997
Richard G. Allison, Ph.D.
Acting Director
Life Sciences Research Office
EXECUTIVE SUMMARY

In order to be responsive to the changes in the field of agricultural biotechnology and risk assessment, the Biotechnology Risk Assessment Research Grants Program (BRARGP) of the United States Department of Agriculture (USDA) identified three prime objectives needed to prepare for the next phase in Program development. These objectives are:

- to evaluate the state of the field of agricultural biotechnology and to determine the future role that risk assessment research should play;
- to evaluate the Program's research approach in the context of its immediate and potential impact on federal regulation of agricultural biotechnology; and,
- to evaluate BRARGP research priorities and make recommendations about future directions.

Within the context of the above objectives, the most pressing programmatic need of the BRARGP was for input from the scientific community about its current program. In particular, BRARGP required an evaluation of the nine areas outlined in the Federal Register announcement (Appendix A) and suggestions for amendments or additional target areas.

In order to accomplish the goals identified by BRARGP, the Life Sciences Research Office (LSRO) of the Federation of American Societies for Experimental Biology (FASEB) conducted a two-step procedure that included solicitation of comments from expert scientists in the field. These comments were synthesized into a draft report followed by the convening of an ad hoc Expert Panel to evaluate those comments and make further recommendations about the BRARGP.

STRENGTHS AND WEAKNESSES OF THE SCIENTIFIC ASPECTS OF USDA'S CURRENT BIOTECHNOLOGY RISK ASSESSMENT PROGRAM

The reviewers universally agreed about the importance and necessity of the BRARGP. There was general agreement that the current Program is achieving at least some of the goals of advancing the science of risk assessment. There were, however, several recurrent themes that reflected some ambivalence and reservations about specific aspects of the overall Program. The concerns about the Program centered around several core issues.

- The overall scope of the Program. The reviewers expressed some concern that the Program as defined in the Federal Register announcement was too broad, particularly in light of the limited funds available.

- The definition of risk. The lack of a clear definition of risk in the Program announcement presents another hurdle in the ability of the Program to attract clear focused proposals.

- The ability of the Program to achieve its expressed goals. The main obstacles cited by the reviewers that could prevent the Program from achieving its goals are a lack of Program focus and limitations in funding.
• **The effective utilization of research findings.** A major concern expressed by the reviewers was with the types of mechanism(s) in place or in development to utilize effectively the information being generated through the Program.

The ad hoc reviewers also offered some critical comments about the annual meeting held by BRARGP. The primary concern was that the format was too restrictive and did not stimulate the interaction between the scientists and the regulatory community.

In addition to commenting on specific aspects of the Program, the ad hoc reviewers offered suggestions on the overall Program management. The focus of these comments was on application procedures, proposal review, and effective dissemination of research findings for the purpose of planning future research agendas.

**Conclusions of the Expert Panel**

The Expert Panel concurred with many of the comments of the reviewers, but focused their attention on several core issues. **The Expert Panel concluded that in light of limited funds, the BRARGP needs to be focused on identifying and addressing gaps in knowledge about risk assessment in biotechnology. More specifically, the focus of this Program should be targeted to risk assessment issues that are unique to agricultural biotechnology. Towards that end the Expert Panel strongly endorsed the concerns raised by many reviewers with regard to the need to provide a clear, concise definition of risk assessment within the context of agricultural biotechnology.**

In particular, the Expert Panel emphasized that the absence of a clear, concise definition of risk within the context of issues related to agricultural biotechnology (as opposed to risk assessment as applied in other contexts, e.g., chemical or hazardous waste exposure scenarios) is a major obstacle that will retard the Program from achieving its goal of providing a strong scientific basis for regulatory decision-making.

The Expert Panel concluded that the definitions included in the USDA CSREES/ARS publication entitled "Risk Assessment Research, 1992-1994: An Overview of the USDA Biotechnology Risk Assessment Research Grant Program," are appropriate and should continue to serve as the guiding precepts in Program planning. They further recommended that these definitions, if still accepted by USDA, should be included in future Program announcements.

The Expert Panel strongly endorsed the concerns expressed by several ad hoc reviewers about the inability of the Program to define "the universe" of risk assessment questions that needs to be addressed. This has contributed, as one ad hoc reviewer put it, to the Program’s inability "in maintaining the focus directly on risk assessment, rather than on general work demonstrating and characterizing risk, attempting to reduce risk, or simply working in a biotechnological system that involved some risk." **The Expert Panel urges that the focus of the Program should be on risk assessment not risk management and that this distinction should be clearly expressed in the Program announcement and communications with the scientific community.**

From a Program management perspective, the Expert Panel urged that, in addition to the inclusion of a refined definition of risk in the Program announcement, an effective tool in the management of the proposal process would be the initiation of a preproposal process. This would allow effective communication between the scientific community and the Program managers, and it would facilitate the submission of focused proposals consistent with programmatic goals.
With regard to comments about the Annual Conference, the Expert Panel agreed with the concept and the importance of bringing together members of the scientific and regulatory communities, but also echoed the concerns made by several reviewers about the lack of a more interactive format. In order to rectify the current weaknesses in the meeting format the Expert Panel suggested a workshop approach as opposed to presentations of current research activities. The focus of the meeting should be more than a straightforward presentation of new research but should involve an interactive process by which gaps in knowledge could be identified for use in Program planning and in the effective implementation of the regulatory agenda. In addition, the Expert Panel recommended that periodic workshops be scheduled to address such specific issues as those raised by the ad hoc reviewers, e.g., experimental design of large scale studies, appropriate statistical procedures, etc.

The Expert Panel emphasized that, if unresolved, the lack of focus in specifying Program objectives will continue to impair the ability of those reviewing proposals to make appropriate decisions about the merit of proposals as they will continue to be forced to choose between scientific excellence (but not necessarily related to risk assessment) and programmatic priority. Given the limited resources for this research area, this conflict will not serve the long-term survival of the Program or advance the science.

REVIEW OF THE NINE AREAS TARGETED BY USDA BRARGP

Although some reservations were expressed, overall, the reviews of the nine areas identified in the Federal Register announcement were favorable. Several reviewers endorsed the distinction between the objectives that advanced the science of risk assessment and those that were viewed as serving the regulatory agenda of the USDA. More specifically, the objectives were often characterized as enabling the USDA program managers to meet specific needs identified by the scientific community while allowing flexibility for exploration into newer areas not currently occupying a specific programmatic niche. This approach was viewed as providing the agency flexibility in supporting targeted areas while allowing for the creative development of new areas.

Objectives 1-3 were viewed by many of the reviewers as reflecting the overall goals of the Program while the other objectives were perceived as focusing on specific research questions. Many of the concerns raised by the ad hoc reviewers in their overview of the Program were echoed in the comments about specific objectives. A noteworthy example of this was the recurring issue of lack of clarity particular with regard to the definition of risk and risk assessment. These were particular concerns relative to objective 1. Another question raised by the ad hoc reviewers was whether sufficient methodologies exist to address the Program's needs at this time. The Expert Panel strongly urged that this issue of definition of risk and risk assessment be resolved and the resolution be incorporated into the next Program announcement. By correcting this problem, the Program will be better equipped to discern what methodological gaps might exist and focus its efforts on addressing those needs.

The preponderance of reviewer comments with regard to objective 2 was negative. The primary concerns were that the limitations in funding and data availability would prevent the accomplishment of the goal of developing new models or information systems. Because of these obstacles, the Expert Panel concluded that it was premature to devote limited resources to this Program initiative at this time. The Expert Panel affirmed the necessity for openness to new ideas in this area and to keep the concept alive in terms of future planning as funding and expanded databases become available.
There was a considerable range of opinion by the ad hoc reviewers relative to objectives 3-6. A recurrent theme was the issue of focus and relevance to the Program's mission.

The Expert Panel offered an "umbrella" recommendation with regard to objectives 3-6. They did not believe that it was their role to write the objectives for the Program; however, with regard to these four objectives, the Panel urged the Program managers to do a reanalysis of these questions and reorient the emphasis to gene transfer. In particular, the objectives should address the following core questions:

- what do we know about gene transfer and its consequences?
- what are the gaps in our knowledge about gene transfer and its consequences?
- what factors can influence gene transfer and its consequences?

The Expert Panel suggested that the objectives be written more broadly so that the goals of the objectives would apply to plants, animals, and microorganisms (including the potential for gene transfer between plants, animals, and microorganisms, including viruses). Moreover, the Expert Panel strongly concurs with those reviewers who concluded that the focus of these objectives should not be on whether gene transfer occurs, but rather what are the potential consequences (i.e., risks).

Perhaps because of the range of areas of expertise among the ad hoc reviewers, only a few felt comfortable enough to offer specific comments directed towards Objective 7. Of those who commented, the general consensus was favorable towards this objective albeit, as one reviewer said, "Perhaps some fine tuning is in order."

The Expert Panel regarded this as an important objective because of its focus on microbial issues. They concluded that the question of antibiotic resistance should be given a high priority and suggested that it is so important that the BRARGP might consider upgrading it to the status of an objective (rather than one issue within objective 7).

Of all the objectives, Objective 8 was the focus of some of the more critical comments from the reviewers. The preponderance of the criticism was directed at a general lack of clarity in the Program description and a specific questioning of the value of the objective.

The Expert Panel considered the criticisms of objective 8 to be valid and concluded that it should not be continued in its current form.

Conceptually, both the reviewers and the Expert Panel endorsed the goals of Objective 9. Reviews of Objective 9 were, with the exception of a few comments about the need for clarifying examples, supportive. The most troubling issues to the ad hoc reviewers were the levels of support needed to conduct such large scale studies as suggested by the Program announcement and feasibility of conducting such research without the cooperation and collaboration of commercial interests.

The Expert Panel recognized that because of limitations in funding and amount of resources required to conduct such large scale studies as called for in this objective, more creative approaches are needed to accomplish the worthy goals of this objective. They suggested that efforts be made to stimulate collaboration between commercial enterprises, who have the resources to conduct such studies, and scientists interested in designing experiments that would result in data useful for the examination of risk. The Expert Panel stressed that the endpoints/consequences (e.g., effects of gene transfer, impact on non-target organisms, impact on the ecology, changes in pathogenicity and host range, creation of new
pathogens, resistance management, etc.) to be evaluated in such studies need to be well-defined and focused on the overriding programmatic goal of identification of gaps in knowledge related to regulation of risk.

COMMENTS ON THE ADEQUACY OF CURRENT SCIENTIFIC KNOWLEDGE ABOUT RISK ASSESSMENT

The reviewers were expansive and according to the Expert Panel "quite comprehensive" in their suggestions for new areas to be targeted. A primary focal point in terms of gaps in knowledge was in the area of statistics and experimental design. Rather than identifying specific scientific questions for investigation, the comments about statistics/experimental design reflected significant concerns about the ability of the Program to achieve its goals irrespective of the validity of the scientific questions to be addressed.

Aside from numerous technical suggestions about potential areas to be addressed by the Program, the ad hoc reviewers commented on potential new directions and criteria in decision making for biotechnology risk assessment. Many of these comments focused on the public's perception about biotechnology and the importance of developing effective methods for communicating scientific findings to a lay audience. In addition, the evaluation of risk-assessment data and the process utilized to reach regulatory decisions needs to be made more inclusive, incorporating expertise and input from the academic, consumer, and corporate communities in the regulatory process.

COMMENTS AND RECOMMENDATIONS OF THE EXPERT PANEL

In terms of the scientific direction of the Program, the Expert Panel considered the comments of the ad hoc reviewers to be comprehensive and generally "on target." There were several themes that the Panel emphasized:

- Risk must be clearly articulated before the Program can begin effectively to examine the need for new methodologies.

- the Program needs to be focused on identifying gaps in knowledge relative to risk of biotechnology in agriculture.

- A major focus of the Program should be on the generic issue of gene transfer and its consequences. The scope of the Program must be clearly stated as including gene transfer in and between plants, animals, and microorganisms including viruses.

- The Expert Panel emphasized the importance of Objective 7 particularly with regard to the issues of antibiotic resistance, which might be considered as a separate Program priority. In addition, the Panel wished to highlight the importance of sponsoring studies investigating the role of microorganisms in gene transfer.

From a Program management perspective the Expert Panel offered the following recommendations:

- To advance the science, draw on new areas of expertise, support regulatory decision-making, and to make an effective case for continued support, the Program should publish periodic reviews or science-based summaries of what is known in the field with an emphasis on new developments that may have resulted from the Program's initiatives. These summaries
should be science-based and suitable for not only the scientific community but also accessible to members of the regulatory community and those engaged in risk communication.

- A process of periodic peer-review of the Program should be initiated in order to insure continued focus of the Program, to identify potential problems and new directions and to identify the Program's accomplishments. The Expert Panel suggested that this be an objective third party process, perhaps involving Expert Panels such as that involved in the generation of this report.

- The Expert Panel recommended that the Program strongly encourage collaboration between commercial enterprises and scientists to perform long-term monitoring (see comments for Objective 9, Chapter III). Moreover, the Panel suggested that the USDA's Animal and Plant Health Inspection Service (APHIS) be encouraged to utilize data generated from these collaborations in its decision-making process.

- To allow for the effective interaction between the scientific and regulatory communities, workshops should be scheduled to allow for strategic planning and establishment of the scientific agenda. These workshops would address some of the issues raised by the ad hoc reviewers, for example, issues related to experimental design and the identification of gaps in knowledge about risk.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foreword</td>
<td>iii</td>
</tr>
<tr>
<td>Executive Summary</td>
<td>v</td>
</tr>
<tr>
<td>I. Introduction</td>
<td>1</td>
</tr>
<tr>
<td>A. Background</td>
<td>1</td>
</tr>
<tr>
<td>B. Objectives</td>
<td>1</td>
</tr>
<tr>
<td>C. Technical Approach</td>
<td>1</td>
</tr>
<tr>
<td>D. Organization and Format of the Report</td>
<td>2</td>
</tr>
<tr>
<td>II. Comments on the Strengths and Weaknesses of the Scientific Aspects of USDA's Current Biotechnology Risk Assessment Research Grants Program (BRARGP)</td>
<td>3</td>
</tr>
<tr>
<td>A. Comments of the ad hoc Reviewers</td>
<td>3</td>
</tr>
<tr>
<td>1. General Comments</td>
<td>3</td>
</tr>
<tr>
<td>2. Specific Concerns</td>
<td>4</td>
</tr>
<tr>
<td>3. The Annual Conference</td>
<td>7</td>
</tr>
<tr>
<td>4. General Recommendations About the Program</td>
<td>9</td>
</tr>
<tr>
<td>B. Conclusions of the Expert Panel</td>
<td>11</td>
</tr>
<tr>
<td>III. Review of the Nine Areas Targeted by the USDA BRARGP</td>
<td>13</td>
</tr>
<tr>
<td>A. General Comments</td>
<td>13</td>
</tr>
<tr>
<td>B. Specific Comments of the Reviewers and Expert Panel on the Nine Objectives</td>
<td>14</td>
</tr>
<tr>
<td>1. Objective 1</td>
<td>14</td>
</tr>
<tr>
<td>2. Objective 2</td>
<td>16</td>
</tr>
<tr>
<td>3. Objective 3</td>
<td>18</td>
</tr>
<tr>
<td>4. Objective 4</td>
<td>19</td>
</tr>
<tr>
<td>5. Objective 5</td>
<td>22</td>
</tr>
<tr>
<td>6. Objective 6</td>
<td>24</td>
</tr>
<tr>
<td>7. Objective 7</td>
<td>25</td>
</tr>
</tbody>
</table>
IV. Comments on the Adequacy of Current Scientific Knowledge About Risk Assessment ......................................... 31

A. Current Gaps in Knowledge and Possible Areas to be Targeted for Future Research Initiatives by the USDA CSREES .................................................. 31

B. Potential New Directions or Criteria for Decision-making in Biotechnology Risk Assessment ................................. 38

C. Potential New Methods and Scientific Disciplines Required to be Included in the Establishment of New Approaches ................................................................. 40

D. Comments and Recommendations of the ad hoc Expert Panel ............................................................. 40

V. Study Participants ......................................................................................................................... 43

APPENDICES
I. INTRODUCTION

A. BACKGROUND

In 1990 Congress authorized the establishment of a competitive grants program through the United States Department of Agriculture (USDA) to fund biotechnology risk assessment research. The purpose of this program, the Biotechnology Risk Assessment Research Grante Program (BRARGP), jointly administered within the USDA by the Cooperative State Research, Education, and Extension Service (CSREES) and the Agricultural Research Service (ARS), is to support science-based regulatory decision making. In order to perform its mission, the BRARGP has utilized input from the scientific and regulatory communities about the research needed to define and support the goals and objectives of the program. This input has been used in developing the biotechnology risk assessment program up to and including the most recent request for applications (Federal Register announcement, Vol. 60, No. 175, September 11, 1995; Appendix A).

In the five years since the advent of this program much has happened in the science of risk assessment specifically as it relates to genetically modified plants, animals, and microbes introduced into the environment. This report is the result of the initiative taken by BRARGP/CSREES to obtain further input from the scientific community about the current program and suggestions for future program development.

B. OBJECTIVES

In order to be responsive to the changes in the field of agricultural biotechnology and risk assessment, the BRARGP identified the following three prime objectives needed in order to prepare for the next phase in program development:

- to evaluate the state of the field of agricultural biotechnology and to determine the future role that risk assessment research should play;
- to evaluate the program's research approach in the context of its immediate and potential impact on federal regulation of agricultural biotechnology; and,
- to evaluate BRARGP research priorities and make recommendations about future directions.

Within the context of the above, the most pressing programmatic need of the BRARGP was for input from the scientific community about its current program. In particular, BRARGP required an evaluation of the nine areas outlined in the Federal Register announcement (Appendix A) and suggestions for amendments or additional target areas.

C. TECHNICAL APPROACH

In order to accomplish the immediate goals identified by BRARGP, the Life Sciences Research Office (LSRO) of the Federation of American Societies for Experimental Biology (FASEB) conducted the two-step procedure outlined below:
Phase 1:

With the assistance of Richard A. Herrett, Ph.D. of the Agricultural Research Institute (ARI), LSRO staff identified 21 scientists familiar with the field of biotechnology risk assessment. These scientists were asked to provide a 3-5 page paper outlining their views with regard to strengths and limitations of the nine areas outlined in the Federal Register announcement (Appendix A). A draft report was prepared containing the synthesis of the comments of the 18 scientists who responded. The complete versions of these comments can be found without attribution in Appendix B. Appendix C is an alphabetical listing of those individuals who contributed comments to this report.

Specifically, these scientists were asked to address the tasks in the following three subject areas:

1. Strengths and weaknesses of the scientific aspects of USDA’s current biotechnology risk assessment program. (In particular, the nine objectives outlined in the Federal Register announcement.)

2. Adequacy of current scientific knowledge about risk assessment. (Identify potential gaps in knowledge and possible areas to be targeted for future research initiatives by the USDA CSREES.)

3. Possible new directions or criteria for decision-making in biotechnology risk assessment. (Include suggestions for potential new methods and scientific disciplines required to be included in the establishment of new approaches.)

Phase 2:

LSRO and ARI identified five individuals (see Chapter V) to serve as an ad hoc Expert Panel. These individuals were asked to review the draft document and provide additional input to be incorporated into a final report for the USDA BRARGP. The purpose of this additional input was to provide the basis for a long-term strategic approach to the continuing review and analysis of the BRARGP programs and goals. Specifically, the Expert Panel was charged with providing an outline, recommendations, and options for an ongoing process to ensure the continued success of the USDA Biotechnology Risk Assessment Research Grants Program. The conclusions and recommendations of the Expert Panel can be found interspersed throughout the report.

D. ORGANIZATION AND FORMAT OF THE REPORT

The format used for this report was to delineate the comments of the ad hoc reviewers with regard to their three charges, i.e., general comments about the scientific aspects of the program, specific comments about the nine areas targeted in the Federal Register announcement, and identification of gaps in the knowledge and recommendations for future programmatic approaches. The ad hoc reviewer statements, identified by the Expert Panel as being of particular merit, have been highlighted. In addition, at the end of each section the Expert Panel offered its own conclusions and recommendations. The comments and conclusions of the Expert Panel are also summarized in the Executive Summary.
II. STRENGTHS AND WEAKNESSES OF THE SCIENTIFIC ASPECTS OF USDA'S CURRENT BIOTECHNOLOGY RISK ASSESSMENT RESEARCH GRANTS PROGRAM (BRARGP)

A. COMMENTS OF THE AD HOC REVIEWERS

1. General comments

The reviewers universally agreed about the importance and necessity of the BRARGP. There was general agreement that the current Program is achieving at least some of the goals of advancing the science of risk assessment. The overall favorable impression of the Program was reflected in the following statement: "In general, the scientific aspects of the USDA's current Biotechnology Risk Assessment Program are quite comprehensive and sound."

Most of the reviewers recognized the continuing need for a science-based process for evaluating risk associated with new products derived from biotechnology before these products are introduced. The role of the BRARGP "...has been, and continues to be, a cost-effective way to conduct this process. The Program should be continued because there are scientific issues yet to be resolved."

The Program was praised for being "competitive and peer-reviewed at the national level, as opposed to being in-house at USDA-ARS or administered semi-competitively at the regional level. This at least opens up participation in the Program and counters the stagnation that seems to set in for most programs in the latter two categories."

Another reviewer praised the Program for "its applied thrust," and continued to say that the "USDA is the primary oversight authority for making science-based decisions about the safety of introductions of genetically modified organisms into the environment. A scientifically valid knowledge base on key risk assessment issues is absolutely necessary for practicing informed oversight." This opinion was seconded by the consultant who stated, "Another major strength of the Program is a healthy balance of relatively applied work with immediate practical value versus high quality basic science aimed at fundamental understanding of biotechnology risk issues."

The universal debate about the relative importance between applied and basic research and the related issue of targeted versus investigator-initiated basic research was evident in the following contrasting reviews:

• "Some targeted areas in the annual Program Announcement are carefully chosen in such a way that they can support good science as well as providing new information genuinely relevant to risk assessment. The questions are clearly formulated and targeted to an existing component of the scientific community whose primary interest may not be risk assessment per se, but whose scientific findings are needed to support informed decision making, and who can be persuaded by the inducement of research funding to address these scientific issues at a higher priority than other equally interesting ones. Such successful targeted areas do exist in the current Program but they are not common."

• This view of the value of targeted research is contrasted by the views of another reviewer who said, "...the goal of supporting risk assessment is disconnected from the criterion for scientific merit. To be scientifically meritorious, risk assessment research should emphasize serious gaps in scientific knowledge, present innovative experimental approaches to addressing the central problems causing those gaps, and describe a rigorous
methodological and analytical plan through which to develop new information. The solicitation makes none of those points within the context of the Program's nine principal research objectives." This reviewer went on to state that "several of these principal research objectives focus on 'problems' of limited scientific or practical interest. It may be that they are included to serve a 'regulatory' interest of the agency. If so, that should be explicitly stated and the Program should not be represented as being driven by scientific merit."

This reviewer offered the following remedy for what was perceived as a potential for funding lower quality proposals. "A clear disadvantage of the approach taken in the solicitation is that the quality of grants funded on the margin of such a program may not be (and likely is not) at the level characteristic of grants funded under more general categories of research where competition is stronger and scientific merit given greater emphasis. This problem can be easily remedied by simply integrating the agency's goal of supporting risk assessment research into the larger, competitive grant program."

- With regard to the issue of attracting the highest quality proposals to meet the stated objectives of the overall Program, one reviewer stated, "USDA has a dismal record of proactive solicitation of proposals from among which to choose the best. Selection of the 'best' of the proposals received 'over the transom' could conceivably result in funding concentrated, to take the extreme case, in only one of the nine areas identified in the Federal Register publication. Alternatively, there could be a mechanism that demands selection of the 'best' proposals in the nine areas, and the issue here is that some of the areas could be represented by very poor 'best' proposals." This reviewer recommended that, "...for such a targeted program, there should be an element of solicitation of proposals, across the spectrum, from investigators who are known to be both interested in, and capable of doing reasonable work, in an area of interest to the agency."

2. Specific concerns

There were several other recurrent themes that reflected some ambivalence and reservations about aspects of the overall Program. The concerns about the Program centered around several core issues; the overall scope of the Program, the definition of risk, the ability of the Program to achieve its expressed goals, and the effective utilization of research findings.

- With regard to the overall scope of the Program one reviewer wrote: "The current risk assessment research program in biotechnology is hampered by its innumeracy and avoidance of sophisticated quantitative approaches. Monitoring should be given greater emphasis -- especially the evaluation of alternative monitoring schemes (as opposed to focusing on one particular approach that may not be appropriate). The Program must address transgenic crops internationally and not be so myopically restricted to North America. Much could be accomplished by contract work aimed at producing products, such as peer-reviewed handbooks, as opposed to random research wanderings. A major practical and intellectual challenge is the comparison of alternative monitoring programs for large-scale agriculture and rare events in a tremendously heterogeneous environment."

A corollary of the overall question of the Program's focus and lack of clarity was the concern expressed by a number of viewers about the issue of the definition of risk:

- One reviewer stated, "There is a lack of a widely accepted definition of risk that is relevant in the biotechnology arena, or even the outline of a standardized process of risk assessment that
is relevant to more than one or two extremely specialized cases. This is the major problem with having a grants program in the area."

- Another reviewer saw the lack of a definition of risk as an obstacle that would prevent both successful applications and review. "It would seem here that the definition of risk assessment has not been elucidated well by USDA. The spread of an agent in the environment can be monitored, as can its survival and ultimate fate. Is a risk assessment in this context a mathematical model based on some hard data derived from a similar released organism? Is the risk the same as the organism's survival? I return here to my previous point that the potential 'adverse outcomes' have not been elucidated sufficiently by USDA, and subsequently, this has caused uncertainty about what is meant by risk assessment."

- This issue was addressed from a slightly different perspective by the reviewer who raised the following question, "How do we evaluate and monitor risks for a technology that is distributed over a huge spatial scale and that encounters in the process an enormous variety of environments and co-occurring organisms?"

- While the Program objectives allow for the identification of "important aspects of judging the risks that may arise from introducing a genetically modified organism into the environment," one reviewer observed that what is lacking in the Program is, "a straightforward and clear statement by USDA about what it is they feel the risks are."

- The question of defining risk within the context of the Program's goals was addressed by the reviewer who wrote: "The definition of risk assessment -- the meaning of risk, and the proper methodology of risk assessment -- are not scientific issues. They are programmatic issues, and it is a misconception to believe that any number of scientific studies can compensate for a fuzziness of thinking in defining the scope of the Program that funds them. There's no scientific basis in believing that the paradigm of risk assessment based on the analysis of failure of nuclear-powered generating plants is relevant to assessing the risk of creating and releasing transgenic organisms. But it might be a useful starting point, and I would like to see the USDA develop a short position paper on what risk assessment in the biotechnological arena should look like and how it would differ from the power-plant analogy. Respondents to the Program solicitation would at least then have a common point of reference."

- Viewed within the context of an overall programmatic goal another reviewer stated that "It is clearly impossible to assure 'absolutely no risk' in an untested situation, so if the potential benefits of any biotechnological research products are ever to be realized, the definition of 'acceptable risk' must be addressed."

- Perhaps related to the lack of a definition of risk is the comment acknowledging the Programs' inability "in maintaining the focus directly on risk assessment, rather than on general work demonstrating and characterizing risk, attempting to reduce risk, or simply working in a biotechnological system that involved some risk." This reviewer noted that this deficiency can lead to shortfall in quality, focused proposals and can ultimately result in a situation where Program reviewers were left to make choices between the best science and programmatic goals.

- In a similar vein was the comment concerning "...a perception, which to some degree I share, that the thrust of the Biotechnology Risk Assessment Research Grants Program has been to document environmental safety of products of biotechnology. Taken in its historical context, the Program was initiated during the Bush-Quayle administration at the token 1% funding

5
level to address the fears of biotechnology which reached a peak in the late 1980s. While many of the public's fears justifiably were laid to rest, some subsets of applications of agricultural biotechnology have been shown to pose environmental risk."

The same reviewer also lamented the policy of nonrenewal of funding for projects identifying risks posed by agricultural biotechnology for the following reasons: "Loss of Program funding poses not only loss of the opportunity for immediate follow-up on results to date, but also loss of genetic materials and key project personnel, and thereby, loss of opportunity for future follow-up."

- Concern was expressed about the relationship between "the objectives as described in the scope of research (and the societal concerns that clearly drive the rationale for the Program) and the timescale of the granting authority." Using objective #9 as an example this reviewer concluded, "one or two year grants in this area presume either an incredibly naive interpretation of the significance of the issues or betray a breathtaking naivete about the nature of the research needed to address them. There is a serious need for a long-term commitment to research about the agro-ecosystem, both in terms of development of new methodology and in terms of a framework for monitoring the consequences of the introduction of new technologies employing these methodologies."

- The concern about the focus of the Program was shared by the reviewer who wrote, "This Program assumes that there is a need for science-based regulation of biotechnology specifically to cover the release of genetically modified organisms (GMOs) in the environment. However, the announcement in the Federal Register does not define GMOs." According to this reviewer this lack of clarity presupposes certain inherent risks from biotechnology. "Since the products of deliberate breeding programs are genetically modified, this Program could be concerned with the release of crop cultivars derived from conventional breeding and selection programs." In noting the absence of concern for products of conventional breeding techniques in the Program announcement, this reviewer concluded that, "this Program is specifically concerned with transgenic organisms produced with the techniques of recombinant DNA." The reviewer goes on to describe the Program as being "motivated more by politics than science," particularly because "no example is yet known of environmental or other damage from the deliberate or accidental release of a genetically modified organism."

- This same reviewer went on to say: "My principal concern is that a logical conclusion of such studies is that we will also become much more concerned about what we now take for granted and rarely question, namely conventional agricultural and other technologies such as plant and animal breeding, aquaculture etc. In my view, the risks from these activities totally dwarf the concerns of this Program. We have only to think about the continuing massive destruction of forests to clear land for cattle grazing, building highways and creating short-term wealth to put our concerns for GMOs in a global perspective. Our priorities should be to conserve what we know we are losing in natural resources and not to waste resources in dealing with exaggerated risks."

Relative to the issue of the Program's commitment and capacity to achieve its goals as laid out in the Program announcement the following comments were offered:

- "As the purpose of these funds is to provide tools and understanding to develop future management procedures, an attempt should be made to attract more proposals dealing directly with risk assessment. The Program announcement should
emphasize even more clearly that proposals should deal with assessment of risk rather than characterization or reduction of risk."

- In light of the fiscal restraints and overall scope of the Program one reviewer expressed scepticism about its chances for success: "Given the scope of research and development effort in agricultural biotechnology, the Program as currently funded (a token 1% of USDA biotechnology expenditures, about $1.7 million) cannot address adequately every significant risk assessment problem identified. This token outlay cannot even begin to support research needed to identify more subtle mechanisms or to quantify longer-term processes giving rise to environmental impacts, or to quantify the full range of processes giving rise to environmental impacts, or areas. The great bulk of USDA's investment in biotechnology research has been to promote technical development, i.e., development of methodologies and of genetically modified lines of plants, animals, and microbes. With the growth of the private sector in agricultural biotechnology, we can safely assume that the private sector will pick up much of the cost of research and development, and that the mix of projects supported by public monies can be changed to increase the investment in risk assessment research, an investment that smaller biotechnology companies cannot make. Hence, USDA can and must expand the support for the Biotechnology Risk Assessment Research Program dramatically."

Concern about the ability to utilize research findings effectively was reflected in the following comments:

- "This Program appears to be an excellent mechanism for obtaining science-based information. What is not clear to me is how the information is used other than after it appears in publications that contribute to the general body of knowledge; I did note the annual conference and annual risk assessment symposia which I have learned are structured so that they are exceedingly costly."

- Another reviewer wrote, "...the mechanism in place is excellent for obtaining sound information for this Program, if the Program is being implemented effectively. Possibly, it would be advantageous to subcontract proposal evaluation to the National Research Initiative Competitive Grants Program. In any case, good information likely is being generated. The major concern may, however, be the effectiveness of mechanisms in place to use the information efficiently and effectively."

3. The Annual Conference

Several of the reviewers commented specifically about the annual meeting held by the USDA Biotechnology Program.

- "This conference provides the opportunity for investigators and USDA officials with oversight responsibilities to interact, to synthesize new understanding, and to identify future research needs. The proceedings of this conference provide a picture of the state of knowledge of biotechnology risk assessment at that moment in time, and are read internationally as well as in the United States."

Concern was expressed by the same reviewer about an attitudinal bias on the part of meeting participants at the annual biotechnology risk assessment conference: "The tone of the annual biotechnology risk assessment meetings sometimes has fallen short of dispassionate discussion of scientific issues." The reviewer further noted that the tone at one recent conference was
"openly hostile to investigators or to environmentalists expressing concern about impacts stemming from environmental application of agricultural biotechnology." This reviewer urged meeting organizers to "make clear the expectation that the meeting will proceed in an atmosphere of professionalism and mutual respect."

- "The convening of a meeting that brings together the investigators is excellent. I have attended these meetings, though and believe they would be more useful if the focus was on crosscutting issues rather than just on reports from individual projects. The effort to distribute results to government officials is a positive also."

- A more critical view was provided by the reviewer who wrote: "The mandatory annual conference for PIs funded by the Program is a waste of time and money. I have attended several of these and they have always been the low point of the annual meeting circuit. Although there are several excellent participants and a few very good papers, there is not scientific cohesion. About a third of the participants are just starting on their funded project and have little more to present than an audiovisual version of their grant proposal. The level of interaction between meeting participants is the lowest I have seen at any regularly-scheduled scientific meeting. Although I was initially excited by the opportunity to meet and interact with US-EPA participants as well as PIs on the USDA-funded projects, I was quite disappointed in my expectations and did not need subsequent annual contact to remind me of this."

This reviewer's sentiments were summarized succinctly by the recommendation that, "The annual meeting should be eliminated and the Program funds devoted to it should be reallocated to funding more grants."

The same reviewer also commented on the value of the published proceedings from this meeting. "Related to the annual conference is the issue of publishing progress reports in the annual conference proceedings. This seems to serve no purpose but to increase the visibility of the Program by the annual production of a publication. It overlooks the fact that none of these data will be relevant to the scientific community if they are not published in peer-reviewed journals. It compromises the PI's submission of data to these journals, many of which require that the material submitted for publication not be published previously elsewhere. It wastes the PI's time in preparing yet another manuscript for a book that will be almost universally ignored.

"It burdens libraries with the annual acquisition of yet another book, that contains information that (if the Risk Assessment Grants Program is successful) should be rapidly superseded by articles in journals whose rising prices are also straining the library's budget."

- Another reviewer was "disappointed in several aspects of the conference I attended last summer in Ottawa. Parts of it were good; there were a few nice papers presented by grantees. However, even though they were expected to attend, very few did! My principal problem however, was its lack of attention to assessing the field. Many of the questions you are asking of your panel now, should have been addressed in the conference. They should have summarized where we are in the various research areas. They should have assembled some focus groups of grantees and others to summarize. They should be asking the question I raised above about when we have sufficient information in some of the areas to enable us to move on to others. Additionally, if the conference is to have impact, it is important to have a timely report; the report from 1995
conference was published just in time for the 1996 conference. That is unacceptable in my view."

4. **General recommendations about the Program**

In addition to the insightful comments about the scientific aspects of the Program many of the reviewers provided thoughtful recommendations about the Program management. The focus of these comments was on application procedures, proposal review, and effective dissemination of research findings for the purpose of planning future research agendas. The latter category was a recurring theme as exemplified by the reviewer who cautioned, "The major concern may, however, be the effectiveness of mechanisms in place to use the information efficiently and effectively."

The following comments were made about the general area of the application process and Program management:

- "I strongly encourage the use of a pre-proposal mechanism for soliciting proposals. This would be a great time saver for scientists. I suggest a 3-page maximum pre-proposal including the budget. Program managers plus several outside reviewers could then eliminate those proposals with inappropriate subject matter, and those with pedantic ideas or from noncompetitive programs, with the aim of obtaining full proposals from about twice the number of applicants that eventually will be funded (~50% funding rate). Decisions as to who will be invited to submit full proposals should be made within 2 weeks of deadlines for receiving preproposals. Full proposals should then be due 60 days later." This reviewer added the suggestion that "it would be advantageous to subcontract proposal evaluation to the National Research Initiative Competitive Grants Program."

- On the issue of insuring the proper focus of proposals, a reviewer wrote, "As the purpose of these funds is to provide tools and understanding to develop future management procedures, an attempt should be made to attract more proposals dealing directly with risk assessment. The Program announcement should emphasize even more clearly that proposals should deal with assessment of risk rather than characterization or reduction of risk. Although this is already inherent in the wording throughout the Program announcement, it seems that it needs to be more plainly stated, perhaps in the purpose or description sections."

- One reviewer offered the following specific suggestions about proposal format, review, and requirements:

  "The instructions to the applicant should be tightened to get proposals which would have a common format. In particular, the length of the summary should be specified, perhaps by providing a page similar to NRI proposals. In fact, some used that page; others rambled on with as many as three pages. Also, some applicants played games with a progress report. Even though they were renewing a project closely related to their current one, several chose to consider it a new submission, and did not give a progress report. The section on the progress report should indicate that they provide a progress report on any project supported by the Risk Assessment Program. This is a policy the NSF follows. The instructions should also require a table of contents."

- "The Program does address the aspects of risk assessment for which information is needed. In some areas specific systems have been identified, and in some cases these specific research needs have been adjusted as information flows into the system. In other areas the needs are only very broadly defined. In my opinion the objectives and goals of this Program should differ
from those competitive grant Programs designed to fund basic research. The solicitations for
the latter programs are, rightfully, broadly couched. The Risk Assessment Program on the
other hand should attempt to clearly define the areas in which research is needed and then let
scientists design the experiments to obtain the needed information. Since the Program has
already funded investigators on various aspects of risk assessment for several years perhaps
it could use them as a base of expertise to better define the research needed in these areas.
This would allow the Program administrators to play a more proactive role as opposed to
relying primarily on input from outside sources."

- One reviewer suggested that the question of how regulatory agencies can effectively acquire
scientific input "is an area for study, i.e., how Federal regulatory agencies obtain scientific
information to develop policy, and how this might be improved, specifically for risk assessment
or more generally."

- On the issue of the productivity of the Program one reviewer summarized his/her thoughts as
follows:

"...the fact that this Program has been funding proposals now for 3-4 years (maybe longer, I
am not sure) yet has produced so little peer-reviewed results in high prestige journals is an
indication that something is wrong. Either the wrong people are being funded, or the wrong
projects are being funded. I think both "wrongs" apply. By now, PIs funded by this Program
should have produced a few papers in Nature or Science, and many papers in Ecological
Applications, Conservation Biology, Molecular Ecology, and other widely-read journals. I have
not seen these papers forthcoming and the influence of work funded by this Program is at best
negligible, and perhaps zero -- I am willing to wager that the science citation scores for PI
papers funded by this Program averages less than 5 per grant -- whereas a score of 50 per
grant should be expected.

Several reviewers commented about the Program’s mission within the context of the Agency’s
overall administrative structure.

- "The Program is administered separately from the largest and most successful competitive
grantes program in the USDA: the National Research Initiative Competitive Grants Program
(NRI-CGP). After going through some significant growing pains, the NRI-CGP is now
administered at a high quality comparable to the National Science Foundation’s competitive
grants program. I can’t understand why the Biotechnology Risk Assessment Program has to
reinvent the wheel." The reviewer observed that,"... it seems wasteful not to take advantage
of the expertise and existing organization in the NRI-CGP. The NRI-CGP should be given the
responsibility for administering the Risk Assessment Program and the additional funds
necessary to take it on."

With regard to the process of choosing research priorities this same reviewer observed, "In
spite of some sensible research priorities whose advertisement in the Federal Register can
attract some of the best researchers in the country to address issues relevant to risk
assessment, the majority of these research priorities, and indeed the very process used to come
up with them, don’t make very much sense. This process needs to be made more transparent,
and the year-to-year output of it more consistent, if the Program is to gain in credibility. If last
year’s odd priority that made the list because of jockeying among the regulators is off this
year’s list for the same reason, of what use is the one-year’s round of proposals that were
actually funded in that area last year? The problem of the programmatic moving target only
exacerbates the problem of the lack of definition of risk assessment I mentioned above."
B. CONCLUSIONS OF THE EXPERT PANEL

The Expert Panel concluded that in light of limited funds, the BRARGP needs to be focused on identifying and addressing gaps in knowledge about risk assessment in biotechnology. More specifically, the focus of this Program should be targeted to risk assessment issues that are unique to agricultural biotechnology. Towards that end the Expert Panel strongly endorsed the concerns raised by many reviewers with regard to the need to provide a clear, concise definition of risk assessment within the context of agricultural biotechnology.

The Expert Panel noted that while not included in the Federal Register announcement, the BRARGP did have such a definition on record. In the USDA CSREES/ARS publication entitled "Risk Assessment Research, 1992-1994: An Overview of the USDA Biotechnology Risk Assessment Research Grants Program," "risk analysis" was described as consisting of the following two components:

Risk assessment: "the science-based evaluation and interpretation of factual information in which a given hazard, if any, is identified, and the consequences associated with the hazard are subsequently explored."

Risk management: defined as "primarily a policy and decision-making process that uses risk assessment data in deciding how to avoid or mitigate the consequences identified in a risk assessment."

In addition to these core definitions the paper describes risk communication as a process that "provides an important link between researchers, regulators, and the public through the sharing of risk analysis information and decisions with interested parties, including consumers."

The Expert Panel concluded that these definitions are appropriate and should continue to serve as the guiding principles in program planning. They emphasized the importance of a clear, concise definition of risk within the context of issues related to agricultural biotechnology. The Panel cautioned that efforts should be made to identify differences that might exist between those paradigms that have been used in other risk-assessment contexts, i.e., chemical or hazardous waste exposure scenarios, and those that might be applicable to agricultural biotechnology. The failure to recognize and act on these potential differences would be a major obstacle that would prevent the Program from achieving its goal of providing a strong scientific basis for regulatory decision making.

Further, the Expert Panel concluded that the previous failure of the Program to define "the universe" of risk assessment questions that it needs to address has contributed, as one ad hoc reviewer put it, to the Program's inability "in maintaining the focus directly on risk assessment, rather than on general work demonstrating and characterizing risk, attempting to reduce risk, or simply working in a biotechnological system that involved some risk." It is the impression of the Expert Panel that the focus of the Program should be on risk assessment, not risk management, and that this distinction should be clearly expressed in the Program announcement and communications with the scientific community.

From a Program management perspective, the Expert Panel suggested that, in addition to the inclusion of a refined definition of risk in the Program announcement, an effective tool in the management of the proposal process would be the initiation of a preproposal process. This would allow effective communication between the scientific community and the Program managers, and it would facilitate the submission of focused proposals consistent with programmatic goals.
With regard to comments about the Annual Conference, the Expert Panel agreed with the concept and the importance of bringing together members of the scientific and regulatory communities, but also echoed the concerns made by several reviewers about the lack of a more interactive format. In order to rectify the current weaknesses in the meeting format the Expert Panel suggested a workshop approach as opposed to standard presentations of current research activities. The focus of the meeting should be not only a presentation of new research but also an interactive process by which gaps in knowledge could be identified for use in Program planning and in effective implementation of the regulatory agenda. In addition, the Expert Panel recommended that periodic workshops be scheduled to address such specific issues as those raised by the ad hoc reviewers, e.g., experimental design of large scale studies, appropriate statistical procedures, etc.

The Expert Panel emphasized that, if unresolved, the lack of focus will continue to impair the ability of those reviewing proposals to make appropriate decisions about the merit of proposals as they will continue to be forced to choose between the best science (but not necessarily related to risk assessment) and Program relevance. Given the limited resources for this research area, the conflict will not serve the long-term survival of the Program or advance the science.
III. REVIEW OF THE NINE AREAS TARGETED BY USDA BRARGP

A. GENERAL COMMENTS

In responding to their charge, most of the reviewers provided comments about individual objectives listed in the Federal Register announcement. The following chapter is a synthesis of those comments organized by objective. Following the reviewers' comments is a summary of the Expert Panel's reaction to the reviewers' comments and the Expert Panel's conclusions about the merits of each objective. In addition, those comments from the ad hoc reviewers that were perceived by the Expert Panel as being of particular merit are highlighted.

Although some reservations were expressed, overall, the reviews of the nine areas identified in the Federal Register announcement were favorable. Several reviewers endorsed the distinction between the objectives that advanced the science of risk assessment and those that were viewed as serving the regulatory agenda of the USDA. More specifically, the objectives were often characterized as enabling the USDA program managers to meet specific needs identified by the scientific community while allowing flexibility for exploration into newer areas not currently occupying a specific programmatic niche. This approach was viewed as providing the agency flexibility in supporting targeted areas while allowing for the creative development of new areas. This opinion was exemplified by the following statements:

- In referring to objectives 1-3, one reviewer concluded that, "These three broad program topic areas serve to promote original research designed by the research community, providing basic knowledge or tools not conceived by USDA-CSREES officials. The opportunity for investigator-initiated risk assessment research is laudable."

In response to input received by Program Managers and in keeping with legislative mandates to be responsive to new issues in the field, objectives 4-9 were intended to address specific areas of risk assessment that had been "identified as eligible for competition as research topics" for the period covered by the Federal Register announcement.

- "The program description for 1996 has been expanded to encourage proposals based on field research as well as whole organism-population level studies. The description has also been amended to stress the need for proposals to be applicable to current regulatory issues surrounding the ecological impact of genetically modified organisms. The first of these expansions delineates specific areas of interest while the second stresses applicability. These modifications indicate that the administrators of the Program are recognizing and addressing the need for evolution of the Program in response to changing needs."

- "...the first three points listed are not research topics per se, but an attempt to describe the scope of the program. The last six points are research topics."

- This comment was echoed and refined by another reviewer who stated, "The first three objective are general in scope. They solicit proposals on any of a broad range of topics associated with biotechnology risk assessment. The last six objectives are more specific. They are tailored to address those issues of most current interest to federal regulators. Thus, the first three research objectives provide USDA CSREES the opportunity to consider research proposals that may not fit the relatively narrow research objective defined by regulators, but may merit funding because they are especially innovative."
b. Expert Panel’s comments

See Expert Panel comments under objective 3.

6. **Objective 6.** Changes in viral host ranges or the types of viral vectors as a result of the use of transgenic plants expressing viral genes.

a. Reviewers’ comments

Many of the comments about this objective were similar to those about objective 5. Overall, the comments were favorable, at least in terms of the scientific importance of the questions to be addressed. Several reviewers noted the similarities between objectives five and six and made suggestions either to combine the two areas or apply similar criteria. Examples of this observation include the following:

- "Research area six is related to area five and addresses the potential for changes in viral host ranges or viral vectors as a result of the expression of viral genes in transgenic plants. This is an important area, particularly with the recognition of the pleiotropic effects of viral genes. The information concerning this area has not changed over the three year period. Once again, perhaps solicitations based upon the criteria discussed above for area five should be considered."

- "It is conceded by all that recombination between a virus and a transgene can occur, but the main consideration is whether the outcome is bad. To date, there has been no suggestion that new, and more deleterious strains or viruses have arisen. The same argument can be made with respect to the broadening of the host range. I feel that the only grants which should be considered in the plant virus area in the future should deal with large scale field trials to see if there is credence to the genesis of bad viruses or expanded host ranges. This may well be done for us by the entry of virus resistant plants into commerce."

Additional comments about objective #6 include:

- "The statement of this point is a bit too broad to serve as a useful objective. Its authors must certainly have some idea what sort of risks they have in mind, and it would be helpful to mention them here."

- While acknowledging the importance of this general area of research one reviewer wrote, "The wording of this topic is somewhat ambiguous. What is meant by ‘types of viral vectors? Is it changes in types of vectors? Intent is not clear."

- "Both (objectives 5 and 6) address extremely low-frequency events, which are going to be very hard to quantify (i.e., without huge confidence intervals). A more useful approach would involve the design of monitoring schemes that could detect undesirable recombination events or host shifts in nature."

- "This research area is broader than area 5, and seems an appropriate area of concern for environmental risk assessment."

- "As to objective #6, the risk of transcapsidation is extremely low and not worthy of attention. The arguments provided for objective #5 apply even more strongly here. It is even less likely that RNA-RNA recombination would present a risk to agriculture or the environment."
"...such studies should include studies of plants that are under inoculum pressure by multiple viruses since such conditions may influence the acquisition of virus by an insect, or make it possible for some insects to transmit that did not normally transmit in the case of single infection. All such studies should be well controlled with non-transgenic plants that are similarly treated. The impact of resistance on selection, as well as the degree of resistance, i.e., near-immune conditions versus highly or moderately resistant plant lines should be included in studies. It is hoped that studies are not carried out only with members of the Solanaceae, but also with crops such as corn and soybeans where the pest problems are different and the acreages of planting likely to be much greater than for horticultural crops.

Furthermore, the contents of alkaloids and other secondary compounds are different with different crops and may affect insect feeding and transmission of disease agents."

b. Expert Panel’s comments

See Expert Panel comments under objective 3.

7. Objective 7. The potential for nontarget effects of introduced plant-defense compounds expressed in genetically modified plant associated microorganisms (e.g., compounds in phyllosphere or rhizosphere inhabiting bacteria) or in plants (e.g., Bacillus thuringiensis delta-endotoxin), especially in regard to persistence of the organisms and material in the environment.

a. Reviewers’ comments

The general consensus was favorable towards this objective albeit, as one reviewer said, "Perhaps some fine tuning is in order." Only a few of the reviewers offered specific comments directed towards this Program area:

- "This is clearly stated and well circumscribed... although it appears to assume that persistence of engineered organisms in the environment is inherently a risk. The use of Bacillus thuringiensis as an example of non-target effects overlooks the widely accepted view that the greatest risk associated with the delta-endotoxin is that their injudicious use will result in rapid insect resistance and hence loss of an otherwise low-risk strategy of pest control to higher risk chemical alternatives."

- "Studies regarding the impacts of Bt on the soil ecosystem are desperately needed-- but, the impacts will depend on soil properties, and therefore, this effort should make sure impacts are evaluated in a wide variety of soil types."

- "This is a specific, important area for research in the context of risk assessment, and intent is clear."

- "Characterization of non-target pesticidal effects of genetically modified microbes or plants is timely and appropriate. This is justified by well-documented declines in valued non-target populations following the widespread adoption of chemical pesticides."

This same reviewer offered this overview of objectives 4-7: "Taken collectively, research areas 4-7 call for sophisticated experimental designs quantifying risks associated with narrowly defined impact pathways. This portion of the Program’s call for proposals underlines the notion that knowledge of risk pathways for genetically modified plants is much more advanced
than for other sectors of agricultural biotechnology. In contrast, risk assessment for genetically modified microbes, arthropods, and aquatic organisms is in an exploratory stage."

- The following refinements were offered by another reviewer who wrote: "There are persistent and lingering questions related to the impacts of transgene-derived proteins on non-target organisms in the environment, including the rhizosphere and soils that contain crop residues, and leaf tissues. **One of the most nagging questions is related to the survival of genes that encode resistance to antibiotics, since such genes are generally included in transformation/selection protocols.** In the selection of grants for funding at least one should be for the study of survival of gene sequences in animal digestive systems. Although many of us consider the likelihood of horizontal transfer between organisms to be extremely unlikely (even fantasy) the public has a concern that has not yet been carefully addressed." The reviewer went on to suggest that, "the proteins that are selected for study should include those that are likely to be included in crops, including PR proteins and phytoalexins, as well as proteins that control specific insects and microbes."

b. **Expert Panel’s comments**

The Expert Panel regarded this as an important objective because of its focus on microbial issues. They concluded that the question of antibiotic resistance should be given a high priority and suggested that it is so important that the BRARGP might consider upgrading it to the status of an objective (rather than one issue within objective 7).

8. **Objective 8. "Identification of genes which can confer additional pathogenicity to animal pathogens."**

a. **Reviewers’ comments**

Of all the objectives, this one was the focus of some of the more strident comments from the reviewers. As seen in the comments listed below, the preponderance of the invective is directed at a perceived lack of clarity in the Program description.

- One reviewer offered this explanation for the lack of specificity of this Program area: "Research area 8, addressing the possibility that introduced genes could recombine with or otherwise increase the pathogenicity of animal pathogens, corresponds to the plant-oriented research areas 5 and 6. The broad generality of research area 8, compared to the specificity of areas 5 and 6, emphasizes how much less we know about the risk pathways and animal pathogens at issue."

- Another reviewer noted: "It is unclear if genes of the host or the pathogen are of interest. If the former, it might be clearer to use wording such as 'increased susceptibility to pathogens,' Perhaps an example would increase clarity."

- Objective #8 was described by one reviewer as "...very concise, to the point that some individuals did not understand the nature of the area being proposed. If included in subsequent announcements, the nature of the 'animal pathogens' should be clarified. For example, are insects 'animals'? Or, are some other animals pathogenic? Or, perhaps the announcement meant pathogens of animals?"

However, the bulk of the commentary on this objective was less magnanimous.
"It is unclear what types of projects are anticipated to involve genes that can confer additional pathogenicity to animal pathogens, although certain of those described above might be placed in this category." This reviewer went on to propose the following revisions to this objective: "It goes without saying that such studies should involve livestock animals and poultry, etc., rather than rodents and other "model" animals that are not part of the (U.S.) diet. Other genes that might impact pathogenicity of animal pathogens might include proteins that affect freezing tolerance, or that encode proteases, toxins and other proteins that might impact pathogenicity of microorganisms. However, because the likelihood that any gene recombinations or other types of gene transfer is extremely low (fantasy) it will be important to fund only those proposals that are of the highest quality by the most suited of research teams. The team must include plant biologists, microbiologists, animal nutritionists, and population biologists/geneticists, and should be funded for 3-5 years, with good preliminary results available to the research and regulatory agencies within 6-18 months. If such a project is to be funded, it should be done correctly so that the results will leave few doubts of their significance and applicability to biotechnology (i.e., no model systems)."

"Among the more specific research areas outlined in points 4-9, point 8 is particularly weak. As written, it is not clear what value this point has to either basic science or to risk assessment and I would recommend eliminating it altogether."

"Sounds like a fishing expedition here; what's the point? Our pathogens aren't pathogenic enough? this like Objective 6. One suspects that it is code for something more specific, that should be spelled out here."

"I do not feel this is worth much effort -- of course, genes that enhance virulence exist -- but so what? I do not see where this research effort will lead us to what is practically useful."

"Research area eight is about as vague and unfocused as possible; any gene, any pathogen, and animal. At least the previous version identified organisms of interest to APHIS, again presumably because these pathogens are currently being engineered for vaccine production or other uses. There seems to be less outside input into potential risks in animals systems as opposed to plant systems. Considerable thought needs to be given to what types of research proposals are needed in this area."

"Do such genes exist? Have there been any applications in this group?"

"I do not understand why objective eight...is a priority. This may reflect poor understanding on my part -- I have little scientific training with warm blooded vertebrates. Nevertheless, at the very least, more context for this objective would be helpful!"

"My view of virulence and pathogenicity in both animals and plants is that the fields are too immature to make any sensible projections of practical work ("identification of genes which can confer additional pathogenicity...") worthwhile."

b. Expert Panel’s comments

The Expert Panel considered the criticisms of objective 8 to be valid and concluded that it should not be continued in its current form.

9. Objective 9. Environmental risk analysis of large scale deployment of genetically engineered organisms; especially commercial uses of such
organisms with special reference to consideration that may not be revealed through small scale evaluations and tests."

a. Reviewers' comments

Conceptually, reviews of this Program area were, for the most part, favorable. With the exception of a few comments about the need for clarifying examples, the comments were supportive.

- "...I would like to see an emphasis on experiments in Category 9. I feel we need this information, which is the ultimate in risk assessment."

- "Research targeted under area 9 is absolutely essential for fostering environmentally safe commercialization of agricultural biotechnology. A salient example of an important problem is scaling up of production of crops expressing Bt endotoxin from the experimental stage (where plant pests encounter this pesticide only rarely) to the commercial scale (where widespread use would cause sufficient selective pressure for resistance that Bt’s future as an effective pesticide would prove limited). Other risk mechanisms involving other products of agricultural biotechnology also might become important only at the landscape scale. Results of studies supported under this research area could prove critically important for strategic development of agricultural biotechnology, in terms of realizing its potential while minimizing negative environmental impacts."

Some reviewers offered suggestions for clarification of the objective:

- "Research area nine was introduced in the solicitation for the 1995 Program. It would have helped my understanding if a ‘for example’ was provided, but perhaps the originators were leaving it to the applicants to make the case. If so, hopefully there have been submissions that may help the Program administrators to phrase the statement in such a way as to be able to hone in on the subject."

- An additional comment about the need for more clarity was offered by the reviewer who wrote, "The objective is very vague. The objective asks for an environmental risk analysis of large scale deployment of genetically engineered organisms. It seems obvious that this objective was written with some circumstance in mind; it would have been better to share that circumstance as an example for potential respondents."

- One reviewer, in support of the objective, offered the following suggestions about criteria for research design and subsequent proposal review: "Large-scale risk assessment should assume both the probability that the gene will migrate into domestic and weedy relatives and, secondly, impact when the gene or genes are transmitted to domestic or weedy relatives. The function of the gene can then be considered as the primary criterion of risk assessment. A gene that modifies seed oil characteristics will likely have different impact on weedy and domestic relatives than herbicide resistance, insect resistance, male sterility, or disease resistance. Large-scale deployment of single transgene resistance to a single insect or disease pest will alter the occurrence of other disease and/or insect pathogens that occur. Market penetrations may change the pattern of diseases or insects if safeguards are not taken. Normally, competition in the marketplace is the preferred safeguard since alternative sources of resistance, both transgenic and nontransgenic, will arise for the most significant pests. Consideration should be given to evaluation of source of transgenes and the genetic background of the plants in which the transgene is deployed. Genetic variation for both factors will minimize risk of new insect and/or disease pest becoming dominant, and also minimize development of resistance a transgene (i.e., Bt loss of effectiveness)."

28
Consideration might also be given to determining how long negative effects might persist once a transgene is no longer used commercially. Would transgenes that have migrated into domesticated and weedy relatives disappear rapidly after large scale use is curtailed?

The use of appropriate statistical models, experimental designs, and use of appropriate statistical consultants are very important criteria that should be used to evaluate all proposals. Appropriate statistical treatment of data will be necessary to predict the impact of one study for similar transgenes or species."

There was, however, some ambivalence expressed about this objective as exemplified by the following comments:

- "I am a little concerned about the purpose of the 9th area of research to be supported. The risks of large scale releases should and could be addressed in the first two areas of research mentioned in the Announcement. While I support obtaining data from large scale field releases, mentioning this area of research as a separate topic may serve to debase the small scale studies that have been done, and unduly heighten the concern of large scale releases."

- Consistent with the opinion expressed above was the conclusion that, "All risk analysis should be aimed at large-scale commercial use of transgenic organisms. Hence, this effort does not need an extra item. I suppose the point here is that data from small, short-term field trials cannot address some concerns that emerge when we go ahead on commercialization. In that event, certainly we need to worry about those phenomena that emerge only after commercialization (such as the evolution of insect resistance to Bt endotoxin)."

- Of interest are the comments of the reviewer who suggested that this Program area be reduced, not because of the lack of a need for information derived from large-scale uses, i.e., introduction of transgenic plants into large acreage commercial applications, but because "It would appear to me that this effort will now become a component of normal agricultural extension activities at the state level. The USDA should implement mechanisms to insure the assignment of this responsibility, thereby decreasing item 9..."

- One criticism of this objective was voiced within the context of limited funds: "Although this has an admirable sound to it, such projects are scarcely feasible with the restricted program budget."

- In questioning the ability of this Program to achieve its stated goals one reviewer offered a valuable suggestion: "How realistic it will be to compare small and large scale releases of GMOs in projects funded by this program is doubtful since nothing that could be attempted here could match the large commercial release covering millions of acres. In my view, this is best done through comparing the records of previous releases of conventional organisms and GMOs."

- The need for collaboration with commercial interests who are active in this areas was reinforced by the reviewer who suggested "...perhaps the most appropriate use of the resources is to work with the providers of the materials, monitoring populations of pests and pathogens, as well as non-target organisms. It is also important to provide support not only for study of macro-organisms (animals, plants, etc.) but also for modified microorganisms. It is anticipated that modified soil and foliar organisms, including Rhizobitan spp., micorrhizal fungi, and other beneficial organisms, as well as microbes that provide biological control of pests and pathogens will soon be ready for the market. Given the history
of the early Lindow experiments, those of Brill, Cook, and numerous private companies, and the public perception of microbes as involved in disease, such studies are important to the industry associated with agricultural biotechnology."

b. Expert Panel's comments

The Expert Panel recognized that because of limitations in funding and amount of resources required to conduct such large scale studies as called for in this objective, more creative approaches are needed to accomplish its worthy goals. The Expert Panel suggested that efforts be made to create effective lines of communication leading to collaboration between commercial enterprises, who have the resources to conduct such studies, and scientists who could design experiments that would successfully examine the risk. The Expert Panel stressed that the endpoints/consequences (e.g., effects of gene transfer, impact on non-target organisms, impact on the ecology, changes in pathogenicity and host range, creation of new pathogens, resistance management, etc.) to be evaluated in such studies be well-defined and focused on the overriding programmatic goal of identification of gaps in knowledge related to regulation of risk.
IV. COMMENTS ON THE ADEQUACY OF CURRENT SCIENTIFIC
KNOWLEDGE ABOUT RISK ASSESSMENT

A. CURRENT GAPS IN KNOWLEDGE AND POSSIBLE AREAS TO BE TARGETED FOR
FUTURE RESEARCH INITIATIVES BY THE USDA CSREES

The reviewers were expansive and, according to the Expert Panel, "quite comprehensive" in their suggestions for new areas to be targeted. As evidenced by the following suggestions, a primary focal point in terms of gaps in knowledge was in the area of statistics and experimental design. Rather than identifying specific scientific questions for investigation, the comments about statistics/experimental design reflected significant concerns about the ability of the Program to achieve its goals irrespective of the validity of the scientific questions to be addressed.

- One reviewer offered some terse comments and recommendations to remedy what he/she perceived as a significant deficiency in the level of sophistication and understanding of researchers in the field of agricultural biotechnology particularly with regard to statistics and experimental design: "The heart of any environmental assessment is the BACI design -- yet, I do not think a single member of the peer review panel on which I served had ever heard of a BACI design. I have worked with epidemiologists and public health scientists -- and their expertise is routinely integrated into standard evaluations of the risks associated with various medical technologies -- this is the opposite of the situation in agriculture (perhaps because agriculture in its enthusiasm for production rarely pauses to think, "consequences"). Thus, some of the highest priority needs are not fundamental research, but education. To that end, in lieu of open-ended research grants -- much would be accomplished if prominent contributors to risk assessment were asked to produce handbooks of statistical and monitoring approaches for genetically engineered organisms. Also needed are similar handbooks from ecologists indicating the sorts of data that should be collected with field trials and commercial plantings (but rarely is collected). Frankly I think this could be done at modest cost, and assuming peer-review of the product, would be more valuable than a lot of the research currently being done."

- "The use of appropriate statistical models, experimental designs, and use of appropriate statistical consultants are very important criteria that should be used to evaluate all proposals. Appropriate statistical treatment of data will be necessary to predict the impact of one study for similar transgenes or species."

- "Problems in assessing Type 1 statistical error probabilities. For example, type I errors only apply to the specific hypotheses being tested, and a spectrum of hypotheses may be of interest. Perhaps covariance structure among variables may be worth studying in the context of risk assessment, especially when very low probabilities of error are of interest."

- The need for more attention to issues of statistical analysis and experimental design was reinforced by the reviewer who suggested "the incorporation of statistical analyses and hard mathematics in both the design of studies and in interpretation of results."

- The design of experiments, particularly field trials, within a risk assessment context was supported as a target area for support by another reviewer who wrote, "The methodology of field trials (e.g. simultaneously in various environments, large scale for short times, small scale for long times, etc.) might profit from both empirical and theoretical study in risk assessment contexts. Also, should third party replication of some field trials be incorporated into some risk assessment work?"
The most critical comments about the importance of statistical/design issues to the effective study of the Program objectives came from the reviewer who expressed concerns about the quality of proposals and level of expertise of those submitting proposals to the Program: "There certainly exists adequate expertise to either apply risk assessment, or to extend existing methods so that they better serve the biotechnology issues. Unfortunately, this expertise is not being attracted to the Program. Indeed, the one time I sat on the panel evaluating risk assessment proposals, I was astounded at the horrible experimental design and statistics of several proposals that were funded. The argument made in favor of these ill-designed proposals was that the biology was truly worthy of attention, even though the experimental design was lacking. Hogwash. Interesting biology studied by inadequate statistics and experimental design is useless. Our risk assessment expertise is fine — but familiarity of agricultural scientists with this expertise and approach is embarrassingly poor." The reviewer summarized, "To put it bluntly -- we have plenty of risk assessment expertise, but the agricultural community is largely ignorant of this field and consequently seems incapable of mounting an appropriate research effort."

Other gaps in knowledge identified by the reviewers included:

"... our lack of knowledge about how mid-scale testing, such as greenhouse or small agricultural plot studies, will correlate with large scale tests and/or releases. This is already acknowledged in point 9 of the Program announcement, but it remains largely unaddressed, probably due to restrictions of our capability to do large-scale tests. This is not inappropriate, as the results of smaller and mid-scale studies must be certain before large-scale tests should be performed, and the field is young. With time and the accumulation of more mid-scale data it will become more feasible to fill this gap. For now, it should remain one of the requested areas of research, as it is in point 9."

"While we are gaining experience with the expression of transgenes from certain types of promoters and certain copy numbers of genes, we know little of the impact of the numbers of new genes, or the types of proteins, or environment on stability of gene expression, gene organization or plant phenotypes. Much of agricultural biotechnology is directed at high input and high productivity agriculture; however, we know little about how the plants will respond under non-optimal culture conditions. Likewise, risk issues may be different under certain agricultural conditions than others. Knowledge of the differences will be essential to the continued growth of agricultural biotechnology. And, while this topic may fall under the heading of fundamental research, it also should be considered part of risk assessment, as risks may change if genes are not stable, or if environmental factors alter fitness, pollen and propagule dispersal and survival, or the interactions between the genetically modified organism and pathogens and pests, etc."

Several specific scientific issues were identified for further investigation including:

"An additional area of research that should be considered for funding under this program is development of new techniques to assess the stability of the introduced gene and integrity of the insertion event. Currently, the USDA requires that information on both of these concerns be included in a safety assessment. It would be consistent to support research in new techniques in PCR, molecular breeding and understanding plant transformation. Advances in these areas would give industry clearer direction as to the best techniques to be used for safety assessments. Furthermore, a clearer understanding as to how genes are inserted into chromosomes as well as more specific means of inserting genes would be an aid in assessing the safety of modified crops. One obvious example is the development of reliable chloroplast
transformation. In this case, the trait would be maternally inherited which would mitigate issues related to gene transfer to weeds."

- "A more specific suggestion for an area of biotechnology that perhaps should be targeted as a research initiative involves the risk assessment of DNA vaccines. DNA vaccines is an expanding field of great potential for use in agricultural animals including mammals, birds, and fish. Proposals addressing the fate of the DNA vaccine molecules with regard to spread, replication, maintenance, and possible integration should be considered under this program."

- It was suggested that in light of the rapid and expanding development of genetically enhanced biocontrol agents, e.g., genetically engineered baculoviruses which contain novel genes designed to enhance their efficacy, that an "information gap" existed particularly with regard to "the performance of these agents, especially with respect to their persistence in the environment and non-target effects."

- "Consideration might also be given to determining how long negative effects might persist once a transgene is no longer used commercially. Would transgenes that have migrated into domesticated and weedy relatives disappear rapidly after large-scale use is curtailed?"

- Two important questions formed the basis for the suggestions of one reviewer:

  "What is the likelihood of genetic variation and exchange between the released organism and any other organism in its new niche? First, the ecology and microecology of the site planned for release of a genetically altered organism must be thoroughly characterized. Resident species must be identified, and potential stresses characterized. The candidate for release must then be assessed for its ability to mutate and exchange genetic material with resident flora under stress conditions. This activity will require the cooperation of the disciplines of ecology, microbiology, and molecular biology.

  "Are there virulence mechanisms which may be of particular concern, and can they be monitored for? Recently, it was shown that plant and animal pathogens shared a common mechanism for causing damage to eukaryotic cells. This has been called the "Type III Secretion System" (Also called Yop secretion). With this unique system, bacteria are capable of firing harmful proteins directly into eukaryotic cells. Microorganisms possessing a Type III secretion system might be poor candidates for genetic alteration and release. Likewise, introduction of a new microorganism into an environment in which resident flora contain type III secretion systems may not be wise."

- One reviewer repeatedly referred to the need to address the issue of allergenicity. The reviewer's concerns are summarized in the following statement: "Many of the new food products developed from genetically modified organisms will have foreign proteins that may cause unexpected allergic reactions in humans consuming these products. Therefore, detection of allergenicity of products produced by genetically modified organisms needs to be considered as a major focus in the biotechnology risk assessment process."

- The concern about the potential for allergenicity of bioengineered new foods was reinforced by another reviewer: "The subject of food allergens in biotechnologically-derived foods is not a new one. However, the recent demonstration that a protein from peanut engineered into soybean expressed full peanut allergenic potential brings up other possibilities which must be considered. Our potential to test for food allergens needs to be enhanced, as well as our ability
to predict allergenicity from structural and sequence data. This activity will require the cooperation of the disciplines of molecular biology and immunology."

- "Research in at least two major areas is needed to better understand the risk of genetically engineering relatively undomesticated organisms:

Research is needed to better understand how transgenes alter the fitness of wild fish, forest trees, nematodes, etc., once they get into the genome of wild populations. This research should focus on the types of genes now being pursued by researchers. For example, most transgenic fish are now being engineered to express novel growth hormone genes, and more research is necessary to understand the potential effects of such genes on the fitness of wild fish.

A number of researchers have proposed using various genetic and other techniques to render transgenic fish and trees sterile, so that they cannot transfer their acquired genes to wild organisms. This approach has considerable appeal. However, there is evidence that techniques for inducing sterility are less than perfect -- e.g. a small percentage of these organisms may revert to fertility. More research on success rates for various sterility techniques and improvements of these techniques could prove extremely useful to minimizing biotech risks."

The delineation of nine areas to be targeted for future consideration was the major theme of one reviewer's comments. These suggested areas included:

- The effects of synthetic sequences not known to exist in nature. Do these represent safer or more questionable additions or substitutions with respect to non-target organisms and the environment? For example, biologically active peptides are being made that are not known to exist in nature, yet have potential biological activity for humans (beneficial) and insects (detrimental). Is there sufficient information to make such assessments, or must such information yet be generated?"

- "Are nucleotide substitutions in proposed added genes safer or not, irrespective of efficacy? Substitutions are being made to increase shelf life, efficacy versus target organisms, and stability within a plant. What is the safety assessment of the substitutions versus the naturally-occurring nucleotides?"

- "In aquatic systems, including fish and shellfish, are genetic modifications safer than stock manipulation? I understand that there are concerns in the aquatic community with the artificial manipulation of wild-type stocks that has raised some concerns about behavior, survival and competition, irrespective of genetic manipulation. When a concern is expressed about genetic manipulation, it would be prudent to have as a counterpoint what is being done in current captive fisheries practices, including shellfish."

- "What is the risk assessment relative to ornamentals produced to provide new or unusual color or shape combinations? That is, are color and shape variants produced by genetic engineering as safe as those generated by breeding? This question could be phrased in terms of the assessment for the attraction or repulsion of microorganisms, insects/arthropods, longevity, gene transfer, etc. Ostensibly, such modifications are safer and are more acceptable to the public. However, data are meager, at least in my view."

- "Microbe marker genes in plants. There is a current controversy over marker genes carrying antibiotic resistance in plants. Antibiotic resistance genes are still a convenient and cheap marker and may be safer than other markers. Thus, risk assessment may need to evaluate the evidence of transfer to microbes, other plants, and animals over what has been reported
to date. If there is no evidence to support such transfer, nevertheless a project that may provide negative data should still be considered so that the results will be publicly reported. Industry should be eligible, if industry agrees to publish the results. Such results may have already been reported to APHIS and may be accessible for analysis through mutual agreement or, if necessary, FOIA."

- "The environmental effects of new pharmaceuticals produced in plants. Some new pharmaceuticals may have potent biological activity against non-target organisms, e.g. birds and mammals. Thus, the environmental effects, including the effects on non-target organisms, normally would include microorganisms of plants and soils; birds and mammals should be considered as well. In this regard, there are some pharmaceuticals I would not have very much concern about, e.g. vaccines (some tests presumably are done already with such materials). However, compounds that might be potent cardiac glycosides or other compounds could be a different story. Both consumption and residue problems should be addressed."

- "Long-term studies. Even though it is difficult, the agency may be able to convince Congress that a few long-term studies are necessary for such types of plants as trees. That is, it would seem that up to ten years may be necessary to assess the risks of modifications as compared to conventional breeding, for trees."

- "Natural Disasters. The spread of genetically-engineered organisms in natural disasters has been neglected. Yet, floods, earthquakes, and hurricanes can spread such microorganisms, plants, and even some animals over short and long distances. What effects might accrue from such natural spread? Such research or model systems might be done using non-genetically modified organisms, to assess the likelihood and real dangers of such spread."

- "Specific spread and survival of the genetically-engineered weed, Arabidopsis, in a multi-year study. Arabidopsis is a model system, which can be grown in small areas, hundreds of mutants are available, and it can be killed with herbicides. Presumably, a great deal of information could be discerned in a short period of time."

Another reviewer offered the following list of potential research areas:

- "Microecology: Particularly with regard to microorganisms, as we discharge them into an environment, we need to learn where they will establish (if they do), and what stress forces will act on them. In short, we need to understand the microecology of the newly introduced organism's niche. This may mean understanding the interplay between it and other microorganisms resident in that environment, and further, each environment will differ somewhat. An understanding of the stresses on a newly introduced microorganism is an absolute need if we are to learn more about its fate, its ability to exchange genetic material, and if we are to assess the possibility of it evolving into a potentially harmful specie."

- "Virulence (particularly its evolution and maintenance): Virulence among microorganisms is still a misunderstood concept. Several theories have arisen with regard to virulence and its place in evolution, and whether virulence is selected or contra-selected. The concept of virulence is the same whether the host is a human, other animal, or plant. In order to characterize risk, a better understanding of virulence is necessary. The various hypotheses regarding the evolution of virulence are testable."

- "Genetic change and genetic exchange: Microorganisms introduced into a stressful environment must do either of two things, adapt or die. This is true for genetically altered microorganisms released into a new environment, as it is true for its non-altered counterpart."
The microbe's ability to adapt to environmental stress affects other aspects of its character, particularly its virulence. There is no doubt that stress modulates virulence, and good reason to believe that stress also triggers increased mutation rates (adaptive mutations). So stress may account for one of the two forces that govern genetic change, increased mutations of the nucleotide sequences within the microbial genome. The other governing force is the horizontal transfer of existing nucleotide sequences between genomes of closely or distantly related microorganisms. Is that governing force, the horizontal transfer of information, affected by stress as well? Mutation and horizontal exchange come together in the mutator phenotype. In mutators, the barriers to genetic exchange are removed, and the promiscuous behavior of the microbe is greatly enhanced. Since horizontal transfer is the means by which large amounts of genetic information might be exchanged between species, it is critical that we understand mutators, their frequency in various ecosystems, and the forces that create them. Mutator phenotype is greatly advantageous to a pathogen, as it enables it to rapidly vary its genetic makeup, through greatly increased mutation rate and by genetic exchange with many other (perhaps better adapted) microorganisms in its new, and probably unstable and hostile environment. Thus, an understanding of mutators and an assessment of a candidate organism for release into the environment is essential for predicting what it might do in its new environment, particularly with regard to genetic exchange with other inhabitants of its new microniche."

- One reviewer suggested the following expansion of the research paradigm because, "...we too little focus on understanding of 'healthy' systems and too much focus on the detection and remediation of problems." This reviewer is concerned about the lack of focus and appreciation of "the ecological roles of what E. O. Wilson has called the 'bacterial proletariat.'" By this term, he refers to the vast and largely unknown microbial world, numbering hundreds of thousands of species and playing untold ecological, biochemical, and no doubt crucial beneficial roles in governing the biosphere. This is a huge gap in our understanding about the living world into which we are pouring new inventions from biotechnology. I am concerned that we should have a much more serious commitment to funding the right kind of research to better understand the roles of microflora associated with plants and animals in the agricultural system."

One reviewer directed comments specifically to questions related to aquatic environments.

- "Evaluation of the potential impacts of organisms expressing introduced genes remains a key area for continued risk assessment research. In the aquatic sector, the following areas of interest are particularly salient:

  - Results of studies of transgenic fishes expressing introduced growth hormone genes have yielded varied results. Our understanding of the characteristics of the transgenic organisms or of the receiving ecosystem that give rise to these varied outcomes is quite incomplete. Given the development of many transgenic lines representing species as different as Atlantic salmon and red abalone, improved understanding of risk pathways is absolutely essential for informed oversight.

  - Antifreeze polypeptide genes have been introduced into several aquaculture species, including Atlantic salmon, tilapia, carp, and giant prawn, experiments aimed at making possible the production of these species in cold waters where production presently is precluded. The potential impacts of colonization of receiving ecosystems by escapees from such culture operations is not understood."
"Culture of marine micro- and macroalgae is a major sector of aquaculture. Biotechnological manipulations have been practiced to increase yields of compounds of commercial interest. Commercial production of genetically modified marine algae is ongoing on a limited scale, although not to my knowledge in U.S. waters. However, at least one U.S. producer is considering production of genetically modified seaweeds. Hence, assessment of risks associated with production of genetically modified marine plants is a timely issue."

"Induction of triploidy has been used as a means of achieving reproductive confinement of introduced aquatic organisms, and posed as a means of doing so for aquatic GMOs. Three issues posed by triploidy induction in aquatic organisms might be addressed in Program-supported research:

- Reversion of triploids to diploidy. Surprising results of a study of triploid Pacific oysters raise the question of whether triploid individuals in at least some species can progressively revert to the diploid condition. Periodic inspection of triploid oysters set in trays in the York River, Virginia by Stan Allen (Rutgers University) and Roger Mann (College of William and Mary) revealed that 20% were mosaiacs apparently in the process of reverting to diploidy. This raises questions of how common or rare is this phenomenon, and of implications regarding use of triploidy as a means of reproductive confinement.

- Effect of triploids on population demographics. Use of sterile triploids reduces, but does not eliminate risks to wild populations of conspecifics. Even sterile organisms compete with conspecifics. For small natural populations, this could limit the number of potential fertile spawners, causing a population bottleneck. Male triploids of at least some species undergo steroidogeneses, produce functional spermatozoa, and may attempt to spawn, leading to loss of the resulting aneuploid broods. Key unanswered questions concern the reproductive behavior of triploids in the field and the potential impact of matings involving triploids on population dynamics.

- Improvement of triploid production and distribution systems."

"Commercialization of certain triploid aquatic species, such as grass carp, has gone forward even though procedures for certifying the triploid status of lots in the sales and distribution pipeline have proven inadequate. This has resulted in stocking of fertile diploids, only to learn after the fact that a lot in question contained such diploids. Such episodes have been suggested as a factor contributing to grass carp colonizing certain river systems in the United States. This also suggests the development of a HACCP (Hazard Assessment Critical Control Point)-based analysis of how better to effect a triploidy certification program within existing market channels. Such a system would provide a prototype for HACCP systems for other aquatic GMOs yet to be commercialized."

There were several comments about the necessity for quality controls and rigorous standards to be applied to the conduct of the types of research supported by this Program.

With regard to the "issue of quality of data and the integrity of the results generated in this research program," one reviewer observed, "We are reading much lately about cases where the reproducibility of data is in question as well as situations of outright fraud. Given the sensitivity of biotechnology risk assessment to the public and the need to ensure the safety of products derived through genetic engineering, research proposals should describe the quality control measures that will be used in conducting the research and analyzing the data. Program Directors could be encouraged to commit to conducting studies either compliant with
or in agreement with spirit of the good laboratory practices (40 CFR 160). The aspect of ensuring the quality and integrity of any study funded through this Program should be included into all proposals.

- "Beyond their narrow utility for risk assessment and risk management for aquatic GMOs, the Performance Standards for Safely Conducting Research with Genetically modified Fish and Shellfish (Agricultural Biotechnology Research Advisory Committee. 1995. Performance standards for safely conducting research with genetically modified fish and shellfish, parts I [Supporting text] and II [Flowcharts and accompanying worksheets]. Documents 95-04 and 95005. National Agricultural Library, Beltsville, MD.) are widely regarded as a prototype for development of similar frameworks in other sectors of biotechnology. Sectors targeted for development of performance standards-type risk assessment/risk management frameworks might include genetically modified arthropods, microbes, or crop plants not of low enough concern that they are subject to only the requirement of notification before release."

- "Certain GMOs that pose limited, known risks may be suitable for outdoor experimentation or conditional commercial use if appropriate confinement measures are utilized, suggesting support for development and publication of targeted risk management frameworks."

B. POTENTIAL NEW DIRECTIONS OR CRITERIA FOR DECISION-MAKING IN BIOTECHNOLOGY RISK ASSESSMENT

Many comments focused on the public's perception about biotechnology and the importance of developing effective methods of communicating the science to a skeptical community of consumers. In addition, there was a general sensitivity to the need for the evaluation of risk-assessment data and decisions to be inclusive, incorporating expertise from the academic, consumer, and corporate communities in the regulatory process. These sentiments are reflected in the following suggestions:

- "It is my impression that the risk assessment process primarily involves scientists in public institutions, including universities and governmental organizations. It is important to involve in either the review or scientific activities of the program a representative of the biotechnology industry as well as one or several representatives for the organizations that oppose the use of biotechnology in the food and agriculture industry. That said, it is important that minority opinions not override conclusions gathered from scientific study."

Acknowledging the importance of the "court of public opinion," this same reviewer offered the following suggestions about public relations: "To make the public more aware of the results of the studies, there should be regular informational releases that stress the role of U.S. governmental agencies in determining the risk and safety of genetically modified organisms and describe completed studies, as well as studies that are in progress. There are regular releases dealing with progress related to medical progress in cancer treatments, diet control, smoking, etc., but very little reaches the public related to genetic modification of agricultural products, and the role that modified organisms can play in low input agriculture, quality of products, etc. The regulatory agencies need to become more accessible and have greater visibility - choose one or more good spokespersons to relay the information. The private companies will undoubtedly have their own methods to get out their messages; regulatory agencies need to provide the balance, some of which will support the claims of industry, while others may not."

- "A serious conundrum is that evaluations of risks from a scientific perspective (for example, probabilities of death) often are at variance with evaluations of risks from personal perspectives (for example, fear of agents that cannot be seen or are not understood). This often
translates into political realities, such that resources are used inappropriately from a scientific perspective. Both because of political reality and because it is an interesting problem, perhaps this conundrum should be considered systematically in the context of biotechnology risk assessment. For example, how might this affect which studies are undertaken and how decisions are made after scientific information has been generated?"

- Another suggestion related to enhanced publicity for the Program and the field in general came from the reviewer who wrote, "The publication of the annual volume should be eliminated, and PIs given every incentive to publish their findings in the peer-reviewed literature. Attention of the popular press to important articles could be directed by press release, much as the institutes at NIH do."

- The issue of interagency cooperation was raised by the reviewer who suggested: "Other agencies should have an interest in risk assessment of genetically-modified organisms. Perhaps cooperative agreements with or MOUs with NOAA, EPA, FDA, the Department of Commerce, as well as USDA-APHIS would further the risk assessment evaluations of genetically-modified organisms that are of interest not only to agriculture."

- In the category of general comments about future directions came the following comment: "I recommend that future planning for the risk assessment program include analysis of the report (enclosed), "Appropriate Oversight for Plants with Inherited Traits for Resistance to Pests," by 11 scientific societies (Coordinating Society: Institute of Food Technologists, 221 North LaSalle Street, Suite 300, Chicago, IL 60601; telephone 312-782-8424; fax 312-782-8348; e-mail: info@ift.org). It addresses issues concerning the risks of agricultural biotechnology in a scientifically and historically rational manner. I particularly endorse their finding that, in considering biotechnology risks, the focus must be on high-probability risk rather than hypothetical or unrecognizable risk."

Other – more technical – suggestions included:

- "There is a need within the field to develop standardized protocols defining the parameters that need to be addressed in assessing the risk involved with each type of biotechnology product being considered. Although there are no formally accepted standards at present, several of the proposals funded last year will serve as examples of the breadth of studies which must be done to assess risk within various types of products. For example, suppose a certain proposal carries out a broad, thorough assessment of various aspects of risk involved with use of a plant virus engineered to express a foreign gene as a vaccine. The results of those studies should eventually be combined with results of other studies assessing other plant viruses engineered to produce vaccines, to generate a guideline set of parameters which must be addressed when any plant virus engineered to produce a vaccine is being considered. In this way, the research in this program serves as models to develop standardized protocols as a management tool to assure that every biotechnology product is thoroughly and uniformly assessed. Proposals which provide complete, thorough examples of assessment for each of the various biotechnology product types should be encouraged."

- While recognizing that much of the needed expertise for addressing risk assessment is currently available one reviewer noted a lack of expertise to address the question: "How do we evaluate and monitor risks for a technology that is distributed over a huge spatial scale and that encounters in the process an enormous variety of environments and co-occurring organisms?" The reviewer suggested that: "USDA should fund efforts aimed at comparing different large-scale monitoring programs and quick field assessments that can cost-effectively examine risks at the scale of a continent. Computer models of different scenarios of disaster
could be run at these large scales, and the monitoring programs could be applied to the data produced by these computer models to see if they successfully identify signals foreshadowing environmental disruption. This research will have value well beyond applications to genetically engineered crops, since the design of large-scale monitoring programs is central to much of environmental and conservation biology. However, all of this work cannot be computer simulation. Fieldwork must be done to quantify costs of monitoring programs and to collect hard data on the biological sources of variability and risk. For instance, if variability between regions dominates, then the key would be to monitor in different regions. Alternatively, if variability is greatest at the level of the field, monitoring programs would need to concentrate sampling within fields. An example of the type of practical recommendation that might result from sampling and computer simulation would be to collect a specific number of samples each from the vicinity of a particular number of fields from each ecoregion (as defined by the US Forest Service system developed by Bailey) in which a crop is grown."

C. POTENTIAL NEW METHODS AND SCIENTIFIC DISCIPLINES REQUIRED TO BE INCLUDED IN THE ESTABLISHMENT OF NEW APPROACHES

With the exception of comments noted previously about the need for more sophistication with regard to issues of statistics and experimental design, few comments were directed specifically at this question.

One exception was the suggestion by the reviewer who wrote: "Risk assessment studies can legitimately include agriculturists, fundamental scientists, scientists engaged in development, ecologists, population biologists, and geneticists, including genome scientists. Methods of analysis should include genomic studies, applying FLP and RFLPs as needed, market genes that can be assayed under field conditions, and techniques to monitor insect and disease situations that impact dispersal of the modified organisms, including microorganisms."

A unique perspective was presented by the reviewer who, while addressing the issue of the impact of public perceptions about biotechnology, suggested that this might a fruitful area of research: "It is unclear to me if the sociology and psychology fields, for example, already address this situation in a useful way, or if an entirely new field of endeavor is required."

D. COMMENTS AND RECOMMENDATIONS OF THE AD HOC EXPERT PANEL

In terms of the scientific direction of the Program, the Expert Panel considered the comments of the ad hoc reviewers to be comprehensive and "on target." There were several themes that the Panel emphasized:

- Risk must be defined clearly before the Program can begin to examine the need for new methodologies effectively.

- the Program needs to be focused on identifying gaps in knowledge relative to risk in agricultural biotechnology.

- A major focus of the Program should be on the generic issue of gene transfer and its consequences. The scope of the Program must be clearly stated as including gene transfer in and between plants, animals, and microorganisms.
The Expert Panel emphasized the importance of Objective 7 particularly with regard to the issues of antibiotic resistance, which might be considered as a separate Program priority. In addition, the Panel wished to highlight the importance of sponsoring studies investigating the role of microorganisms in gene transfer.

From a program management perspective the Expert Panel offered the following recommendations:

- To advance the science, attract new areas of expertise, support regulatory decision-making, and to make an effective case for continued support the Program should publish periodic reviews or science-based summaries of what is known in the field with an emphasis on new developments that may have resulted from the Program's initiatives. These summaries should be science-based and suitable for not only the scientific community but also accessible to members of the regulatory community and those engaged in risk communication.

- A process of periodic peer-review of the Program should be initiated in order to insure continued focus of the Program, to identify potential problems and new directions, if warranted, and to identify the Program's accomplishments. The Expert Panel suggested that this be an objective third party process, perhaps involving expert panels such as that involved in the generation of this report.

- The Expert Panel recommended that the Program strongly encourage collaboration between commercial enterprises and scientists to perform long-term monitoring (see comments for Objective 9, Chapter III). Moreover, the Panel suggested that the USDA's Animal and Plant Health Inspection Service (APHIS) be encouraged to utilize data generated from these collaborations in its decision-making process.

- To allow for the effective interaction between the scientific and regulatory communities, workshops should be planned to allow for strategic planning of the scientific agenda. These workshops would address some of the issues raised by the ad hoc reviewers, in particular, issues related to experimental design and the identification of gaps in knowledge about risk.
V. STUDY PARTICIPANTS

Evaluation of the Agricultural Biotechnology Risk Assessment Program:

Comments from the Scientific Community and Recommendations for Future Planning

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Richard A. Herrett, Ph.D.
Executive Director
APPENDIX A
Agricultural Research Service; Cooperative State Research, Education and Extension Service

Biotechnology Risk Assessment Research Grants Program; Fiscal Year 1996; Solicitation of Applications

Purpose

Applications are invited for competitive grant awards under the Biotechnology Risk Assessment Research Grants Program (the "Program") for fiscal year 1996. The authority for the Program is contained in section 1668 of Pub. L. No. 101–624 (the Food, Agriculture, Conservation, and Trade Act of 1990, 7 U.S.C. 5921). The Program is administered by the Cooperative State Research, education and Extension Service (CSREES) and the Agricultural Research Service (ARS) of the U.S. Department of Agriculture.

The purpose of the Program is to assist Federal regulatory agencies in making science-based decisions about the safety of introducing genetically modified plants, animals, and microorganisms into the environment. The Program accomplishes this purpose by providing scientific information derived from the risk assessment research conducted under it. Research proposals submitted to the Program must be applicable to the purpose of the Program to be considered. Awards will not be made for clinical trials, commercial product development, product marketing strategies, or other research not appropriate to risk assessment.

Applicant Eligibility

Proposals may be submitted by any United States public or private research or educational institution or organization.

Available Funding

Subject to the availability of funds, the anticipated amount available for support of the program in fiscal year 1996 is $1.7 million.

It is expected that Congress, in the final version of the Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Act, 1996 (H.R. 1787), will prohibit CSREES from using the funds available for fiscal year 1996 to pay indirect costs exceeding 14 percent of the total Federal funds provided under each award on competitively-awarded research grants.

In addition, it is expected that, pursuant to the final version of the Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Act, 1996 (H.R. 1787), in the case of any equipment or product that may be authorized to be purchased with the funds provided under this Program, entities will be encouraged to use such funds to purchase only American-made equipment or products.

Program Description

Under the Program, USDA will competitively award research grants to support science-based biotechnology regulation and thus help address concerns about the effects of introducing genetically modified organisms into the environment and to help regulators develop policies concerning such introduction. Proposals are invited in the area of biotechnology risk assessment research as appropriate to agricultural plants, animals and microbes. Proposals based upon field research and whole organism-population level studies are strongly encouraged. Although emphasis will be given to risk assessment research involving genetically modified organisms, model systems using nongenetically modified organisms also will be considered if they can provide information that could lead to improved assessment of potential risks associated with the introduction of genetically modified organisms into the environment. Proposals should be applicable to current regulatory issues surrounding the ecological impacts of genetically modified organisms.

Proposal Evaluation

Proposals will be evaluated by the administrator assisted by a peer panel of scientists for scientific merit, qualifications of project personnel, adequacy of facilities, and relevance for current regulatory issues.

Areas of Research to be Supported in Fiscal Year 1996

Proposals addressing the following research topics are requested:

1. Development of new risk assessment methods (e.g., monitoring organism escape, measuring biological impacts), and risk assessment procedures (e.g., comparative analysis of ecosystems, models to predict risks) that could be used in risk assessment of genetically modified fungi, bacteria, viruses (including animal vaccines), plants, arthropods, fish, birds, and mammals. Applicants should address the need for, and development of, new risk assessment methods in the course of addressing a specific and defined risk assessment issue, especially as pertains to genetically modified organisms. The development of better risk assessment methods for field testing genetically modified organisms also will be considered.

2. Creation of information systems and computer models to support regulatory agency decision-making in regards to potential impacts to the environment over time (e.g., computer models to describe the interaction of environmental and organismal factors especially for establishment and dispersal of the organism).

3. Risk assessment of the environmental fate (e.g. survival, reproductive fitness, genetic stability, horizontal gene transfer) as correlated with effects (e.g., loss of genetic diversity, enhanced competition) of genetically modified fungi, bacteria, viruses, plants, arthropods, fish, birds, and mammals introduced into the environment (i.e., not in a contained laboratory, greenhouse or building); and studies or identification of traits which may influence fate and effects.

In response to requests to Program Directors and Federal regulatory agencies, as stipulated in the authorizing legislation for the Program, section 1668 of Public Law 101–624, the following specific areas of risk assessment research have been identified as eligible for competition as research topics for this year:

4. The bidirectional rates, effects of selection pressures, mechanisms and impact of gene transfer between currently genetically transformable crop species and existing North American weedy, free living relatives of those crops including studies of methods of mitigation of potential gene exchange. Research could rely on reanalysis of published information and/or laboratory/field studies.

5. The potential for recombination between plant viruses and plant-encoded noncapsid viral genes (e.g. replicase), especially for those viruses in supergroup B (carmovirus, tobravirus, luteovirus, sobemovirus). Such studies should identify recombination potentials and, if demonstrated, define frequencies and effect on symptom expression. Comparisons with recombination frequencies between naturally occurring viral sequences are encouraged.

6. Changes in viral host ranges or the types of viral vectors as a result of the use of transgenic plants expressing viral genes.

7. The potential for nontarget effects of introduced plant-defense compounds expressed in genetically modified plant-associated microorganisms (e.g., compounds in phylosphere or rhizosphere-inhabiting bacteria) or in...
plants (e.g., Bacillus thuringiensis delta-endotoxin), especially in regard to persistence of the organisms and material in the environment.

8. Identification of genes which can confer additional pathogenicity to animal pathogens.

9. Environmental risk analysis of large scale deployment of genetically engineered organisms, especially commercial uses of such organisms, with special reference to consideration that may not be revealed through small scale evaluations and tests.

All research proposals submitted should include a statement describing the relevance of the proposed project to one or more of the research topics requested. When appropriate, detailed descriptions of statistical analyses to be done should be included in the proposal. The inclusion of statisticians as co-principal investigators or contractors is encouraged.

Note: Individual investigators whose research projects are funded under the Program will be required to attend, present data and provide a manuscript on the results of their research at an Annual Conference. Attendance costs at such a conference will not need to be included in the budgets of proposed research projects; such costs will be paid from funds provided under a cooperative agreement between CSREES and the University of Maryland for an annual risk assessment symposium. Additionally, a final project report on research results will be required in a fixed protocol, electronic format, suitable for distribution by USDA.

Applicable Regulations

This Program is subject to the administrative provisions found in 7 CFR part 3415 (58 FR 65646, December 15, 1993), which set forth procedures to be followed when submitting grant proposals, rules governing the evaluation of proposals, the awarding of grants, and post-award administration of such grants. Several other Federal statutes and regulations apply to grant proposals considered for review or to grants awarded under this Program. These include, but are not limited to:

7 CFR Part 1.1—USDA implementation of the Freedom of Information Act;
7 CFR Part 1c—USDA implementation of the Federal Policy for the Protection of Human Subjects;
7 CFR Part 3—USDA implementation of OMB Circular A-129 regarding debt collection;
7 CFR Part 15, Subpart A—USDA implementation of Title VI of the Civil Rights Act of 1964;
7 CFR Part 520—ARS implementation of the National Environmental Policy Act;
7 CFR Part 3016—USDA Uniform Administrative Requirements for Grants and Cooperative Agreements to State and Local Governments;
7 CFR Part 3017, as amended—USDA implementation of Governmentwide Debarment and Suspension (Nonprocurement) and Governmentwide Requirements for Drug-Free Workplace (Grants);
7 CFR Part 3018—USDA implementation of New Restrictions on Lobbying, imposes new prohibitions and requirements for disclosure and certification related to lobbying on recipients of Federal contracts, grants, cooperative agreements, and loans;
7 CFR Part 3051—Audits of Institutions of Higher Education and Other Nonprofit Institutions;
7 CFR Part 3407—CSREES implementation of the National Environmental Policy Act;
29 U.S.C. 794, section 504—Rehabilitation Act of 1973, and 7 CFR Part 158 (USDA implementation of the statute), prohibiting discrimination based upon physical or mental handicap in federally assisted programs;
35 U.S.C. 200 et seq.—Bayh-Dole Act, controlling allocation of rights to inventions made by employees of small business firms and domestic nonprofit organizations, including universities, in Federally assisted programs (implementing regulations are contained in 37 CFR part 401).

Programmatic Contact

For additional information on the Program, please contact:
Dr. Edward K. Kaleikau, Cooperative State Research, Education, and Extension Service, U.S. Department of Agriculture, Ag Box 2241, Washington, DC 20250–2241, Telephone: (202) 401–1901 or
Dr. Robert M. Faust, Agricultural Research Service, U.S. Department of Agriculture, Room 338, Building 005, BARC-West, Beltsville, MD 20705, Telephone: (301) 504–6918.

How to Obtain Application Materials

Copies of this solicitation, the administrative provisions for the Program (7 CFR Part 3415), and the Application Kit contains required forms, certifications, and instructions for preparing and submitting grant applications. The administrative provisions include guidelines for proposal format.

Copies of this solicitation, the administrative provisions, and the Application Kit may be obtained by contacting:

Application materials may also be requested via Internet by sending a message with your name, mailing address (not e-mail) and telephone number psb@reseauda.gov which states that you wish to receive a copy of the application materials for the Fiscal Year 1996 Biotechnology Risk Assessment Research Grants Program. The materials will then be mailed to you (not e-mailed) as quickly as possible.

Proposal Format

The format guidelines for full research proposals, found in the administrative provisions for the Program at § 3415.4(d), should be followed for the preparation of proposals under the Program in fiscal year 1996. (Note that the Department elects not to solicit preproposals nor conference grant proposals in fiscal year 1996.)

Compliance with the National Environmental Policy Act (NEPA)

As outlined in 7 CFR part 3407 and 7 CFR part 520 (the CSREES and ARS regulations implementing the National Environmental Policy Act of 1969), environmental data for any proposed project is to be provided to CSREES and ARS so that CSREES and ARS may determine whether any further action is needed. The applicant shall review the following categorical exclusions and determine if the proposed project may fall within one of the categories.

1. Department of Agriculture Categorical Exclusions (7 CFR 1b.3)

1(i) Policy development, planning and implementation which are related to routine activities such as personnel, organizational changes, or similar administrative functions;
1(ii) Activities which deal solely with the funding of programs, such as program budget proposals, disbursements, and transfer or reprogramming of funds;
(iii) Inventories, research activities, and studies, such as resource inventories and routine data collection when such actions are clearly limited in context and intensity;
(iv) Educational and informational programs and activities;
(v) Civil and criminal law enforcement and investigative activities;
(vi) Activities which are advisory and consultative to other agencies and public and private entities; and
(vii) Activities related to trade representation and market development activities abroad.

(2) CSREES and ARS Categorical Exclusions (7 CFR 3407.6 and 7 CFR 520.3)

Based on previous experience, the following categories of CSREES and ARS actions are excluded because they have been found to have limited scope and intensity and to have no significant individual or cumulative impacts on the quality of the human environment:
(i) The following categories of research programs or projects of limited size and magnitude or with only short-term effects on the environment:
(A) Research conducted within any laboratory, greenhouse, or other contained facility where research practices and safeguards prevent environmental impacts;
(B) Surveys, inventories, and similar studies that have limited context and minimal intensity in terms of changes in the environment; and
(C) Testing outside of the laboratory, such as in small isolated field plots, which involves the routine use of familiar chemicals or biological materials.

(iii) Routine renovation, rehabilitation, or revitalization of physical facilities, including the acquisition and installation of equipment, where such activity is limited in scope and intensity.

In order for CSREES and ARS to determine whether any further action is needed with respect to NEPA, pertinent information regarding the possible environmental impacts of a particular project is necessary; therefore, a separate statement must be included in the proposal indicating whether the applicant is of the opinion that the project falls within a categorical exclusion and the reasons therefor. If it is the applicant's opinion that the project proposed falls within the categorical exclusions, the specific exclusions must be identified. The information submitted shall be identified as "NEPA Considerations" and the narrative statement shall be placed after the coversheet of the proposal.

Even though a project may fall within the categorical exclusions, CSREES and ARS may determine that an Environmental Assessment or an Environmental Impact Statement is necessary for an activity, if substantial controversy on environmental grounds exists or if other extraordinary conditions or circumstances are present which may cause such activity to have a significant environmental effect.

Proposal Submission

What to Submit

An original and 14 copies of a proposal must be submitted. Each copy of each proposal must be stapled securely in the upper left-hand corner (DO NOT BIND). All copies of the proposal must be submitted in one package.

Where and When to Submit

Proposals must be received by 4:30 p.m. eastern standard time on December 11, 1995. Proposals sent by First Class mail must be sent to the following address:

Telephone: (202) 401–5048

Proposals that are delivered by Express mail, a courier service, or by hand must be submitted to the following address (note that the zip code differs from that shown above): Proposal Services Branch, Awards Management Division, Cooperative State Research, Education and Extension Service, U.S. Department of Agriculture, Room 303, Aerospace Center, 901 D Street, SW., Washington, DC 20024, Telephone: (202) 401–5048

Supplementary Information

The Biotechnology Risk Assessment Research Grants Program is listed in the Catalog of Federal Domestic Assistance under No. 10.219. For reasons set forth in the final rule-related Notice to 7 CFR Part 3015, subpart V (48 FR 29115, June 24, 1983), this Program is excluded from the scope of Executive Order No. 12372 which requires intergovernmental consultation with State and local officials.

Under the provisions of the Paperwork Reduction Act of 1980 (44 U.S.C. 3504(h)), the collection of information requirements contained in this Notice have been approved under OMB Document No. 0524–0022.

Done at Washington, DC, on this 1st day of September, 1995.

William D. Carlson,
Acting Administrator, Cooperative State Research, Education, and Extension Service.

Robert J. Reginato,
Acting Administrator, Agricultural Research Service.

[FR Doc. 95–22464 Filed 9–8–95; 8:45 am]
BILLING CODE 3410–22–M
Comments on Risk Assessment Research Grants Program

Item 1 - (cover letter)

General strengths and weaknesses of scientific aspects

In general, the scientific aspects of USDA's current biotechnology risk assessment program are quite comprehensive and sound. Many important aspects of judging the risk that may arise from introducing a genetically modified organism into the environment are covered in the nine objectives. What is lacking, however, is a straightforward and clear statement by USDA about what it is they feel the risks are. In a limited number of objectives, notably 6, 7, and 8, these are alluded to, but left open to interpretation. For example, changing viral host ranges is a self-explanatory risk, but "non-target effects of introduced plant-defense compounds" is somewhat more vague. Objective 8, "Identification of genes which can confer additional pathogenicity to animal pathogens" is likewise vague. What is missing is a clear statement of how such an occurrence would come to be (i.e., gene transfer to an animal pathogen), and what outcome represents the risk.

It seems that the risks posed by introduction of genetically modified organisms fall into three broad categories: 1. Risks posed to the environment, 2. Risks posed to plant or animal resources, and 3. Risks posed directly or indirectly to humans. It might have been valuable if the Federal Register notice had been framed with these (and perhaps other) risks stated up-front, perhaps in a preamble, and if the objectives had been stratified to address one or more of the stated risks.

I would comment on each specific objective as follows:

Objective 1 - I am not certain whether monitoring organism escape is a "new risk assessment method," and "measuring biological impacts" is very vague. As stated above, biological impacts on what, and what risk (adverse outcome) is feared? Perhaps the vagueness was purposefully crafted into the objectives so as to solicit the greatest spectrum of suggestions, but this could be unfair to respondents, as their suggestion(s) may fall well outside the actual scope of the concerns that USDA would be interested in funding.

Objective 2 - This objective sounds good, but is the database there to support development of computer models? Without data from actual trials, obtained from monitoring some endpoint, I don't know what the computer would use to make comparisons and quantify the risk for a particular adverse outcome. Without some structure from USDA, this objective seems too vague.

Objective 3 - This objective seems to have sufficient detail and examples to permit some good responses. At least we have an overall theme, "environmental fate" (defined as survival, reproductive fitness, genetic stability, horizontal gene transfer) and some examples of what the feared adverse outcome (effects) might be, "loss of genetic diversity, enhanced competition," etc.

I will return to some of these points later, when suggestions about item (3) in the cover letter are addressed.

Objective 4 - Bidirectional rates and the rest of the questions posed in this objective are all researchable and quantifiable. This objective is adequately defined.
Objective 5 - The “potential for recombination between plant viruses and plant-encoded, noncapsid viral genes” is a researchable and quantifiable topic. There is obvious risk posed by such occurrences to plant crops.

Objectives 6 - 8 - As previously stated, these objectives are clear as to what the addressed risk is, and are researchable and quantifiable areas.

Objective 9 - This objective is very vague. The objective asks for an environmental risk analysis of large scale deployment of genetically engineered organisms. It seems obvious that this objective was written with some circumstance in mind; it would have been better to share that circumstance as an example for potential respondents.

Item 2 -

Adequacy of current scientific knowledge of risk assessment

The current knowledge about risk assessment varies with the outcome in question. For example, in risk assessment for pesticide carcinogenesis, the outcome is theoretical and based on animal and other non-human-derived data.

Some outcomes, such as frequency of genetic exchange, can be modeled and extrapolated to other systems, probably giving risk estimates of greater accuracy than carcinogenesis models.

It has been conceded that microbiological risk assessment is in its infancy. The National Advisory Committee on Microbiological Criteria for Foods formed a Risk Assessment Subcommittee, which has struggled with this issue for three years. Thus far, only an outline of approaches has been produced, and pitfalls identified. Among the pitfalls, variable host susceptibility, variable virulence, and infective dose stood out as data gaps that prevented greater progress in risk assessment.

It would seem here that the definition of risk assessment has not been elucidated well by USDA. The spread of an agent in the environment can be monitored, as can its survival and ultimate fate. Is a risk assessment in this context a mathematical model based on some hard data derived from a similar released organism? Is the risk the same as the organism’s survival? I return here to my previous point that the potential “adverse outcomes” have not been elucidated sufficiently by USDA, and subsequently, this has caused uncertainty about what is meant by risk assessment.

Potential Gaps in Knowledge and Future Research Initiatives

There are several themes I believe should be further researched, as they present gaps in our present knowledge, and impact on various of the USDA objectives. I will describe these areas as follows:

1. Microecology

Particularly with regard to microorganisms, as we discharge them into an environment, we need to learn where they will establish (if they do), and what stress forces will act on them. In short, we need to understand the microecology of the newly introduced organism’s niche. This may mean understanding the interplay between it and other microorganisms resident in that environment, and further, each environment will differ somewhat. An understanding of the stresses on a newly introduced microorganism is an absolute need if we are to learn more about its fate, its ability to exchange genetic material, and if we are to assess the possibility of it evolving into a potentially harmful specie.
2. Virulence (particularly its evolution and maintenance)

Virulence among microorganisms is still a misunderstood concept. Several theories have arisen with regard to virulence and its place in evolution, and whether virulence is selected or contra-selected. The concept of virulence is the same whether the host is a human, other animal, or plant. In order to characterize risk, a better understanding of virulence is necessary. The various hypotheses regarding the evolution of virulence are testable. An excellent review was recently authored by Levin1.

3. Genetic change and genetic exchange

Microorganisms introduced into a stressful environment must do either of two things, adapt or die. This is true for genetically altered microorganisms released into a new environment, as it is true for its non-altered counterpart. The microbe's ability to adapt to environmental stress affects other aspects of its character, particularly its virulence. There is no doubt that stress modulates virulence, and good reason to believe that stress also triggers increased mutation rates (adaptive mutations)2. So stress may account for one of the two forces that govern genetic change, increased mutations of the nucleotide sequences within the microbial genome. The other governing force is the horizontal transfer of existing nucleotide sequences between genomes of closely or distantly related microorganisms. Is that governing force, the horizontal transfer of information, affected by stress as well? Mutation and horizontal exchange come together in the mutator phenotype. In mutators, the barriers to genetic exchange are removed, and the promiscuous behavior of the microbe is greatly enhanced3. Since horizontal transfer is the means by which large amounts of genetic information might be exchanged between species, it is critical that we understand mutators, their frequency in various ecosystems, and the forces that create them. Mutator phenotype is greatly advantageous to a pathogen, as it enables it to rapidly vary its genetic makeup, through greatly increased mutation rate and by genetic exchange with many other (perhaps better adapted) microorganisms in its new, and probably unstable and hostile environment. Thus, an understanding of mutators and an assessment of a candidate organism for release into the environment is essential for predicting what it might do in its new environment, particularly with regard to genetic exchange with other inhabitants of its new microniche.

Item 3 -

Possible new directions or criteria for decision making

There are several new directions, or if not new, directions that I believe need emphasis when considering the risk posed by the introduction of genetically modified organisms into the environment. These can be stated as questions and then approaches to answering them.

1. What is the likelihood of genetic variation and exchange between the released organism and any other organism in its new niche?

First, the ecology and microecology of the site planned for release of a genetically altered organism must be thoroughly characterized. Resident species must be identified, and potential stresses characterized. The candidate for release must then be assessed for its ability to mutate and

1 Levin, B.R. 1996. The evolution and maintenance of virulence. Emerg Infect Dis 2:


exchange genetic material with resident flora under stress conditions. This activity will require the cooperation of the disciplines of ecology, microbiology, and molecular biology.

2. Are there virulence mechanisms which may be of particular concern, and can they be monitored for?

Recently, it was shown that plant and animal pathogens shared a common mechanism for causing damage to eukaryotic cells. This has been called the “Type III Secretion System” (also called Yop secretion). With this unique system, bacteria are capable of firing harmful proteins directly into eukaryotic cells\(^4\). Microorganisms possessing a Type III secretion system might be poor candidates for genetic alteration and release. Likewise, introduction of a new microorganism into an environment in which resident flora contain type III secretion systems may not be wise.

I'll return to a point made earlier. Before risk can be characterized adequately, as thorough an understanding of virulence as possible must be acquired. Acquisition of a new virulence trait is not necessarily an endpoint to be feared, as a pathogen must first contact the prospective host, and this may not occur in certain circumstances. This relates somewhat to Objective 7 of the USDA proposal. This activity will require the cooperation of the disciplines of microbiology (specialty in virulence mechanisms) and molecular biology (specialty in control mechanisms of virulence).

3. Can human food allergens be generated by genetic exchange or transferred from plant to plant?

The subject of food allergens in biotechnologically-derived foods is not a new one. However, the recent demonstration that a protein from peanut engineered into soybean expressed full peanut allergenic potential brings up other possibilities which must be considered. Our potential to test for food allergens needs to be enhanced, as well as our ability to predict allergenicity from structural and sequence data. This activity will require the cooperation of the disciplines of molecular biology and immunology.

COMMENTS ON USDA CSREES PROGRAM

The announcement of a call for competitive grant proposals in the Federal Register on September 11, 1995 (pages 47236 to 47238) defined nine areas of research activities. These areas had been chosen to help expand our knowledge base related to risks associated with the release of genetically engineered organisms into the environment. I would like to comment on the importance and strength or weaknesses of the 1996 plan.

IMPORTANCE

Application of the tools of molecular genetics to crop improvement and modification of microbes is continuing at an accelerating pace in the United States. This includes activity in both the not-for-profit and for-profit sectors. New products with benefits to consumers and farmers are "in the pipeline," as are products which promise to be of value in environmental cleanup and protection. It is, therefore, essential to have a science-based means of assessing any potential risks of these new products to determine the risk-benefit relationship before they are introduced into commercial or public use. The Biotechnology Risk Assessment Research Grants Program has been, and continues to be, a cost-effective way to conduct this process. The program should be continued because there are scientific issues yet to be resolved.

STRENGTHS OF THE PROGRAM

Research topic areas 1, 3, and 7 in the above-mentioned announcement form the core of current risk assessment needs. We must continue to identify, develop, and utilize new methods for risk assessment, to determine the environmental fate of genetically modified organisms and to determine non-target effects of genetically modified organisms. New approaches will strengthen our science-based understanding of how new organisms survive in the environment. As scientists have a better perspective on potential new products, they can devise new strategies to track and evaluate their performance and impact(s) on release. This part of the grant program is essential and should be continued.

LOWER PRIORITY ITEMS

Research topic 2 is the creation of information systems and computer models to support regulatory decision making. This process is very dependent upon the "raw data" generated by other activities supported by this grant program. I would keep this part of the activities at a modest level, and call upon regulatory segments of USDA and EPA to assign their permanent personnel to the information systems component.

Research area 4 was designed to analyze existing information. To date, to my knowledge, this has not led to any definition of "information gaps." In the absence of any further detail, I would rate this as a low priority area for more research.
RESEARCH AREAS OF TARGETED IMPORTANCE

Research items 5, 6, and 7 were designed to generate important data on rather specific new topic areas of plant protection. Since the results of these investigations are not yet publicly available, it is probably not a high priority to focus more effort on these studies as the planning for the next phase of this grant program is being evaluated. The results of ongoing studies will provide information related to the need of further risk studies.

INCREASED CLARITY

Item 8 in the above-mentioned announcement was very concise, to the point that some individuals did not understand the nature of the area being proposed. If included in subsequent announcements, the nature of the "animal pathogens" should be clarified. For example, are insects "animals"? Or, are some other animals pathogenic? Or, perhaps the announcement meant pathogens of animals?

LARGE-SCALE TESTING

There are now commercial introductions of transgenic plants that are being grown on very large acreage. It is important to summarize the performance of these plants, and it may be possible to evaluate non-intentional effects of their growth by analyses of publicly available information. It would appear to me that this effort will now become a component of normal agricultural extension activities at the state level. The USDA should implement mechanisms to insure the assignment of this responsibility, thereby decreasing item 9 of the above-mentioned announcement.

NEW NEEDS

There is one topic area that has not been emphasized previously. I would note that a "next generation" of genetically enhanced biocontrol agents is rapidly progressing as academic and industrial labs are evaluating genetically engineered baculoviruses which contain novel genes designed to enhance their efficacy. A special risk assessment area in which there is an information gap is the performance of these agents, especially with respect to persistence in the environment and non-target effects.

SUMMARY

This risk-assessment program has been an important component of insuring public acceptance of biotechnology derived crop plants in the U.S. The program should be continued and refined to characterize new potential transgenic products.
COMMENTS ON USDA-CRGO (CSREES) GRANT PROGRAM: 
BIOTECHNOLOGY RISK ASSESSMENT

The USDA-CRGO has described a Biotechnology Risk Assessment Research Grants Program and requested my evaluation and suggestions about the program, specifically the:

1. Strengths and weaknesses of the scientific aspects of the risk assessment program at the USDA.

2. Adequacy of current scientific knowledge about risk assessment.

3. Possible new directions or criteria for decision making in risk assessment.

Introduction

The USDA policy for risk assessment has been developed out of the need for oversight of modified organisms developed via genetic modification through applications of technologies that involve recombinant DNA and genetic transformation. Much of the impetus for establishing the regulatory framework that has been put in place derived from the scientific community that was engaged in such research in the early 1980's and following the establishment of NIH guidelines for recombinant DNA research in laboratories. The work of S. Lindow and colleagues to modify and field test a simple soil microbe to reduce ice nucleation on plant leaves brought the potentials for use and misuse of the technology to the public eye and brought the need for recommendations to the attention of the USDA and other governmental bodies, leading to the activities of a number of advisory groups. This in turn led to the current guidelines; the guidelines are built to be flexible and can be modified as new knowledge is gained.

The procedures for gaining approval for field testing genetically modified organisms (GMOs) are not widely known in the scientific community and there is the impression that approvals are time consuming and filled with forms and other hurdles. On the other hand, since relatively few scientists have actually made application some of the reputed difficulties may be more perceived than real. To date I have not applied for approval for restricted field tests although I have been involved in providing information for those who have used our materials for field trials. With regard to the specific areas of research to be supported in FY 1996 I have the following comments.

Strengths and Weaknesses of the Scientific Aspects of the USDA Risk Assessment Program

(1) Because of the large numbers of GMOs that are anticipated to be developed for applications in agriculture that involve environmental release it is essential that the process to evaluate proposals be highly efficient. The USDA has already begun to classify certain types of crop plants and genes as requiring notification only; to my
knowledge this program is working well. Similar mechanisms are needed for field tests that will involve fish and other animals, bacteria, fungi, as well as other crop plants. Establishing criteria to determine whether or not a class of organisms or genes should be substantially deregulated requires familiarity by the governing bodies; such familiarity should be based in data derived from greenhouse and small and large field trials not on computer models and predictions. It is my opinion that research grants should be awarded to study the survival, distribution and survival of members of each of the groups of organisms that are anticipated for release in the near future, and that selection of the organisms should change as the science changes. However, risk assessment should be facile, and aided by the use of modern marker genes that make detection easy and low cost and developed to handle hundreds of samples per day. We need a saturating amount of data for a few well-selected systems rather than many studies of many different systems. This may involve the use of fluorescent proteins or other markers, and assays that do not require purification from samples that will be collected from field sources. Indeed, certain of the methods must be conducted and analyzed in situ.

I agree that there is a need to create information systems and computer modes to aid the regulatory agencies is dealing with results of prior field tests so as to predict the safety of other field releases as well as to identify the holes in the database. However, as I perceive it to be very difficult to make accurate predictions based only upon models, I would not recommend support of proposals that are based strictly on theory of population dynamics. Agriculture is affected by non-predictable factors, including temperature, rainfall, prevailing winds, etc. and models are only as good as the data from which they were derived. Thus, I support the concept of gathering data from prior and future field studies (such as those supported by this and prior grants programs) to create databases that will subsequently be used to develop models. However, unless the regulatory agencies have agreed in advance to use the data in the regulatory processes, this type of research may have limited value.

The study of risk assessment of environmental fate as affected by genetic modification, seems a black box into which all types of modified and unfit organisms might fit. I hope that if applications are received in this category that they are first judged by their utility to the seed and breeding industry, or at least to provide a solid rationale for the study. All of us in the science of transgenics recognize that the under- or overexpression of genes, of either useful or non-useful traits, can be developed. Under the assumption that resources are limited, studies of such plants should be limited to those that will have broad implications for the biotechnology industry.

This category is one that is generally recognized as significant for the development of the agricultural biotechnology industry and should be one of the foci of the grants program. There are, and probably will continue to be, concerns of the impacts of genetic flow from transgenic to non-transgenic plants, including wild relatives of cultivated plants. Because there are relatively few examples of native plants that are cultivated, the program should first request or consider applications that involve those crops that have abundant wild relatives. Studies of squash plants and their relatives, or modified sunflowers, or members of the rosaceae are the most important, and will likely be subjected to market studies before other native crops. The program should
also consider funding a project that deals with the impacts of the transfer of non-novel genes into these crops as well as the impacts of transgenes. Some of us feel that criticisms of the use of certain transgenes (for example, those that confer resistance to diseases and pests) are often unduly scrutinized while transfer of genes and traits via classical methods of crop/animal breeding are not as closely scrutinized.

(5) The potential for genetic recombination between transgenes derived from viral genomes represented by the supergroup B viruses and viruses that infect the transgenic plants are worthy of further study. This is especially true if the transgenes include sequences derived from genes other than capsid proteins since such genes are more likely to affect virus replication and virulence than are the capsid proteins. That said, there are known examples in which capsid protein sequences can affect virulence; however, this is less likely to be the case for non-structural proteins. Grants should be given for research to investigate the role in recombination of: (1) noncoding as well as coding sequences; (2) nonfunctional protein mutants as well as wild type proteins; (3) consider first the replicase/polymerases since plants with such sequences are likely to reach market first; studies of other proteins should follow as development progresses to near-market situations. Studies should encourage multi-cropping situations as well as multiple crops in succession in the same field or area. Studies of the effects of recombination under nonselective conditions in transgenic plants are necessary. It is also important to include in all tests the impacts of recombination in transgenic plants by single as well as multiple viruses, and if possible, the impacts of insect transmission of the recombinant on the derivation of novel viruses and virus strains. While there is also a need to consider the effects of transgenes on the virulence of surviving virus in a resistant field and the durability of a transgene, this is an important question for the seed company more than the USDA grants program.

(6) The potential impact of transgenic plants to change or select viruses with different host range is an important issue and has been partially addressed in (5). As indicated, such studies should include studies of plants that are under inoculum pressure by multiple viruses since such conditions may influence the acquisition of virus by an insect, or make it possible for some insects to transmit that did not normally transmit in the case of single infection. All such studies should be well controlled with non-transgenic plants that are similarly treated. The impact of resistance on selection, as well as the degree of resistance, i.e., near-immune conditions versus highly or moderately resistant plant lines should be included in studies. It is hoped that studies are not carried out only with members of the Solanaceae, but also with crops such as corn and soybeans where the pest problems are different and the acreages of planting likely to be much greater than for horticultural crops. Furthermore, the contents of alkaloids and other secondary compounds are different with different crops and may affect insect feeding and transmission of disease agents.

(7) There are persistent and lingering questions related to the impacts of transgene-derived proteins on non-target organisms in the environment, including the rhizosphere and soils that contain crop residues, and leaf tissues. One of the most nagging questions is related to the survival of genes that encode resistance to
antibiotics, since such genes are generally included in transformation/selection protocols. In the selection of grants for funding at least one should be for the study of survival of gene sequences in animal digestive systems. Although many of us consider the likelihood of horizontal transfer between organisms to be extremely unlikely (even fantasy) the public has a concern that has not yet been carefully addressed. Indeed, aside from the approval of the NPTII protein and gene, no other selectable marker has yet received approval from the EPA or USDA, a fact that may well delay marketing of a number of crop products. The proteins that are selected for study should include those that are likely to be included in crops, including PR proteins and phytoalexins, as well as proteins that control specific insects and microbes.

(8) It is unclear what types of projects are anticipated to involve genes that can confer additional pathogenicity to animal pathogens, although certain of those described above might be placed in this category. For example, transfer of antibiotic resistance to animal pathogenic bacteria; as indicated, this remains an important question that requires resolution as early as possible. It goes without saying that such studies should involve livestock animals and poultry, etc., rather than rodents and other "model" animals that are not part of the (U.S.) diet. Other genes that might impact pathogenicity of animal pathogens might include proteins that affect freezing tolerance, or that encode proteases, toxins and other proteins that might impact pathogenicity of microorganisms. However, because the unlikelihood that any gene recombinations or other types of gene transfer is extremely low (fantasy) it will be important to fund only those proposals that are of the highest quality by the most suited of research teams. The team must include plant biologists, microbiologists, animal nutritionists, and population biologists/geneticists, and should be funded for 3-5 years, with good preliminary results available to the research and regulatory agencies within 6-18 months. If such a project is to be funded, it should be done correctly so that the results will leave few doubts of their significance and applicability to biotechnology (i.e., no model systems).

(9) The need to test genetically modified organisms under conditions of large scale is recognized as important; however, it is clear that many of the largest "field tests" are the commercial releases of soybean, cotton, potato, corn, tomato and others soon to be released. Therefore, perhaps the most appropriate use of the resources is to work with the providers of the materials, monitoring populations of pests and pathogens, as well as non-target organisms. It is also important to provide support not only for study of macro-organisms (animals, plants, etc.) but also for modified microorganisms. It is anticipated that modified soil and foliar organisms, including Rhizobitan spp., micorhizal fungi, and other beneficial organisms, as well as microbes that provide biological control of pests and pathogens will soon be ready for the market. Given the history of the early Lindow experiments, those of Brill, Cook, and numerous private companies, and the public perception of microbes as involved in disease, such studies are important to the industry associated with agricultural biotechnology.
Adequacy of Current Scientific Knowledge about Risk Assessment

In addressing items 1-9 above, I have attempted to point out both the long-term and short-term needs in terms of risk assessment. As I see it, there is a continued need for risk assessment as related to products that are being developed for the market place: the health of agriculture as an economy as well as a sustainable activity demands that we keep risk assessment abreast of product development. Given the paucity of funds for research in risk assessment, perhaps that is all that can be expected. However, based upon the reluctance of certain segments of the scientific community, environmental activists, and some of the members of the European community to accept the growing role of genetic modification in improvement of methods and products of agriculture, the Agency should continue to reassess the priorities for research in risk assessment. Nevertheless current gaps in knowledge and technologies for risk assessment (as above) will change as we gain knowledge. While we are gaining experience with the expression of transgenes from certain types of promoters and certain copy numbers of genes, we know little of the impact of the numbers of new genes, or the types of proteins, or environment on stability of gene expression, gene organization or plant phenotypes. Much of agricultural biotechnology is directed at high input and high productivity agriculture; however, we know little about how the plants will respond under non-optimal culture conditions. Likewise, risk issues may be different under certain agricultural conditions than others. Knowledge of the differences will be essential to the continued growth of agricultural biotechnology. And, while this topic may fall under the heading of fundamental research, it also should be considered part of risk assessment, as risks may change if genes are not stable, or if environmental factors alter fitness, pollen and propagule dispersal and survival, or the interactions between the genetically modified organism and pathogens and pests, etc.

Possible New Directions or Criteria for Decision Making in Risk Assessment

It is my impression that the risk assessment process primarily involves scientists in public institutions, including universities and governmental organizations. It is important to involve in either the review or scientific activities of the program representative of the biotechnology industry as well as one or several representatives for the organizations that oppose the use of biotechnology in the food and agriculture industry. That said, it is important that minority opinions not override conclusions gathered from scientific study. Risk assessment studies can legitimately include agriculturists, fundamental scientists, scientists engaged in development, ecologists, population biologists, and geneticists, including genome scientists. Methods of analysis should include genomic studies, applying FLP and RFLPs as needed, market genes that can be assayed under field conditions, and techniques to monitor insect and disease situations that impact dispersal of the modified organisms, including microorganisms.

To make the public more aware of the results of the studies, there should be regular informational releases that stress the role of U.S. governmental agencies in determining the risk and safety of genetically modified organisms and describe completed studies, as well as studies that are in progress. There are regular releases dealing with progress related to medical progress in cancer treatments, diet control, smoking, etc., but very little reaches the public related to genetic modification of agricultural products, and the role of modified
organisms can play in low input agriculture, quality of products, etc. The regulatory agencies need to become more accessible and have greater visibility — choose one or more good spokespersons to relay the information. The private companies will undoubtedly have their own methods to get out their messages; regulatory agencies need to provide the balance, some of which will support the claims of industry, while others may not.

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Strengths and Weaknesses of the Scientific Aspects of the USDA’s Current Biotechnology Risk Assessment Program.

USDA’s current Biotechnology Risk Assessment Program has thorough consideration in addressing the potential biological and environmental impacts of genetically modified organisms (i.e., bacteria, fungi, viruses, plants, insects, fish, birds, and mammals). The strengths of this program include: (1) developing new risk assessments and risk assessment procedures; (2) creating computer models and information systems to assist regulatory agency decision-making in regards to potential impacts of genetically modified organisms to the environment over time; (3) developing parameters to assess the environmental fate of genetically modified organisms introduced into the environment; (4) investigating the bidirectional rates, effects of selection pressures, impacts of gene transfer between genetically modified organisms and the existing local organisms; (5) determining the potential for recombination between viruses and host encoded viral genes, changes in viral host ranges, genes that can confer additional pathogenicity to animal or plant pathogens and the potentials of non-target effects of introduced plant-defense compounds expressed in plant-associated microorganisms or plants. The whole program has a very comprehensive coverage of the fates, stability and impacts of transgenes on environment. However, this program fails to address the biological impacts of transgene products consumed by humans. The problem of potential allergenicity caused by transgene products could be a severe problem and needs to be included in the risk assessment consideration.

Adequacy of Current Scientific Knowledge About Risk Assessment.

Currently, the scientific knowledge in assessing the fate, impact and the interaction of transgenes with other organisms in the environment is very adequate. It is not difficult to design experiments to determine the potential horizontal flow of the transgenes in the genetically modified organisms in the environment. However, the scientific basis for assessing the allergenicity, in particular the acute allergic reaction, of transgene products in human remains to be established.

Possible New Directions or Criteria for Decision-Making in Biotechnology Risk Assessment.

A new additional criterion for decision-making in biotechnology risk assessment is the determination of allergenicity of transgene products made by genetically modified organisms. Many of the new food products developed from genetically modified organisms will have foreign proteins that may cause unexpected allergic reactions in humans consuming these products. Therefore, detection of allergenicity of products produced by genetically modified organisms needs to be considered as a major factor in the biotechnology risk assessment process.
Comments on USDA's biotechnology risk assessment program.

This program assumes that there is a need for science based regulation of biotechnology specifically to cover the release of genetically modified organisms (GMOs) in the environment. However, the announcement in the Federal Register does not define GMOs. Since the products of deliberate breeding programs are genetically modified this program could be concerned with the release of crop cultivars derived from conventional breeding and selection programs. Although such releases can, and do, have profound environmental effects as a consequence of large scale agriculture, forestry, fisheries, and other biotechnologies (for example the use of microorganisms for recovering minerals from mine spoils, and sewage treatment plants), I suspect that these are not a source of concern here. I have therefore assumed that this program is specifically concerned with transgenic organisms produced with the techniques of recombinant DNA. Whether or not such a program is necessary is not considered in the document. Since no example is yet known of environmental or other damage from the deliberate or accidental release of a genetically modified organism I must conclude that the USDA program is motivated more by politics than science. By presupposing that there are conceivable hazards associated with environmental releases, and seeking methods to establish the likelihood of their occurrence, the program appears to be designed to help the agency to be responsible to, and answer, those who criticize the products of genetic engineering rather than to open up new research frontiers in science. The critics ignore the conclusion reached by the National Research Council (Testing Genetically Modified Organisms: Framework for Decisions, 1989, National Academy Press) that the products of genetic engineering are not inherently any different from those of conventional breeding and therefore need no special criteria for judging the risks they may pose. The information obtained through this program should therefore be judged on its usefulness for all organisms released into the environment not just transgenic forms.

The RFP identifies 9 research topics:

1. New methods for monitoring the spread of introduced or invading organisms could well be useful in a range of studies in ecology, habitat management, and in situ resource conservation. They may also be useful in agriculture and husbandry to measure the impact of organisms that can exist independently of the artificial environments they were originally designed for.

    Addressing the need for these methods can only be done in the context of specific and defined risk assessment issues. Here I find some weakness since the risks involved are hypothetical. For some these are easier to foresee than others. Take for example a recombinant baculovirus engineered to express a scorpion venom toxin that is designed to control certain lepidopteran larvae. Obvious risk questions are what is the host range of the engineered virus, how long will it persist, and what is the effect of the venom protein on non-target hosts? Less obvious
questions involve the impact of the virus on the target insect population and the
effect of decimating this population on other members of the ecosystem. The
answers to these questions, and the methods developed to find them, are likely to be
highly specific to this particular instance of using an engineered baculovirus. I
would have hoped to see more generic approaches emerge from the program but
doubt that they will.

2. Information systems and models to support regulatory decisions can be helpful in
forcing the consideration of issues that might otherwise be overlooked. However,
they must be validated if they are to be used with any assurance. The RFP is weak in
not calling for experimental validation.

3. This section is hard to understand. I am not clear what "Risk assessment of the
environmental fate as correlated with effects of GMOs introduced into the
environment" means. It appears to ask what risks can be predicted from an
organism that survives in the ecosystem and what traits will enhance competition
and displacement of other genotypes? Most experimental approaches here are likely
to be of the "suck it and see" kind. However, competition studies in the field, no
matter how sophisticated the measurements are, merely indicate the outcome
under a particular set of circumstances. How relevant this is can only be determined
through many repeated comparisons.

The accidental large scale release of fish from captive fisheries appears to have
threatened natural populations in some areas. In my view these threats are more
serious than those posed by GMOs because they are already occurring without
adequate controls.

4. Gene transfer between transformable crops and weedy, free living, crop relatives
is of some interest. In the case of herbicide resistance genes it is of direct concern
since spread of the genes will limit the usefulness of the herbicides in controlling
the weed relative. However, the issue is one of conserving the usefulness of
agricultural chemicals rather than ecosystem safety. Thus it is widely recommended
that herbicide resistance should not be used in sorghum because of the risk of its
transfer to Johnson grass, and that it should not be used in rice in areas where red
rice occurs as a weed. The application of herbicides is of far greater ecological
consequence than the use of transgenic crops with resistance, although the
availability of resistant crops may well mean that much more herbicide is used, with
its attendant risks. But we seem to be quite unconcerned about these risks here. The
risk that weeds in general, not just those related to the transgenic crop, will become
resistant as a result of natural evolutionary changes is a much greater threat to the
longevity and usefulness of chemicals. Herbicide resistant Johnson grass could
arise in this way in large scale applications of selective herbicides applied to any
crop in which it is a weed, not only to sorghum. Herbicides also select weed species
that are not affected by them. As a result the spectrum of weed species can be
profoundly changed by herbicide use. Why are we not concerned about that and its
ecosystem impact?
The likelihood of a transgene from a related crop species creating a more noxious weed, or problem plant, appears to be remote. For example the introduction of insect or disease resistance through conventional plant breeding has not had any remarkable effects on the survival, or the ecosystem impact, of related wild species even though it has been tested on an extremely large scale in agricultural practice over the last 50 years or more. Why would we expect engineered resistance to behave any differently? Is there any reason to suppose that features such as improvements in the quality of the harvested product (high methionine corn, improved baking quality in wheat, delayed ripening in tomato, improved digestibility in forages, expression of viral antigens that confer immunity through the digestive tract, etc., etc.) would generate a risk that needs to be examined in this way? It is conceivable that adaptations to extremes of temperature or water stress could confer selective advantages on a related wild species. Reanalysis of published data should provide a good indication of how seriously to take this threat.

5. The possibility that virus resistant transgenic plants that express parts of viral genomes might serve as a medium for genetic exchanges with other infecting viruses has attracted attention. The proposal that such work should involve comparisons with naturally occurring viral recombination is very sound.

6. I am not sufficiently familiar with the literature to comment on the likelihood that transgenic plants expressing viral genes will alter viral host range.

7. The suggestion that the products of engineered resistance in transgenic crops, or inhibitory compounds in microbes used for biological control, might persist and have unintended effects is interesting. The very extensive experience obtained in using BT as an insecticide has failed to show any evidence of this. Pesticidal or toxic proteins are almost invariably degraded rapidly by soil organisms and are most unlikely to present a threat. In such cases the remedy is obvious. Regulators need only require evidence that the active compound has a satisfactorily short half life in the environment once it has done its job of protection. I am very much opposed to regarding cloned resistance genes and their products as pesticides and thus subject to FIFRA.

8. The nature of pathogenicity and how it is controlled is an important aspect of plant and animal pathology. The addition of a scorpion venom toxin gene to a baculovirus to control insect larvae is an example of how such research can be applied. I have covered this example in section 1 above.

9. The effects of the scale of releases, whether of a GMO or not, are important since their impact on the ecosystem may well be in direct proportion. How realistic it will be to compare small and large scale releases of GMOs in projects funded by this program is doubtful since nothing that could be attempted here could match the large commercial releases covering millions of acres. In my view this is best done through comparing the records of previous releases of conventional organisms and
GMOs. For example the data obtained by Monsanto in large scale commercial plantings of transgenic cotton expressing the Bt gene in 1996 may provide some indications of unexpected effects on the ecosystems involved.

The RFP reminds investigators of the importance of statistical analysis and makes the useful suggestion of including statisticians as co-PIs or contractors.

Risk assessment is a well established discipline in its own right. I believe there was an oversight in failing to encourage PIs to work with colleagues with expertise in this area since it could lead to synergisms that have not often occurred in biotechnology. For example meta-analysis could be helpful in some of the cases this program will be concerned with. This is a system of analysis that uses apparently disparate facts, and seemingly unrelated information, to arrive at relatively informed conclusions. I doubt that there are many tools or methods lacking to serve this program. The development of models may well be useful provided they lead to tests that validate their predictions.

My principal concern is that a logical conclusion of such studies is that we will also become much more concerned about what we now take for granted and rarely question, namely conventional agricultural and other technologies such as plant and animal breeding, aquaculture etc. In my view the risks from these activities totally dwarf the concerns of this program. We have only to think about the continuing massive destruction of forests to clear land for cattle grazing, building highways and creating short term wealth to put our concerns for GMOs in a global perspective. Our priorities should be to conserve what we know we are losing in natural resources and not to waste resources in dealing with exaggerated risks.
Comments concerning the United States Department of Agriculture (USDA) Cooperative State Research, Education, and Extension Service's (CSREES's) Biotechnology Risk Assessment Grants Program

Here are my comments concerning the United States Department of Agriculture (USDA) Cooperative State Research, Education, and Extension Service's (CSREES's) Biotechnology Risk Assessment Grants Program, as requested by FASEB's Life Science's Research Office as part of its contract with USDA CSREES. I will first make some general comments about the Biotechnology Risk Assessment Grants Program and then address the three areas about which FASEB has requested comment.

General comment: The Biotechnology Risk Assessment Grants Program is essential

Environmentally responsible development of biotechnology products is essential to the long-term success and acceptance of these products. Experience with environmental problems caused by other modern technologies, such as chemical pesticides to nuclear power, has caused many members of the public to recognize that technology can be a double-edged sword, bringing risks as well as benefits. Clearly, there is a strong societal interest in ensuring that the biotechnology industry develops in an environmentally sound manner.

USDA CSREES's Biotechnology Risk Assessment Grants Program is now the only federal research program devoted to funding research to examine risks associated with the development of biotechnology products. EPA at one time also funded some research on biotechnology risks. In recent years, however, EPA has faced significant budgetary constraints and the agency now funds very little, if any research concerning biotechnology risks. Thus USDA CSREES's program is more critical than ever to better understanding the risks of biotechnology products. Moreover, since most of the environmental risks of biotechnology products are associated with the use of biotechnology in agriculture, it is appropriate that USDA's research arm bear major responsibility for research on these risks.

1. Appropriateness of USDA CSREES's nine objectives

USDA CSREES's nine research objectives appear to be structured in a manner that should allow the agency to make the best advantage of the competitive grants process. The first three objectives are general in scope. They solicit proposals on any of a broad range of topics associated with biotechnology risk assessment. The last six objectives are more specific. They are tailored to address those issues of most current interest to federal regulators. Thus, the first three research objectives provide USDA CSREES the opportunity to consider research proposal that may not fit the relatively narrow research objectives defined by regulators, but may merit funding because they are especially innovative. The final six objectives give a special edge to those proposals which address scientific questions of particular practical utility, because regulators need answers to these questions in order to make better informed decisions.

That said, I offer the following specific comments on some of the nine objectives:

Objective 2, the development of information systems and computer models, is less important than objectives one and three. Computer models can play an important role in elucidating particular ecological phenomena (e.g. predator-prey cycles), in large part because they allow researchers to examine the logical outcomes of making various assumptions about these phenomena. However, computer models tend to be relatively unreliable for predicting outcomes of specific ecological events, since models cannot possibly capture all the factors at work in the natural world.
Statistically well-designed experiments remain absolutely necessary to understanding ecological relationships. Even experiments that are themselves simulations – because they are performed, for example, in greenhouses – can capture outcomes that would not be found in simulations. Thus, while it may be entirely appropriate for the Biotechnology Risk Assessment Grants Program to fund research products involving computer modeling, in general, I would place a high premium on projects that involve the collection “real” data from “real” experiments.

Objective four, is particularly important because crop plants are the vast majority of organisms being genetically engineered for use in agriculture. Better understanding of what is widely believed to be the major ecological risk of transgenic crops -- the transfer of acquired genes to related wild plants -- is essential to biotechnology risk assessment.

I would, however, change the emphasis of objective four. There is now substantial evidence that gene transfer from crop plants to related wild plants can occur. There are undoubtedly still a number of individual crops for which more information about the potential of gene transfer to specific wild plants would be useful. Nevertheless, the primary focus of research concerning gene transfer should now be the consequences of gene transfer, rather than whether it occurs. In particular, considerably more research is needed to better understand how transgenes alter the fitness of wild plants once they get into the wild genome. This research should examine both the levels of expression of transgenes in crop-wild plant hybrids, and the circumstances in which introgression of these genes into wild plant populations increases fitness.

Objectives five and six, which concern risks from transgenic plants with genes from plant viruses, should remain a high priority. Discussion of these risks is now largely based on educated guesses rather than data.

I do not understand why objective eight, “Identification of genes which can confer additional pathogenicity to animal pathogens,” is a priority. This may reflect poor understanding on my part -- I have little scientific training with warm blooded vertebrates. Nevertheless, at the very least more context for this objective would be helpful!

2. and 3. Adequacy of scientific knowledge/Possible new directions

As illustrated by the discussion above, considerably more knowledge is needed to assess the risks of agricultural biotechnology products. The one area in which research may be reaching a point of diminishing returns is research documenting the occurrence of gene transfer by crop plants to wild plants.

Future research should target the wide variety of organisms besides conventional crop plants now being engineered. Over 40 different types of plants have now been field tested in the US, including forest trees such as poplar, spruce, and sweetgum and ornamentals and turf plants such as chrysanthemum, petunia, and creeping bentgrass. The first two field tests of genetically engineered invertebrates, a mite and a nematode, were approved by USDA this past year. Several transgenic fish are now nearing commercialization, and molluscs and shrimp were recently transformed for the first time.

Some of these varied organisms may pose far greater risks than most conventional crop plants -- which comprise the vast majority of transgenic organisms field tested to date. Many crop plants are heavily domesticated and thus exhibit relatively low rates of survival and reproduction in natural ecosystems. Thus, the risk of these crops themselves becoming pests is generally low. Moreover, the risks of gene transfer from genetically engineered conventional crops to wild plants are reduced by the fact that hybrid offspring will carry a “genetic load” from the domesticated crop parent. In contrast, forest trees, mites, and most fish, are largely or entirely undomesticated. For example, offspring of transgenic trees, including crosses with other transgenic trees and hybrid offspring of genetically engineered trees and wild trees, will not carry a heavy genetic load and can be expected to exhibit relatively high survival and reproduction rates. If genes acquired via genetic engineering confer a selective advantage, they can be expected to quickly flow into wild populations.

2
Research in at least two major areas is needed to better understand the risk of genetically engineering relatively undomesticated organisms:

Research is needed to better understand how transgenes alter the fitness of wild fish, forest trees, nematodes, etc., once they get into the genome of wild populations. This research should focus on the types of genes now being pursued by researchers. For example, most transgenic fish are now being engineered to express novel growth hormone genes, and more research is necessary to understand the potential effects of such genes on the fitness of wild fish.

A number of researchers have proposed using various genetic and other techniques to render transgenic fish and trees sterile, so that they cannot transfer their acquired genes to wild organisms. This approach has considerable appeal. However, there is evidence that techniques for inducing sterility are less than perfect -- e.g. a small percentage of these organisms may revert to fertility. More research on success rates for various sterility techniques and improvements of these techniques could prove extremely useful to minimizing biotech risks.
Comments on the USDA CSREES 1996 Federal Register Announcement for the Biotechnology Risk Assessment Research Grants Program

At the invitation and request of Dick Herrett of ARI, I am responding to the call from LSRO for comment on the USDA CSREES 1996 Federal Register announcement for the Biotechnology Risk Assessment Research Grants Program. I respond to this invitation and request with the perspective of both being an active university research scientist [with an interest in the ecological underpinnings of agriculture] and having extensive prior experience in the biotechnology industry [I was the Executive Vice President for Research and Development (for 8 years) of a leading plant biotechnology company].

I am a strong advocate of a Federal commitment to research in the area of biotechnology risk assessment. My "take" on the issue can be framed by focussing on two reflections regarding the recent history of agricultural technology introduction.

1. We poorly understand the long-term consequences of the first "wave" of genetic technologies that are now common-place in agriculture. I refer, for example, to the introduction of crop varieties that are bred for responsiveness to concentrated inputs such as fertilizers and pesticides and to the harnessing of knowledge about reproductive biology for the development of new breeding systems, making possible hybrid crops, and mass production of planting materials by clonal propagation. These advances have no doubt had the potential for significant, if not massive, ecological consequences. But virtually nothing is rigorously known about such consequences because the questions were not posed and besides the research technologies available were, at best, crude. From our experience, whatever the consequences have been, agriculture is nonetheless an "unqualified" success story, at least in North America. The negative potential of today's agricultural technologies can be clearly seen in other parts of the world. Pesticide use in the tropics, and degradation of land in eastern Europe arising from agricultural practices are examples. In North America we clearly benefited from Silent Spring and other early warnings that resulted in avoidance and even some mitigation of disaster. My point is, however, that little prior thought or even concern was given to ecological consequences. We should not, it seems to me, have been so arrogant in the past. I think we now realize this and must take the proper steps so as not to repeat the mistake next time around.

2. The technologies that are being introduced into agriculture during the closing years of the 20th century have the potential both to revolutionize and to paralyze agriculture. This is again in one sense another "crap-shoot". That we think we "made out" OK the last time should make us extremely cautious, however, since we do not really understand how our agroecosystems work, AND since the technologies being advanced this time are (by the testimony of their advocates, no less) even more powerful than those we "experimented with" the last time around. What do I mean by these two statements? It seems to me that we have a situation in which we are treating the environment as resilient and our resource base as inexhaustible. I think this is an incredibly arrogant and risky thing to do. We really little understand the biological, chemical, and much less the social, consequences of emerging agricultural
technologies. After all, our experience with these technologies is brief at anything other than political timescales. Moreover, we know from the past that many of the effects of agricultural practices that we do not anticipate take decades to accumulate to the point of detection being inescapable.

All of that said, and with all of the lingering but unmet need for humility implied, let me now turn to the questions you have asked. My contribution will be focussed on some positive reactions and some probing, potentially negative, concerns.

The Positive.

As I have said above, I am an advocate of research focussed on the environmental consequences of biotechnology. Indeed, my own research efforts are largely committed to the development of new knowledge about the biology, including ecology, of agroecosystems and to the development of powerful methods for analysis and assessment. I am therefore in favor of the focus of this program on field-based work. Processes that occur under field conditions will almost certainly be different, in scale if not in molecular detail, than those that occur in the "same" system studied under more controlled, reductionist conditions. The focus on field-based studies could, however, act to repel applications from the most basic scientists, or discourage alliances between basic and field oriented researchers. This aspect of the program would, I think be strengthened if steps were taken to solicit strong interdisciplinary proposals from groups of investigators that include both basic and more applied expertise. I reiterate that I believe the orientation toward studies of field phenomena is very significant.

There are some other aspects of the program that I also find favorable. The convening of a meeting that brings together the investigators is excellent. I have attended these meetings, though, and believe they would be more useful if the focus was on cross-cutting issues rather than just on reports from individual projects. The effort to distribute results to government officials is a positive, also.

The Concerns.

To me, the major concern about this grants program is the discontinuity between the objectives as described in the scope of research (and the societal concerns that clearly drive the rationale for the program) and the timescale of the granting authority. This issue is most clearly illustrated by the description of the last specific research area, number 9. One or two year grants in this area presume either an incredibly naive interpretation of the significance of the issues or betray a breath-taking naivete about the nature of the research needed to address them. There is a serious need for a long-term commitment to research about the agroecosystem, both in terms of development of new methodology and in terms of a framework for monitoring the consequences of the introduction of new technologies employing these methodologies. This program is barely a start in the right direction. A drop in the bucket.

My second, but not secondary, concern relates to the spectrum of grant-making and the resulting portfolio of projects that will be supported by this program. The point here is the
confluence of questions about the size of the overall program and the complementarity of the projects proposed and funded. USDA has a dismal record of proactive solicitation of proposals from among which to choose the best. Selection of the "best" of the proposals received "over the transom" could conceivably result in funding concentrated, to take the extreme case, in only one of the nine areas identified in the Federal Register publication. Alternatively, there could be a mechanism that demands selection of the "best" proposals in the 9 areas, and the issue here is that some of the areas could be represented by very poor "best" proposals. My bottom line here is that for such a targeted program, there should be an element of solicitation of proposals, across the spectrum, from investigators who are known to be both interested in, and capable of doing reasonable work, in an area of interest to the agency.

Other Comments on the Federal Register Announcement.

I find the area defined in item 5 to be unnecessarily narrow.

I thought that areas 5 and 6 were narrow AND intimately interrelated. They should be combined.

My view of virulence and pathogenicity in both animals and plants is that the fields are too immature to make any sensible projections of practical work ("identification of genes which can confer additional pathogenicity...") worthwhile. This relates to point 8.

Finally, you asked in your letter for any comments about gaps in knowledge or new directions that this program might take. As a scientist and a citizen, my view is that we too little focus on understanding of "healthy" systems and too much focus on the detection and remediation of problems. There is a vast, unknown, and central mystery about how the biosphere functions that is just coming into view today. It has to do with the diversity and nature of the ecological roles of what E. O. Wilson has called the "bacterial proletariat". By this term, he refers to the vast and largely unknown microbial world, numbering hundreds of thousands of species and playing untold ecological, biochemical, and no doubt crucial beneficial roles in governing the biosphere. This is a huge gap in our understanding about the living world into which we are pouring new inventions from biotechnology. I am concerned that we should have a much more serious commitment to funding the right kind of research to better understand the roles of microflora associated with plants and animals in the agricultural system. Such work promises to teach us much that will in turn make risk assessment both more informed and more informative.
EVALUATION OF CURRENT USDA-CSREES BIOTECHNOLOGY RISK ASSESSMENT RESEARCH GRANTS PROGRAM

USDA justifiably has invested a large amount of its research support into agricultural biotechnology research and development. Under provisions of the Farm Bill of 1990 (PL 101-624), USDA earmarks 1% of its biotechnology research budget for biotechnology risk assessment.

1. Strength and weaknesses of current program:

In my estimation, the key strength of the Biotechnology Risk Assessment Research Program is its applied thrust. USDA is the primary oversight authority for making science-based decisions about the safety of introductions of genetically modified organisms (GMOs) into the environment. A scientifically valid knowledge base on key risk assessment issues is absolutely necessary for practicing informed oversight.

I also regard as highly appropriate the broad scope of research activities that are regarded as germane to the goal of promoting environmentally safe application of agricultural biotechnology. All genetically modified organisms relevant to agriculture, from production crops or livestock to soil microbes, may be the focus of proposed risk assessment research.

FASEB specifically asked me to comment on the nine areas of research to be supported in FY 1996, as outlined in the Federal Register announcement. The first three topics are defined in broad, generic terms:

- Research area 1 broadly targets development of risk assessment methods and procedures, appropriately addressing the need to gain new means of collecting useful risk assessment knowledge.

- Research area 2 supports creation of information systems and computer models to support oversight regarding potential long-term environmental impacts of agricultural biotechnology. Information systems are needed to enable oversight authorities to effectively collect, process, and disseminate scientific data and to document oversight activities. Well-crafted computer models could support: (1) extension of results of short-term experiments through time in a manner not otherwise available, (2) sensitivity analysis of ecological processes to characteristics of the genetically modified organisms or of the environment, and building on numbers 1 and 2, (3) development of hypotheses and experimental designs for studies to be carried out in the field.

- Perhaps the heart of the risk assessment program is embodied in research area 3, encouraging risk assessment of environmental fate and effects of genetically modified organisms. Collection of data on performance of GMOs in well-designed laboratory or outdoor mesocosms provides the empirical
knowledge needed to inform oversight, as an input to models, and to define new hypotheses for further product development or risk assessment research.

These three broad Program topic areas serve to promote original research designed by the research community, providing basic knowledge or tools not conceived by USDA-CSREES officials. The opportunity for investigator-initiated risk assessment research is laudable.

Targeted areas of research 4-7 address identified gaps in knowledge needed for effective oversight of agricultural biotechnology:

- It has been widely agreed that transmission of ecologically significant traits among genetically modified crops and weedy relatives is a key mechanism posing environmental impacts. Hence, support for studies in this narrow area of research is appropriate.

- The possibility of recombination between plants bearing introduced gene constructs incorporating viral DNA sequences and viruses in the environment poses concern that new, pathogenic viruses could result. The call for proposals under research area 5 is narrow. I lack the perspective to judge the appropriateness of targeting interest in viral supergroup B.

- Research targeted under area 6 addresses concern that viruses may gain the ability to switch hosts, presumably because of recombination with viral genes in transgenic plants. This research area is broader than area 5, and seems an appropriate area of concern for environmental risk assessment.

- Characterization of non-target pesticidal effects of genetically modified microbes or plants is timely and appropriate. This is justified by well-documented declines in valued non-target populations following the widespread adoption of chemical pesticides.

Taken collectively, research areas 4-7 call for sophisticated experimental designs quantifying risks associated with narrowly defined impact pathways. This portion of the Program's call for proposals underlines the notion that knowledge of risk pathways for genetically modified plants is much more advanced than for other sectors of agricultural biotechnology. In contrast, risk assessment for genetically modified microbes, arthropods, and aquatic organisms is in an exploratory stage.

Research area 8, addressing the possibility that introduced genes could recombine with or otherwise increase the pathogenicity of animal pathogens, corresponds to the plant-oriented research areas 5 and 6. The broad generality of research area 8, compared to the specificity of areas 5 and 6, emphasizes how much less we know about the risk pathways and animal pathogens at issue.

Research targeted under area 9 is absolutely essential for fostering environmentally safe commercialization of agricultural biotechnology. A salient example of an important problem is scaling up of production of crops expressing bt endotoxin from the experimental stage
(where plant pests encounter this pesticide only rarely) to the commercial scale (where widespread use would cause sufficient selective pressure for resistance that bt's future as an effective pesticide would prove limited). Other risk mechanisms involving other products of agricultural biotechnology also might become important only at the landscape scale. Results of studies supported under this research area could prove critically important for strategic development of agricultural biotechnology, in terms of realizing its potential while minimizing negative environmental impacts.

As set out in the Federal Register announcement, investigators whose research projects are funded under the Program are required to attend, present data, and provide a manuscript on the results of their research at an annual conference. This conference provides the opportunity for investigators and USDA officials with oversight responsibilities to interact, to synthesize new understanding, and to identify future research needs. The proceedings of this conference provide a picture of the state of knowledge of biotechnology risk assessment at that moment in time, and are read internationally as well as in the United States. However, as noted below, the tone of the conference has not always been one of detached, scientific objectivity.

I turn my attention now to the weaknesses of the Biotechnology Risk Assessment Research Grants Program. Given the scope of research and development effort in agricultural biotechnology, the Program as currently funded (a token 1% of USDA biotechnology expenditures, about $1.7 million) cannot address adequately every significant risk assessment problem identified. This token outlay cannot even begin to support research needed to identify more subtle mechanisms or to quantify longer-term processes giving rise to environmental impacts, or to quantify the full range of processes occurring over landscape-scale areas. The great bulk of USDA's investment in biotechnology research has been to promote technical development, i.e., development of methodologies and of genetically modified lines of plants, animals and microbes. With the growth of the private sector in agricultural biotechnology, we can safely assume that the private sector will pick up much of the cost of research and development, and that the mix of projects supported by public monies can be changed to increase the investment in risk assessment research, an investment that that smaller biotechnology companies cannot make. Hence, USDA can and must expand the support for the Biotechnology Risk Assessment Research Program dramatically.

A second weakness of the program relates to a perception, which to some degree I share, that the thrust of the Biotechnology Risk Assessment Research Grants Program has been to document environmental safety of products of biotechnology. Taken in its historical context, the Program was initiated during the Bush-Quayle administration at the token 1% funding level to address the fears of biotechnology which reached a peak in the late 1980s. While many of the public's fears justifiably were laid to rest, some subset of applications of agricultural biotechnology have been shown to pose environmental risk. Against the background of some findings of risk, I make two disappointing observations:

- The tone of the annual biotechnology risk assessment meetings sometimes has fallen short of dispassionate discussion of scientific issues. The tone of the 1994 meeting in Monterey, California was described to me in negative terms by an
Associate Chair of USDA's Agricultural Biotechnology Research Advisory Committee and by the Director of USDA's Office of Agricultural Biotechnology. Many participants were openly hostile to investigators or to environmentalists expressing concern about impacts stemming from environmental application of agricultural biotechnology. In fairness, it must be noted that this particular meeting was held in association with other agencies from the United States, the European Commission and Japan. Still, convenors of the meeting simply must make clear the expectation that the meeting will proceed in an atmosphere of professionalism and mutual respect.

A second concern relates to non-renewal of funding for projects identifying risks posed by agricultural biotechnology, for example, the study of transgenic medaka mentioned in the following section. Loss of Program funding poses not only loss of the opportunity for immediate follow-up on results-to-date, but also loss of genetic materials and key project personnel, and thereby, loss of opportunity for future follow-up.

2. Adequacy of current scientific knowledge about risk assessment:

The adequacy of current knowledge of risks posed by agricultural biotechnology differs among sectors. The degree of confidence in the environmental safety of many genetically modified crop plants is such that field tests for a list of species are subject only to the requirement that responsible parties notify USDA of the intent to go forward with a release. A very different situation is posed by genetically modified arthropods, or by genetically modified aquatic organisms, on which I focus below.

Broad application of genetically modified aquatic organisms (aquatic GMOs) in aquaculture and fisheries management will depend on demonstration that particular GMOs can be used in the environment both effectively and safely. However, our base of knowledge for assessing ecological and genetic safety of aquatic GMOs currently is limited. The range of anticipated possible impacts of aquatic GMOs on ecosystems or conspecifics have been described in a number of scientific journal articles (1-4, 7), and were the subject of several workshops (e.g., 6, 8). Briefly, we can anticipate ecological risks to a range of species with which an aquatic GMO interacts in the accessible ecosystem, and additionally, genetic risks to conspecific natural populations. Ecological risks include the possibility of heightened predation or competition, colonization by or persistence of aquatic GMOs in ecosystems outside the native range of the species, and possibly, alteration of population or community dynamics due to activities of the aquatic GMO. Should the GMO be fertile, it could interbreed with natural populations. Any impacts would depend on the fitness of novel genotypes in the wild. We have to consider cases where fitness relative to the wild type is high, and also the opposite case where maladaptive traits might be introduced into native populations. Reproduction of aquatic GMOs would prolong any ecological effects beyond the one generation at issue for sterile GMOs.

Concerns regarding possible environmental impacts of aquatic GMOs contributed to support of targeted studies supported by the USDA-CSREES Biotechnology Risk Assessment
Research Grants Program. The first two Program-supported studies of aquatic GMOs have yielded results. Results of outdoor pond-based studies on transgenic channel catfish by Rex Dunham of Auburn University show that transgenic and non-transgenic individuals interbreed freely, that survival and growth of transgenics in unfed ponds is equal to or less than that of non-transgenics, and that predator avoidance is not affected by the transgene. Among transgenic common carp, expected inheritance rates were not observed for the transgene, suggesting differential mortality or unstable integration. However, from 30 grams on, transgenic carp exhibited equal or greater survival than non-transgenic, control carp. Under a dissolved oxygen challenge, transgenic carp lived longer before they died than non-transgenic controls. Laboratory studies of transgenic medaka by Bill Muir and colleagues at Purdue University indicated that large males gain a higher frequency of matings, but that transgenic offspring exhibit decreased viability; computer modelling suggests that the demographic viability of medaka populations could be threatened by introduction of transgenics. Possible impacts of monosex or triploid grass carp stocks will be assessed by Bill Shelton of Oklahoma State University, leading to insights on the efficacy and environmental safety of these means of reproductive confinement.

The range of fish, shellfish, and plant species subject to biotechnological manipulation for aquaculture or fisheries management purposes is broad, as is the range of risk factors at issue. At the token 1% funding level, no more than one risk assessment grant likely will be supported per funding cycle in the aquatic sector. Given the high level of investment in research and development on aquatic GMOs, and the rapid march toward commercialization of certain aquatic GMOs, we cannot realistically expect that the knowledge base on risk assessment for aquatic GMOs will develop rapidly enough to support informed oversight.

3. Possible new directions:

Given the rapid development of agricultural biotechnology generally, and of aquatic biotechnology in particular, I suggest that the Program's request for proposals in coming funding cycles include the following areas for support:

Evaluation of the potential impacts of organisms expressing introduced genes remains a key area for continued risk assessment research. In the aquatic sector, the following areas of interest are particularly salient:

- Results of studies of transgenic fishes expressing introduced growth hormone genes have yielded varied results. Our understanding of the characteristics of the transgenic organisms or of the receiving ecosystem that give rise to these varied outcomes is quite incomplete. Given the development of many transgenic lines representing species as different as Atlantic salmon and red abalone, improved understanding of risk pathways is absolutely essential for informed oversight.

- Antifreeze polypeptide genes have been introduced into several aquaculture species, including Atlantic salmon, tilapia, carp, and giant prawn, experiments aimed at making possible the production of these species in cold waters where
production presently is precluded. The potential impacts of colonization of receiving ecosystems by escapees from such culture operations is not understood.

Culture of marine micro- and macroalgae is a major sector of aquaculture. Biotechnological manipulations have been practiced to increase yields of compounds of commercial interest. Commercial production of genetically modified marine algae is ongoing on a limited scale, although not to my knowledge in U.S. waters. However, at least one U.S. producer is considering production of genetically modified seaweeds. Hence, assessment of risks associated with production of genetically modified marine plants is a timely issue.

Induction of triploidy has been used as a means of achieving reproductive confinement of introduced aquatic organisms, and posed as a means of doing so for aquatic GMOs. Three issues posed by triploidy induction in aquatic organisms might be addressed in

Program-supported research:

- Reversion of triploids to diploidy. Surprising results of a study of triploid Pacific oysters raise the question of whether triploid individuals in at least some species can progressively revert to the diploid condition. Periodic inspection of triploid oysters set in trays in the York River, Virginia by Stan Allen (Rutgers University) and Roger Mann (College of William and Mary) revealed that 20% were mosaics apparently in the process of reverting to diploidy. This raises questions of how common or rare is this phenomenon, and of implications regarding use of triploidy as a means or reproductive confinement.

- Effect of triploids on population demographics. Use of sterile triploids reduces, but does not eliminate risks to wild populations of conspecifics. Even sterile organisms compete with conspecifics. For small natural populations, this could limit the number of potential fertile spawners, causing a population bottleneck. Male triploids of at least some species undergo steroidogeneses, produce functional spermatozoa, and may attempt to spawn, leading to loss of the resulting aneuploid broods. Key unanswered questions concern the reproductive behavior of triploids in the field and the potential impact of matings involving triploids on population dynamics.

- Improvement of triploid production and distribution systems.

Commercialization of certain triploid aquatic species, such as grass carp, has gone forward even though procedures for certifying the triploid status of lots in the sales and distribution pipeline have proven inadequate. This has resulted in stocking of fertile diploids, only to learn after the fact that a lot in question contained such diploids. Such episodes have been suggested as a factor contributing to grass carp colonizing certain river systems in the United States. This also suggests the development of a HACCP (Hazard Assessment Critical Control Point)-based analysis of how better to effect a triploidy certification program within existing
market channels. Such a system would provide a prototype for HACCP systems for other aquatic GMOs yet to be commercialized.

Beyond their narrow utility for risk assessment and risk management for aquatic GMOs, the Performance Standards for Safely Conducting Research with Genetically modified Fish and Shellfish (1) are widely regarded as a prototype for development of similar frameworks in other sectors of biotechnology. Sectors targeted for development of performance standards-type risk assessment/risk management frameworks might include genetically modified arthropods, microbes, or crop plants not of low enough concern that they are subject to only the requirement of notification before release.

Certain GMOs that pose limited, known risks may be suitable for outdoor experimentation or conditional commercial use if appropriate confinement measures are utilized, suggesting support for development and publication of targeted risk management frameworks.

Literature cited:


6. Agricultural Biotechnology Research Advisory Committee. 1995. Performance standards for safely conducting research with genetically modified fish and shellfish, parts I (Supporting text) and II (Flowcharts and accompanying worksheets). Documents 95-04 and 95-05. National Agricultural Library, Beltsville, MD.


A. Strengths and weaknesses of the scientific aspects of USDA's current Biotechnology Risk Assessment Research Grants Program, especially the nine objectives advertised in the Federal Register.

General strengths include:

a. The Program is competitive and peer-reviewed at the national level, as opposed to being in-house at USDA-ARS or administered semi-competitively at the Regional level. This at least opens up participation in the program and counters the stagnation that seems to set in for most programs in the latter two categories.

b. Some targeted areas in the annual Program Announcement are carefully chosen in such a way that they can support good science as well as providing new information genuinely relevant to risk assessment. The questions are clearly formulated and targeted to an existing component of the scientific community whose primary interest may not be risk assessment per se, but who scientific findings are needed to support informed decision-making, and who can be persuaded by the inducement of research funding to address these scientific issues at a higher priority than other, equally interesting ones. Such successful targeted area do exist in the current program but they are not common.

c. The Program can be an efficient way to direct resources to specific studies in an area where excellent proposals would not fare well in other funding agencies or panels because they are not trendy or fashionable enough. This presumes that there is already a critical mass of good researchers already producing excellent work in a related area, and that a bridge can be made between this successful area and a situation where there is an actual risk to worry about. Not all areas fulfill this criterion, and careful consideration must be given to their identification.

Weaknesses include the following:

a. There is a lack of a widely-accepted definition of risk that is relevant in the biotechnological arena, or even the outline of a standardized process of risk assessment that is relevant to more than one or two extremely specialized cases. This is the major problem with having a grants program in the area.

b. The mandatory annual conference for PIs funded by the program is a waste of time and money. I have attended several of these and they have always been the low point of the annual meeting circuit. Although there are several excellent participants and a few very good papers, there is not scientific cohesion. About a third of the participants are just starting on their funded project and have little more to present that an audiovisual version of their grant proposal. The level of interaction between meeting participants is the lowest I have seen at any regularly-scheduled scientific meeting. Although I was initially excited by the opportunity to meet and interact with US-EPA participants as well as PIs on the USDA-funded projects, I was quite disappointed in my expectations and did not need subsequent annual contact to remind me of this.
c. Related to the annual conference is the issue of publishing progress reports in the annual conference proceedings. This seems to serve no purpose but to increase the visibility of the program by the annual production of a publication. It overlooks the fact that none of these data will be relevant to the scientific community if they are not published in peer-reviewed journals. It compromises the PIs submission of data to these journals, many of which require that the material submitted for publication not be published elsewhere. It wastes the PIs time in preparing yet another manuscript for a book that will be almost universally ignored.

It burdens libraries with the annual acquisition of yet another book, that contains information that (if the Risk Assessment Grants Program is successful) should be rapidly superseded by articles in journals whose rising prices are also straining the library’s budget.

d. The program is administered separately from the largest and most successful competitive grants program in the USDA: the National Research Initiative Competitive Grants Program (NRI-CGP). After going through some significant growing pains, the NRI-CGP is now administered at a high quality comparable to the National Science Foundation’s competitive grants program. I can’t understand why the Biotechnology Risk Assessment Program has to reinvent the wheel. Perhaps it’s because in the past, the Risk Assessment Program has appeared to function as the fiefdom of an ambitious administrator intent on building his own power structure in the Department. While this may no longer be true, it seems wasteful not to take advantage of the expertise and existing organization in the NRI-CGP. The NRI-CGP should be given the responsibility for administering the Risk Assessment Program and the additional funds necessary to take it on.

e. In spite of some sensible research priorities whose advertisement in the Federal Register can attract some of the best researchers in the country to address issues relevant to risk assessment, the majority of these research priorities, and indeed the very process used to come up with them, don’t make very much sense. This process needs to be made more transparent, and the year-to-year output of it more consistent, if the program is to gain in credibility. If last year’s odd priority that made the list because of jockeying among the regulators is off this year’s list for the same reason, of what use is the one-year’s round of proposals that were actually funded in that area last year? The problem of the programmatic moving target only exacerbates the problem of the lack of definition of risk assessment I mentioned above.

Specific comments on Objectives

The Federal Register announcement lists nine points it identifies as “research topics.” In fact, the first three points listed are not research topics per se, but an attempt to describe the scope of the program. The last six points are research topics. Maybe a different nomenclature would be more accurate.

1. Development of new risk assessment methods and procedures that could be used in risk assessment ...

This seems to be a reasonable although vague statement of the overall scope of the program. It’s not too inspiring, because anything can be sold as a new method without substantially contributing to more scientific knowledge or actually making a
contribution to solving an existing problem. I would like to see a more concrete definition of risk and risk assessment as it pertains to this particular funding program.

2. Creation of information systems/computer models to support regulatory agency decision-making ...

Vague and meaningless except insofar as it imparts the impression that most regulatory agencies don’t know what they are doing. While this may be true, these agencies have the responsibility of coming up with these information systems and models themselves, or of providing direct extramural funding as needed if they can’t.

3. Risk assessment of environment fate as correlated with effects ...

The "fate-effects" jargon appears to be meaningless, and is not clarified by the examples given. These might be code words for something meaningful; if so that version should appear in the Federal Register.

4. Gene transfer between crops and weeds ...

This is a clearly-defined, coherent research area of direct relevance to several important risks, for example the risk that herbicide resistance genes could spread from crops to weeds. The is an Objective that can successfully draw promising proposals from a diverse and flourishing portion of the scientific community, which can result in new scientific findings that are interesting in their own right as well as being timely and applicable to a specific and clearly circumscribed biotechnology risk. The last statement of the objective inviting proposals to reanalyze published information is a bit odd and should be eliminated.

5. Recombination between viruses and plant-encoded virus genes ...

This Objective is just as coherent scientifically as Objective 4, but the nature of the biotechnological risk is less obvious. It should be stated.

6. Changes in viral host ranges ...

The statement of this point is a bit too broad to serve as a useful Objective. Its authors must certainly have some idea what sort of risks they have in mind, and it would be helpful to mention them here.

7. Non-target effects of transgenic plant-defense compounds ...

This is clearly stated and well circumscribed, just as Objective 4, although it appears to assume that persistence of engineered organism in the environment is inherently a risk. The use of Bacillus thuringiensis as an example of non-target effects overlooks the widely accepted view that the greatest risk associated with the delta-endotoxins is that their injudicious use will result in rapid insect resistance and hence loss of an otherwise low-risk strategy of pest control to higher-risk chemical alternatives.
8. Identification of genes conferring additional pathogenicity to animal pathogens.

Sounds like a fishing expedition here; what's the point? Our pathogens aren't pathogenic enough? This is like Objective 6. One suspects that it is code for something more specific, that should be spelled out here.

9. Environmental risk analysis of large-scale releases ...

Although this has an admirable sound to it, such projects are scarcely feasible with the restricted program budget.

B. Adequacy of current scientific knowledge about risk assessment

The definition of risk assessment — the meaning of risk, and the proper methodology of risk assessment — are not scientific issues. They are programmatic issues, and it is a misconception to believe that any number of scientific studies can compensate for a fuzziness of thinking in defining the scope of the program that funds them. There's no scientific basis in believing that the paradigm of risk assessment based on the analysis of failure of nuclear-powered generating plants is relevant to assessing the risk of creating and releasing transgenic organisms. But if might be a useful starting point, and I would like to see the USDA develop a short position paper on what risk assessment in the biotechnological arena should look like and how it would differ from the power-plant analogy. Respondents to the program solicitation would at least then have a common point of reference.

C. Possible new directions/criteria for decision-making in biotechnology risk assessment

Here are my recommendations:

1. The Program should come under the control of the USDA NRI-CGP.

2. It should devise and publish a clear statement of what is and is not to be included in risk and risk assessment as it pertains to biotechnology.

3. The process for determining research priorities should be opened up and it should provide more year-to-year constancy.

4. The annual meeting should be eliminated and the program funds devoted to it should be reallocated to funding more grants.

5. The publication of the annual volume should be eliminated, and PIs given every incentive to publish their findings in the peer-reviewed literature. Attention of the popular press to important articles could be directed by press release, much as the institutes at NIH do.

* * * * * * * * *
A. The nine objectives:

Although the nine listed objectives make sense in general, my experience (from having sat on the USDA panel that evaluates risk assessment proposals) and reading the literature is that the necessary work is not getting done. For that reason I will discuss each of the objectives and suggest refinements. There is a need for new risk assessment approaches and information pertaining to genetically engineered organisms.

1. Developing, evaluating, and implementing risk assessment approaches requires considerable quantitative sophistication -- and the necessary quantitative studies are not being encouraged. For instance, it would be extremely useful to conduct computer simulations comparing different monitoring programs as a way of asking if with sampling error and inherent biological variability, those programs could detect a spread of genes or exacerbated weediness before the problem became truly serious. Secondly, existing field trials and even commercial plantings are not being adequately drawn on as a source of data. It is a shame that no one designed a classic "before-and-after control and impact" (BACI) analysis of assorted Bt cotton fields from last summer with respect to soil chemistry and microbial communities.

2. I am skeptical of funds diverted towards information systems. The government should be managing the pertinent information in a simple way. The idea of computer models in support of decision-making is equally absurd (because something is computerized does not make it quantitatively sound). Decision-making requires an integration of costs, benefits, public concerns, and so forth. The science of risk assessment can lay out scenarios and the likelihoods of various events. But models directly aimed at making the decisions are naive and will not work. The proposals elicited by this targeted area were at best silly during the year I sat on the USDA peer review panel.

3. Risk assessment regarding the environmental fate of genes is obviously pertinent. But I am unclear as to how this item differs from item 1, except more detail is given? The mentioning of selection pressures stands out as distinctive, and the prospects of transgenes altering the outcome of natural selection and hence perhaps altering the attributes of a wild species that receive a transgene is something that should become a focus of activity. Because studies of evolution are so time-consuming, this is an area where work on model systems would be appropriate. Additionally, if one wanted to determine whether a transgene for Bt might make a weed more aggressive, it would be a good idea to experimentally simulate the transgene (without inserting it into the weed) -- for example spray applications of Bt might simulate the introgression of a Bt gene.
4. This should NOT be restricted to North American crops. Biotechnology is international, and restricting our studies to North American crops is analogous to restricting research on oil spills to North American oil spills, or research on HIV to HIV in North America. This is absurd. Indeed, if something disastrous were to happen as a result of genetically engineered rice in Vietnam, for example, it would have consequences for transgenic crops around the world. Research should be encouraged on crops that pose the most important risks, or that offer the best opportunities for new insight, regardless of the country in which those crops are grown. I would much rather see a good study on transgenic rice in southeast Asia (which could feed a billion people), than on transgenic sunflower seeds in Ohio.

5 and 6. both address extremely low-frequency events, which are going to be very hard to quantify (i.e. without huge confidence intervals).

A more useful approach would involve the design of monitoring schemes that could detect undesirable recombination events or host shifts in nature.

7. Studies regarding the impacts of Bt on the soil ecosystem are desperately needed -- but, the impacts will depend on soil properties, and therefore this effort should make sure impacts are evaluated in a wide variety of soil types.

8. I do not feel this is worth much effort -- of course, genes that enhance virulence exist -- but so what? I do not see where this research effort will lead us that is practically useful.

9. All risk analysis should be aimed at large-scale commercial use of transgenic organisms. Hence this effort does not need an extra item. I suppose the point here is that data from small, short-term field trials cannot address some concerns that emerge when we go ahead on commercialization. In that event, certainly we need to worry about those phenomena that emerge only after commercialization (such as the evolution of insect resistance to Bt endotoxins).

B. Adequacy of current expertise regarding risk assessment:

There certainly exists adequate expertise to either apply risk assessment, or to extend existing methods so that they better serve the biotechnology issues. Unfortunately, this expertise is not being attracted to the program. Indeed, the one time I sat on the panel evaluating risk assessment proposals, I was astounded at the horrible experimental design and statistics of several proposals that were funded. The argument made in favor of these ill-designed proposals was that the biology was truly worthy of attention, even though the experimental design was lacking. Hogwash. Interesting biology studied by inadequate statistics and experimental design is useless. Our risk assessment expertise is fine -- but familiarity of agricultural scientists with this expertise and approach is embarrassingly poor. One example will suffice. The heart of any environmental assessment is the BACI design - - yet, I do not think a single member of the peer review panel on which I served had ever heard of a BACI design. I have worked with epidemiologists and public health scientists --
and their expertise is routinely integrated into standard evaluations of the risks associated with various medical technologies -- this is the opposite of the situation in agriculture (perhaps because agriculture in its enthusiasm for production rarely pauses to think, "consequences"). Thus, some of the highest priority needs are not fundamental research, but education. To that end, in lieu of open-ended research grants -- much would be accomplished if prominent contributors to risk assessment were asked to produce handbooks of statistical and monitoring approaches for genetically engineered organisms. Also needed are similar handbooks from ecologists indicating the sorts of data that should be collected with field trails and commercial plantings (but rarely is collected). Frankly I think this could be done at modest cost, and assuming peer-review of the product, would be more valuable than a lot of the research currently being done. To put it bluntly -- we have plenty of risk assessment expertise, but the agricultural community is largely ignorant of this field and consequently seems incapable of mounting an appropriate research effort.

C. New directions for risk assessment?

Above, I insisted we already had a great deal of the needed risk assessment expertise. That is true for all but one question: how do we evaluate and monitor risks for a technology that is distributed over a huge spatial scale and that encounters in the process an enormous variety of environments and co-occurring organisms? Here is where basic research needs to be done. USDA should fund efforts aimed at comparing different largescale monitoring programs and quick field assessments that can cost-effectively examine risks at the scale of a continent. Computer models of different scenarios of disaster could be run at these large scales, and the monitoring programs could be applied to the data produced by these computer models to see if they successfully identify signals foreshadowing environmental disruption. This research will have value well beyond applications to genetically engineered crops, since the design of large-scale monitoring programs is central to much of environmental and conservation biology. However, all of this work cannot be computer simulation. Fieldwork must be done to quantify costs of monitoring programs and to collect hard data on the biological sources of variability and risk. For instance, if variability between regions dominates, then the key would be to monitor in different regions. Alternatively, if variability is greatest at the level of the field, monitoring programs would need to concentrate sampling within fields. An example of the type of practical recommendation that might result from sampling and computer simulation would be to collect a specific number of samples each from the vicinity of a particular number of fields from each ecoregion (as defined by the US Forest Service system developed by Bailey) in which a crop is grown.

D. A "bottom line" summary:

The current risk assessment research program in biotechnology is hampered by its innumeracy and avoidance of sophisticated quantitative approaches. Monitoring should be given greater emphasis -- especially the evaluation of alternative monitoring schemes (as opposed to focusing on one particular approach that may not be appropriate). The program must address transgenic crops internationally and not be so myopically restricted to North America. Much could be accomplished by contract work aimed at producing products, such as peer-reviewed handbooks, as opposed to random research wanderings. A major practical
and intellectual challenge is the comparison of alternative monitoring program for large-scale agriculture and rare events in a tremendously heterogeneous environment. Finally, the fact that this program has been funding proposals now for 3-4 years (maybe longer, I am not sure) yet has produced so little peer-reviewed results in high prestige journals is an indication that something is wrong. Either the wrong people are being funded, or the wrong projects are being funded. I think both "wrongs" apply. By now, PI's funded by this program should have produced a few papers in Nature or Science, and many papers in Ecological Applications, Conservation Biology, Molecular Ecology, and other widely-read journals. I have not seen these papers forthcoming and the influence of work funded by this program is at best negligible, and perhaps zero -- I am willing to wager that the science citation scores for PI papers funded by this program averages less than 5 per grant -- whereas a score of 50 per grant should be expected.
Comments on The USDA CSREES Biotechnology Risk Assessment Program

Strengths and weaknesses of current program

My area of interest is the molecular biology of viruses, and my own research involves several years of experience with viruses of plant and fish hosts. My "expertise" in biotechnology risk assessment is not due to any direct involvement via my own research, but rather to general knowledge of the field and participation in the USDA CSREES Biotechnology Risk Assessment Program as a reviewer on last year's panel. In the coming year I will be the panel manager for this program. Thus, many of my comments will be reflective of what I perceived as strengths and weaknesses of the program last spring.

Overall I was very positively impressed by both the breadth and quality of proposals submitted to the program, and by the quality of critical scientific review each proposal received during the panel meeting. A major strength of the current program is the diversity of biotechnology research areas being funded, involving each of the major taxonomic groups of importance to biotechnology (plants, vertebrate animals, insects, fungi, bacteria, viruses). The only imbalance at all discernible was a high number of proposals dealing with bacterial and viral biotechnology. This is to be expected due to the depth of background knowledge in these fields and the relative ease in generating significant data within a reasonable time frame with these organisms. Some emphasis on these systems is quite justifiable as they represent a high proportion of the biotechnological products facing release, and they may well function as more rapid and sensitive indicators of environmental risk than larger organisms.

Another major strength of the program is a healthy balance of relatively applied work with immediate practical value versus high quality basic science aimed at fundamental understanding of biotechnology risk issues. In my opinion both of these elements are essential and should be included in the overall program.

The only significant weakness I perceived in last year's program was some difficulty in maintaining the focus directly on risk assessment, rather than on more general work demonstrating and characterizing risk, attempting to reduce risk, or simply working in a biotechnological system that involved some risk. Nearly all of the proposals submitted last year involved some aspect of biotechnology risk, but there was a lack of a sufficient number of high quality proposals dealing directly with risk assessment. This lead to frequent discussion by the review panel of how to weigh excellence of the science versus direct relatedness to risk assessment in assigning overall priority ratings to several proposals. As the purpose of these funds is to provide tools and understanding to develop future management procedures, an attempt should be made to attract more proposals dealing directly with risk assessment. The program announcement should emphasize even more clearly that proposals should deal with assessment of risk rather than characterization or reduction of risk. Although this is already inherent in the wording throughout the program announcement, it seems that it needs to be more plainly stated, perhaps in the purpose or description sections.
With regard to the nine objectives outlined in the Federal Register announcement, the first three general points are very well written and thorough, and together accurately describe the broad goals of the program. Among the more specific research areas outlined in points 4-9, point 8 is particularly weak. As written it is not clear what value this point has to either basic science or to risk assessment, and I would recommend eliminating it altogether. The other points are all acceptable and give reasonable examples of the kind of research encouraged. These may be modified as suggestions of additional new areas of risk assessment are found to have merit.

Current scientific knowledge about risk assessment

Due to the early stage of risk assessment as a science there are several essential foundations which have not yet developed into a solid framework on which to build this field. As yet there is no generally accepted way of defining a level of "acceptable risk". It is clearly impossible to assure "absolutely no risk" in an untested situation, so if the potential benefits of any biotechnological research products are ever to be realized the definition of "acceptable risk" must be addressed. It is essential to establish some level of confidence that is judged to be necessary and sufficient to allow testing in ever larger scales, eventually leading to the release and use of products judged to be "safe". The need for this is a significant barrier to the field, but it is more of a conceptual and management issue than a scientific issue. The role of risk assessment science will be to support that conceptual decision with soundly based assessments of the risks involved.

Another general gap is our lack of knowledge about how mid-scale testing, such as greenhouse or small agricultural plot studies, will correlate with large scale tests and/or releases. This is already acknowledged in point 9 of the program announcement, but it remains largely unaddressed, probably due to restrictions of our capability to do large-scale tests. This is not inappropriate, as the results of smaller and mid-scale studies must be certain before large-scale tests should be performed, and the field is young. With time and the accumulation of more mid-scale data it will become more feasible to fill this gap. For now, it should remain one of the requested areas of research, as it is in point 9.

An aspect of the field which needs more attention is the incorporation of statistical analyses and hard mathematics in both the design of studies and in interpretation of results. This is already recognized, as evidenced by the paragraph after point 9 in the announcement, but several proposals were still noted to be weak in this respect. A more specific suggestion for an area of biotechnology that perhaps should be targeted as a research initiative involves the risk assessment of DNA vaccines. DNA vaccines is an expanding field of great potential for use in agricultural animals including mammals, birds, and fish. Proposals addressing the fate of the DNA vaccine molecules with regard to spread, replication, maintenance, and possible integration should be considered under this program.

New directions and criteria for decision-making

There is a need within the field to develop standardized protocols defining the parameters that need to be addressed in assessing the risk involved with each type of biotechnology product being considered. Although there are no formally accepted standards at present, several of the proposals funded last year will serve as examples of the breadth of studies
which must be done to assess risk within various types of products. For example, suppose a certain proposal carries out a broad, thorough assessment of various aspects of risk involved with use of a plant virus engineered to express a foreign gene as a vaccine. The results of those studies should eventually be combined with results of other studies assessing other plant viruses engineered to produce vaccines, to generate a guideline set of parameters which must be addressed when any plant virus engineered to produce a vaccine is being considered. In this way, the research in this program serves as models to develop standardized protocols as a management tool to assure that every biotechnology product is thoroughly and uniformly assessed. Proposals which provide complete thorough examples of assessment for each of the various biotechnology product types should be encouraged.
 COMMENTS ON USDA BIOTECHNOLOGY RISK ASSESSMENT RESEARCH GRANTS PROGRAM

It is a privilege and a pleasure to provide comments to the Life Sciences Research Office of FASEB on the Federal Register Announcement (Vol. 60, No. 175, Monday, September 11, 1995). Because my work is focused on genetically modified plants, I restrict my comments to this subject. As directed by your letter, I have tried to address the points in the nine objectives outlined in the Federal Register Announcement while including some ideas on areas of research which might be included under the Program Description. In addition, I have tried to provide comments that will aid in establishing a research program that will improve the overall knowledge and utility of genetic engineering as a means to improve agriculture.

The wording of the first area of research to be supported emphasizes the development of new risk assessment methods. By its wording, this area seems to exclude improvements made to existing methodology. One of the key challenges in developing improved plants through genetic modification is validation of the methods used to obtain field data. To date, much data and observations from modified crops have been collected from field tests and used to support nonregulated status of many crops. The methods used and conclusions of no significant environmental risk associate with these crops are frequently being challenged. To ensure that the highest quality science is behind each risk assessment, research focused to ensure the validity of these data and the conclusions derived should be supported. Thus, in addition to development of new risk assessment methods, proposals focused on validating existing methodology should be considered.

Regarding area #2 of research to be supported (Creation of information systems and computer models...), I would like to add some thoughts. This area should explicitly include supporting research with model systems using nongenetically modified organisms as described in the Program Description. One benefit would be that data from existing crops could be used as references to assess the accuracy of new computer models. Furthermore, researchers should be encouraged to use data currently available from crop breeding programs which have worked to develop traits such as improved quality, disease and pest resistance in the past. Analogies between introduction of these traits and many of the traits that will be introduced through genetic engineering are obvious. In addition, the USDA decision-making process would benefit from additional models based on the wealth of experience that exists with the development of crops improved through classical breeding. Research in assessing the actual impact of introduction of new traits (as evident from previous releases of improved crop varieties) should be supported as the basis for developing better models for the future. These results could also be used to support risk assessments and decision-making processes regarding crops derived through genetic engineering.

An area of research worthy of support which should be included in the fourth area mentioned in the Federal Register Announcement is mechanisms of broader dissemination of traits through gene transfer (i.e. bridging mechanisms). The true scope of gene transfer can only be fully assessed when all the potential bridges into more distantly related species of plants are understood. It is insufficient to simply assess the movement of a trait into an immediate relative, and ignore the potential for further movement. Research in the compatibility of distantly related species of plants (crop and weed) should be encouraged and supported.

I am a little concerned about the purpose of the 9th area of research to be supported. The risks of large scale releases should and could be addressed in the first two areas of research mentioned in the Announcement. While I support obtaining data from large scale field releases, mentioning this area of research as a separate topic may serve to debase the small scale studies that have been done, and unduly heighten the concern of large scale releases.

One area of research related to large scale field releases that would benefit USDA and Industry would be in resistance management. Having qualified scientists conduct resistance management on crops (e.g. Bt Cotton and Bt Corn) would reduce the burden on industry and provided valuable 3rd party information to the public. I feel that support for proposals to conduct pest resistance management studies should be considered under this program.

An additional area of research that should be considered for funding under this program is development of new techniques to assess the stability of the introduced gene and integrity of the insertion event. Currently, the USDA
requires that information on both of these concerns be included in a safety assessment. It would be consistent to support research in new techniques in PCR, molecular breeding and understanding plant transformation. Advances in these areas would give industry clearer direction as to the best techniques to be used for safety assessments. Furthermore, a clearer understanding as to how genes are inserted into chromosomes as well as more specific means of inserting genes would be an aid in assessing the safety of modified crops. One obvious example is the development of reliable chloroplast transformation. In this case, the trait would be maternally inherited which would mitigate issues related to gene transfer to weeds.

Lastly, I would like to comment on the issue of quality of data and the integrity of the results generated in this research program. We are reading much lately about cases where the reproducibility of data is in question as well as situations of outright fraud. Given the sensitivity of biotechnology risk assessment to the public and the need to ensure the safety of products derived through genetic engineering, research proposals should describe the quality control measures that will be used in conducting the research and analyzing the data. Program Directors could be encouraged to commit to conducting studies either compliant with or in agreement with spirit of the good laboratory practices (40 CFR 160). The aspect of ensuring the quality and integrity of any study funded through this program should be included into all proposals.

In closing, the program described in the Federal Register Announcement is well designed. It is an important part of developing a lead position in the United States in agricultural biotechnology which will be critical for maintaining our competitive position in agriculture. With high quality research proposals and well-executed experimental work in the area of risk assessment both the US public and industry will benefit.
Comments and Suggestions About the USDA Biotechnology Risk Assessment Research Grants Program

Overall, the topics to be considered for support in the 1996 Biotechnology Risk Assessment Research Grants Program cover the areas generally considered to be pertinent to risk assessment. The first three, as well as the ninth, areas are very broadly defined, whereas the other five are rather specifically delineated.

It is my opinion that since this program has been in existence for several years now, those involved in administering the Program should have developed a sense of specific needs that should be targeted and to have adjusted the objectives of the Program accordingly. Involvement in the peer panel review process and attendance at the annual conference at which funded investigators present their data should certainly put them in a position to do so. As a measure of the extent to which the targets have been adjusted, I have compared the program descriptions and areas of research to be supported in the 1996 program with those in the 1994 and 1995 programs.

The program description for 1996 has been expanded to encourage proposals based on field research as well as whole organism-population level studies. The description has also been amended to stress the need for proposals to be applicable to current regulatory issues surrounding the ecological impacts of genetically modified organisms. The first of these expansions delineates specific areas of interest while the second stresses applicability. These modifications indicate that the administrators of the Program are recognizing and addressing the need for evolution of the Program in response to changing needs.

In contrast, the descriptions of research areas 1-3 have remained unchanged over the three year period. Whether this reflects a lack of or a surplus of proposals in these areas is not apparent. However, it seems that there might be a better response to the solicitation if the descriptions were more focused. In the early days of the Program such broadly defined topics were probably needed and perhaps they still are needed today, but the administrators need to give some thought to whether they need to better define the types of research the feel are needed.

Research area four involves the specific topic of gene transfer between transformable crop species and weedy relatives. This is a topic of considerable interest to ecologists and is prominently featured in the document Perils Among the Promise. The announcement for the 1995 Program listed species specifically of interest to APHIS, whereas the 1996 Program does not. APHIS is presumably in a position to know the crops that have already been transformed and for which data might therefore be needed sooner than for other crops. It would seem that this is an area in which species-specific data rather than model system data are needed. I believe that priorities for the species to be studied should be set when possible, with input not only from outside agencies but also from within the program itself.

Research area five deals with another “hot topic”, that of recombination between plant viruses and plant-encoded viral genes. The emphasis on viruses in “super group B” has been unchanged over the three year period. The emphasis on luteoviruses is understandable, as this family contains what are arguably the most important plant viral pathogens, and transformation of important crops (potatoes, cereals) has been accomplished. However, the other families mentioned contain viruses which are not important pathogens, except perhaps in rare cases, and hence are not likely to attract commercial development and/or
widespread development. On the other hand, viruses in, for example, the cucumovirus and potyvirus families are widespread and damaging. A number of crops have already been transformed with genes from these viruses. Perhaps consideration should be given to redirecting the emphases to these and/or other more relevant viruses. The 1996 version does additionally encourages comparison with recombination frequencies between “naturally occurring viral sequences”. This is a highly desirable addition which should also be targeted to the viruses most likely to be the source of genes for plant transformation.

Research area six is related to area five and addresses the potential for changes in viral host ranges or viral vectors as a result of the expression of viral genes in transgenic plants. This is an important area, particularly with the recognition of the pleiotropic effects of viral genes. The information concerning this area has not changed over the three year period. Once again, perhaps solicitations based upon the criteria discussed above for area five should be considered.

The description for research area seven has not been changed over the three year period, and the comments made in the second paragraph of this assessment apply here. Perhaps some fine tuning is in order.

Research area eight is about as vague and unfocused as possible: any gene, any pathogen, any animal. At least the previous version identified organisms of interest to APHIS, again presumably because these pathogens are currently being engineered for vaccine production or other uses. There seems to be less outside input into potential risks in animal systems as opposed to plant systems. Considerable thought needs to be given to what types of research proposals are needed in this area.

Research area nine was introduced in the solicitation for the 1995 Program. It would have helped my understanding if a “for example” was provided, but perhaps the originators were leaving it to the applicants to make the case. If so, hopefully these have been submissions that may help the Program administrators to phrase the statement in such a way as to be able to hone in on the subject.

In summary, the Program does address the aspects of risk assessment for which information is needed. In some areas specific systems have been identified, and in some cases these specific research needs have been adjusted as information flows into the system. In other areas the needs are only very broadly defined. In my opinion the objectives and goals of this program should differ from those competitive grant programs designed to fund basic research. The solicitations for the latter programs are, rightfully, broadly couched. The Risk Assessment Program on the other hand should attempt to clearly define the areas in which research is needed and then let scientists design the experiments to obtain the needed information. Since the Program has already funded, investigators on various aspects of risk assessment for several years perhaps it could use them as a base of expertise to better define the research needed in these areas. This would allow the Program administrators to play a more proactive role as opposed to relying primarily on input from outside sources.
Evaluation of the USDA CSREES Biotechnology Risk Assessment Research Grants Program

Thank you for contacting me for the evaluation of the USDA CSREES Biotechnology Risk Assessment Research Grants Program. As director of two biotechnology programs that serve the entire University of California system and that promote research in agricultural biotechnology, as well as other fields, I am both aware of the needs for research funding and critical opportunities. It is from within that experience that I offer comments on the Risk Assessment Research Grants Program.

At the outset, it bears emphasis that assessment of any competitive grant program requires substantially more information than was provided. The Federal Register solicitation, alone, provides little or no perspective on the actual operation and impact of the grants program. At best, it presents a limited view only of what the program is intended to address. If you truly wish to assess the program, I and other reviewers must be provided with additional information, minimally including the following:

1. a complete list of funded projects (including investigator names, project titles, abstracts, and statement of aims, award amount and award period);
2. a complete list of unfunded proposals (including similar information);
3. a description of both the criteria and the guidance provided to reviewers on applying those criteria in evaluating proposals and making recommendations on funding;
4. a description of the expertise of reviewers participating in the peer review process;
5. a summary of the governance structure of the program;
6. a summary of the agency's future plans for the direction of the program.

With this information, I would be pleased to address your request (item 1 of your letter) to evaluate the program with respect to its scientific aspects. As I am sure you can appreciate, the scientific merit of the program is intimately related to the scientific and technical integrity of the funded projects and the review process.

The comments provided below reflect solely on the solicitation. As described there, the goal of supporting risk assessment is disconnected from the criterion for scientific merit. To be scientifically meritorious, risk assessment research should emphasize serious gaps in scientific knowledge, present innovative experimental approaches to addressing the central problems causing those gaps, and describe a rigorous methodological and analytical plan through which to develop new information. The solicitation makes none of those points within the context of the program's nine principal research objectives. In fact, as discussed below, several of these principal research objectives focus on "problems" of limited scientific or practical interest. It may be that they are included to serve a "regulatory" interest of the agency. If so, that should be explicitly stated and the program should not be represented as being driven by scientific merit.

A scientifically meritorious program should also be evaluated within the context of the spectrum of pressing, scientifically important research needs and available funding. Viewed from within that context, the research objectives defined in the solicitation are of significantly lower quality and importance compared to those addressed in the larger competitive grant program at USDA from which funding for the risk assessment program was set aside. A clear disadvantage of the approach taken.
in the solicitation is that the quality of grants funded on the margin of such a program may not be (and likely is not) at the level characteristic of grants funded under more general categories of research where competition is stronger and scientific merit given greater emphasis. This problem can be easily remedied by simply integrating the agency's goal of supporting risk assessment research into the larger, competitive grant program. For example, risk assessment of RNA-RNA recombination addressed in objective #5 could be incorporated into research on plant viruses in general, which would result in the widest possible exploration of systems in which recombination might occur. The benefit of such a plan is to accomplish risk-related research in a much greater variety of systems in research subjected to rigorous evaluation as a whole. Special emphasis can be placed on the desire of the agency to support such projects. It has been my experience in running competitive grant programs in biotechnology for more than 11 years, that this approach will attract stronger proposals that are likely to provide greater impact.

Returning to the nine objectives defined in the solicitation, the program's expectations on outcomes and scientific utility should be made explicit in the specific context of each objective. For example, proposed research should focus on risks that are not likely to be readily identified and managed by standard breeding, farming, and regulatory practices routinely applied to small or large scale field uses of organisms. The program should also emphasize that all research in biotechnology risk assessment is expected to define anticipated outcomes, scientifically grounded in an appreciation of the background level of events, such as RNA-RNA recombination, that are already operative in the environment and in agricultural systems in the absence of genetic engineering.

Setting priorities for research objectives to be supported through the risk assessment program should be undertaken in a manner that acknowledges the relative importance of other factors that affect the biosphere. For example, there is great value in pursuing biological controls for pest problems and there are many success stories. Unfortunately, the economic return on biocontrol research is slow and private sector interest is low. Placing emphasis on modest risks or risks that can be managed through standard practices will likely further discourage both basic scientists and commercial interest in pursuing needed fundamental research and subsequent product development. The need for scientific rigor and "good sense" in addressing "emerging" biotechnology risks is illustrated by a recent report of a biotechnology "risk." A recent study of field tests of Bt cotton (Science, 273:423, 1996) demonstrated that 99% of a 20 million acre experimental crop exhibited very good pest resistance, allowing for a decrease in chemical pesticide usage. The benefits of the trial included lower cost to the farmer and reduced inputs to the environment. Some observers interpreted the report's finding of any population of resistant insects as an indication of substantial risk.

In relation to objective #4, the potential for exchange of genetic material is not, itself, sufficient rationale for funding a risk assessment project. Corn and wheat are major crops of interest for genetic engineering. There are few species capable of crossbreeding with them in the United States. Moreover, it is highly unlikely that such domesticated species would ever revert to a wild or weedy state, although absolute certainty would require long-term study. Looked at in another way, it is highly unlikely that the kinds of transgenes widely used in research, today, would provide a selective advantage to wild relatives living nearby sexually compatible crop plants (Science, 274:180-181, 1996). Moreover, while there is potential for crops, such as radish, to transfer genetic material to weedy neighbors, these plants are generally not emphasized in current research efforts and potential outcrossing problems can and have been routinely controlled by growers through buffer zones and other field design strategies.

The issue of genetic exchange has been fully settled by the National Academy of Sciences (1987), the National Research Council (1989), and hundreds of risk assessment projects undertaken in response to USDA and other regulatory requirements, worldwide. As the 1989 NRC report emphasized,
problems with contamination of new variants by other crops is not a new concern. Gene flow is routinely managed by plant breeders and commercial seed companies using standard plant breeding practices. There is, therefore, no broad support for the kinds of research called for under objective #4.

Objective #5 has similarly been amply addressed. It is well established that RNA-RNA recombination can occur between transgenically-expressed RNA and related RNA of an infecting plant virus. The rate of such recombination presumably is within a order of magnitude or two of the rate for recombination between RNA's of different infecting viruses in order for the events to have been observed. The rate will be highly dependent on characteristics of the specific construction and circumstances. The occurrence of transgenic RNA-virus RNA recombination is a given and cannot be prevented under field conditions.

The important questions are: what will be the outcome of such a recombination and will the outcome be significant when viewed against the background of naturally-occurring recombination in plants infected with two or more viruses? In addition, are the recombination events significant in the environmental context and what is the risk compared to the potential benefit? Most recombinants can be expected to be less virulent than either of the parental viruses, based on the properties of the bulk of the recombinant viruses produced in the laboratory to date.

The possibility cannot be excluded that virulent viruses will arise from recombination between transgenic RNA and viral RNA in an infected plant. However, recombinants of all kinds result from very rare events. Changing agricultural practices and modification of natural environments can be expected to bring existing viruses into contact with new potential hosts (as they always have) and provide new opportunities for recombination in dual and multiple virus infections. No planned experiment is likely to provide guidance as to the likelihood of significant effects from the transgenic expression of a virally-derived RNA molecule in the context of background recombination events.

As to objective #6, the risk of transcapsidation is extremely low and not worthy of attention. The arguments provided for objective #5 apply even more strongly here. It is even less likely that RNA-RNA recombination would present a risk to agriculture or the environment.

As addressed in objective #9, natural hybridization is always a possibility with full-scale release of any organism. Crossbreeding is not a unique risk in the context our 100-year history in academic and professional plant breeding. In fact, exchanging genetic material by sexual hybridization is subject to a much greater degree of randomness than with genetic engineering. Crossbreeding risks cannot be specially ascribed to genetically engineered organisms. If such risks are of concern to USDA, they would be better addressed in the broader and historically effective context of plant breeding standards. For example, breeding for pest resistance via hybridization or mutational techniques has not demonstrated increased risk to humans, livestock, nor the environment. Viewed this way, there is no scientific justification for evaluating genetically engineered organisms outside of the context of conventional farming.

I recommend that future planning for the risk assessment program include analysis of the report (enclosed), "Appropriate Oversight for Plants with Inherited Traits for Resistance to Pests," by 11 scientific societies. It addresses issues concerning the risks of agricultural biotechnology in a scientifically and historically rational manner. I particularly endorse their finding that, in considering biotechnology risks, "the focus must be on high-probability risk rather than hypothetical or unrecognizable risk."
Although I do not have information on the peer review process, I offer the recommendation that all proposals be reviewed by experts with experience in academic or commercial plant breeding. This simple step will help to ensure that funding not be wasted on research projects that address risks that are already well managed or could be well managed by standard research and plant breeding practices.
Critique of USDA CSREES
Biotechnology Risk Assessment Research Grants Program

As outlined in the Federal Register (60 (No. 175):47236-47238), this program is
designed to provide input to Federal regulatory agencies to aid their risk assessment
activities. This program appears to be an excellent mechanism for obtaining science-
based information. What is not clear to me is how the information is used other than
after it appears in publications that contribute to the general body of knowledge; I did
note the annual conference and annual risk assessment symposia, which I have learned
are structured so that they are exceedingly costly. Perhaps this is an area for study, i.e.
how Federal regulatory agencies obtain scientific information to develop policy, and how
this might be improved, specifically for risk assessment or more generally.

Under the heading "Applicant Eligibility," it might be useful to state specifically
that Federal agencies also are eligible. The "Program Description" and "Proposal
Evaluation" sections of the Solicitation are well done.

The main focus of this critique is directed to the nine items under "Areas of
Research to be Supported." I will start with a few general comments. Animal research,
perhaps appropriately, appears to be under represented, although several of the nine
items do include animals. However, only item No. 8 is specific to animals, whereas
several items are specific to plants. Also, the second paragraph under Research Topic 3 is
difficult to interpret. It probably doesn't belong under that topic. It implies that Topics 4
through 9 are subsets of Topics 1 through 3, and are the real topics being solicited. This
should be clarified.


This topic is of great importance, and wording is clear, although a bit redundant.

Research Topic 2. Creation of information systems and computer models.

Information systems and computer models are two very different areas of
endeavor. Both are important and both use computers. I question the wisdom of
creating new information systems, and suggest emphasis instead be placed on
using or improving existing information systems for biotechnology risk assessment
purposes.


This topic also is of extreme interest and importance and the description is clear.

This is clearly an important area for research, and the intent is clear from the wording.

Research Topic 5. Recombination of plant and virus genes.

This is a fairly specific topic of both theoretical and practical importance. In fact it is so important and obvious that I suspect there already are numerous research projects funded and in progress through USDA National Research Initiative grants and NSF supported research. In other words, this basic biology area may be less appropriate for funding in a risk assessment context than some of the other areas, which are less likely to be included in other programs. If Supergroup B virus genes (or some other subset) are being neglected in this context, perhaps this is the right program for such funding after all.

Research Topic 6. Changes in viral host ranges in transgenic plants.

The wording of this topic is somewhat ambiguous. What is meant by “types of viral vectors”? Is it changes in types of vectors? Intent is not clear. The general area of research is important.

Research Topic 7. Potential nontarget effects of introduced plant-defense compounds.

This is a specific, important area for research in the context of risk assessment, and intent is clear.

Research Topic 8. Identification of genes that increase pathogenicity of pathogens.

It is unclear if genes of the host or the pathogen are of interest. If the former, it might be clearer to use wording such as “increased susceptibility to pathogens.” Perhaps an example would increase clarity.


This also is an area of interest and importance, and the intent is clear.

Other Potential Research Topics

1. Problems in assessing Type 1 statistical error probabilities. For example, type I errors only apply to the specific hypotheses being tested, and a spectrum of hypotheses may be of interest. Perhaps covariance structure among variables may be worth studying
in the context of risk assessment, especially when very low probabilities of error are of interest.

2. It seems to me that field trials are a very robust method of risk assessment. The methodology of field trials (e.g. simultaneously in various environments, large scale for short times, small scale for long times, etc.) might profit from both empirical and theoretical study in risk assessment contexts. Also, should third party replication of some field trials be incorporated into some risk assessment work?

Possible New Directions for Decision-Making in Biotechnology Risk Assessment

A serious conundrum is that evaluations of risks from a scientific perspective (for example, probabilities of death) often are at variance with evaluations of risks from personal perspectives (for example, fear of agents that cannot be seen or are not understood). This often translates into political realities, such that resources are used inappropriately from a scientific perspective. Both because of political reality and because it is an interesting problem, perhaps this conundrum should be considered systematically in the context of biotechnology risk assessment. For example, how might this affect which studies are undertaken and how decisions are made after scientific information has been generated. It is unclear to me if the sociology and psychology fields, for example, already address this situation in a useful way, or if an entirely new field of endeavor is required. The problem will not go away.

Other Comments

It might be appropriate to state that 8-12 proposals have been funded most years.

An outcomes assessment analysis might be warranted. The present study may already have this as a component. Examples of information of interest would be: numbers and topics of proposals funded, numbers and topics of journal articles published as a result of this program, documentation of other information communicated, and who uses the information generated by this program.

I strongly encourage use of a pre-proposal mechanism for soliciting proposals. This would be a great time saver for scientists. I suggest a 3-page maximum pre-proposal including the budget. Program managers plus several outside reviewers could then eliminate those proposals with inappropriate subject matter, and those with pedantic ideas or from noncompetitive programs, with the aim of obtaining full proposals from about twice the number of applicants that eventually will be funded (~50% funding rate). Decisions as to who will be invited to submit full proposals should be made within 2 weeks of deadlines for receiving pre-proposals. Full proposals should then be due 60 days later.

The categorical exclusions are listed under the NEPA compliance heading. Is this accurate? Are all of these NEPA-related? The categorical exclusions are good in that they direct the efforts of scientists away from inappropriate proposal subject matter.
There is, however, some confusion because in later paragraphs it is implied that excluded projects can be considered after all. This needs clarification.

A final comment: My nitpicking at details should not obfuscate broader aspects of this program. As stated earlier, the mechanism in place is excellent for obtaining sound information for this program if the program is being implemented effectively. Possibly it would be advantageous to subcontract proposal evaluation to the National Research Initiative Competitive Grants Program. In any case, good information likely is being generated. The major concern may, however, be the effectiveness of mechanisms in place to use the information efficiently and effectively.
1. New Risk Assessment Methods

New risk assessment methods should emphasize both the species that has been genetically engineered and the origin and function of the gene introduced into the agricultural species. Risk assessment methods determined by (a) scale of tests, (b) reproductive system, and (c) function of the transgene should be evaluated. The scale of proposed tests should be the first measure of risk. Small-scale tests of less than 1 ha, especially under conditions in which the plant species is isolated from other commercial or weedy plantings by spatial, seasonal, or physical barriers pose little risk and should be allowed to progress with little interference. Risk is minimal in these circumstances. Increased scale testing requires more careful examination of risk factors imposed by the species and the transgene under test. The reproductive system of the transgenic plant implies different probabilities of risk. Self-pollinated species with low levels of outcrossing are inherently of less risk than those that are cross-pollinated and which have either wind or insect pollination. Thus, soybeans should have a different level of risk compared to sunflower or sorghum. Lastly, the gene being tested is a major determinant of risk. The level of risk depends on both the origin and gene product of the transgene. An endogenous gene originating in the same species, and tested in either an up- or down-regulated fashion poses very little risk. However, a gene originating in a divergent species which produces a protein potentially toxic to humans has a high potential risk and should be considered much more conservatively.

A gene for insect resistance might include measurements of acquiring resistance among artificially reared insect colonies as one measure of risk assessment. Monitoring risk should include measuring transgene transfer within adjacent same-species borders, and should employ use of high throughput molecular marker technology to sample larger numbers of progeny from border plants.

2. Information Systems and Models


Databases and models which characterize gene flow between domesticated and wild species could predict gene flow of transgenes as the scale of use increases. Further, such studies using newer molecular tools should be supported by public research in major crop species in advance of consideration of transgenes in those crops.

Similar arguments can be made for genetically engineered bacteria, viruses, and microorganisms.
3. **Risk Assessment**

The standards mentioned under Question 1 can be considered in this context as well. The nature of the gene may be of primary importance. Consideration in early testing should focus on primary importance. Consideration in early testing should focus on gene function per se and its context or existence in any heterologous species. Larger scale testing (see below) should focus on the assumption of risk if the gene under question is transferred to cultivated or weedy relatives. Risk assessment and bidirectional flow (see below) are very important areas for consideration of eligible topics for research in the coming year. Gene flow of transgenes, especially for marker genes of minimal impact to the environment, and of molecular markers in which fitness is neutral, between cultivated and weedy relatives should be investigated. Such studies could then be used to evaluate risk assessment of transgenes which have positive impact in domesticated applications.

Risk assessment of species in which bidirectional gene flow is likely will need a different standard of assessment. For example, in species in which gene flow between domesticated and weedy relatives is common, the transgene under test would need to be evaluated in the context of assuming that the transgene will migrate into domestic and weedy relatives as the scale of testing and use increases. Thus, the impact of the transgene should be evaluated on the basis of its fitness in weedy relatives.

The risk assessment of insect and/or disease resistance transgenes should be evaluated based on comparison of fitness of other genes that may occur naturally. The studies of disease and insect resistance genes in wild species of barley, wheat, and other cereals in natural ecotypes could be used to infer fate of transgenes under similar situations. Genes such as herbicide resistance can be assessed based on probabilities of herbicide resistance occurring as mutations, and availability of other herbicide chemistries to control either domesticated or weedy relatives.

4. **Bidirectional Gene Flow**

The existing data on gene flow between domesticated species (see above) will be very useful in assessing probabilities of gene flow of transgenes, and in considering the risk assessment of transgenes. Species in which outcrossing is very likely, and in which pollen is carried by wind or insects, require more data on bidirectional gene flow. Thus, sorghum and sunflower need to have more information (see 2 above) than tomatoes or soybean which are much less likely to "escape" into domesticated or weedy relatives. Common agronomic practices may mitigate bidirectional gene flow. For example, alfalfa management outside seed production areas minimize bidirectional gene flow. Studies on management practices, including use of herbicides and tillage practices, should be encouraged in species such as sorghum and sunflower in which weedy relatives are likely both in cultivated fields and in adjoining noncultivated areas.

5. **Recombination between Plant Viruses and Plant-Encoded Genes**

Risk in this area seems to be low. However, studies should be encouraged which characterize the underlying mechanisms by which recombination of viral proteins, including the replicases, occur in nature. The gemini viruses which attack tomatoes and peppers in Mexico and the Middle East offer an attractive model system in which to investigate the probability of such
recombination. Further, the deployment of defective replicases in plants would appear to minimize the probabilities of recombination between plants and viral species.

6.

7. No comment

8. No comment

9. Large-scale Deployment Risks

Large-scale risks for transgene deployment include (a) the probability that gene or genes will be transmitted to domesticated and weedy relatives, (b) modification of insect and disease patterns in cultivated species, (c) relative abundance of alternative sources of same-function transgenes, and (d) relative abundance of nontransgenic alternatives.

Large-scale risk assessment should assume both the probability that the gene will migrate into domestic and weedy relatives and, secondly, impact when the gene or genes are transmitted to domestic and weedy relatives (see above). The function of the gene can then be considered as the primary criterion of risk assessment. A gene that modifies seed oil characteristics will likely have different impact on weedy and domestic relatives than herbicide resistance, insect resistance, male sterility, or disease resistance. Large-scale deployment of single transgene resistance to a single insect or disease pest will alter the occurrence of other disease and/or insect pathogens that occur. Market penetration may change the pattern of diseases or insects if safeguards are not taken. Normally, competition in the marketplace is the preferred safeguard since alternative sources of resistance, both transgenic and nontransgenic, will arise for the most significant insect pests. Consideration should be given to evaluation of source of transgenes AND the genetic background of the plants in which the transgene is deployed. Genetic variation for both factors will minimize risk of new insect and/or disease pest becoming dominant, and also minimize development of resistance a transgene (i.e., bt loss of effectiveness).

Consideration might also be given to determining how long negative effects might persist once a transgene is not longer used commercially. Would transgenes that have migrated into domesticated and weedy relatives disappear rapidly after large-scale use is curtailed?

The use of appropriate statistical models, experimental designs, and use of appropriate statistical consultants are very important criterion that should be used to evaluate all proposals. Appropriate statistical treatment of data will be necessary to predict the impact of one study for similar transgenes or species.

* * * * * * * * *

3
LSRO-USDA CSREES BIOTECHNOLOGY RISK ASSESSMENT
RESEARCH GRANTS PROGRAM

1. Generally, I found the scientific aspects of the USDA's current biotechnology risk assessment program to be quite comprehensive and appropriate, given the state of knowledge that we have. The only potential omission is in item 2, which deals with the creation of information systems and computer models. It would have been helpful to indicate that identification of deficiencies should be considered as appropriate as well. While it would be desirable to have such systems and models in place, my knowledge would suggest that a major impediment is the lack of knowledge and also the lack of access to proprietary data that may impinge on potential impacts to the environment. It is not clear whether CSREES can access information given to APHIS as part of its oversight activities, that might be extremely helpful to the whole question of environmental impacts of genetically-modified organisms.

2. The adequacy of current scientific knowledge about risk assessment is limited due to its relatively new time frame in the environment, i.e. about a decade in the field. The following are potential gaps in knowledge and possible areas for consideration:

A. The effects of synthetic sequences not known to exist in nature.

Do these represent safer or more questionable additions or substitutions with respect to non-target organisms and the environment? For example, biologically active peptides are being made that are not known to exist in nature, yet have potential biological activity for humans (beneficial) and insects (detrimental). Is there sufficient information to make such assessments, or must such information yet be generated?

B. Are nucleotide substitutions in proposed added genes safer or not, irrespective of efficacy?

Substitutions are being made to increase shelf life, efficacy versus target organisms, and stability within a plant. What is the safety assessment of the substitutions versus the naturally-occurring nucleotides?

C. In aquatic systems, including fish and shellfish, are genetic modifications safer than stock manipulation?

I understand that there are concerns in the aquatic community with the artificial manipulation of wild-type stocks that has raised some concerns about behavior, survival and competition, irrespective of genetic manipulation. When a concern is expressed about genetic manipulation, it would be prudent to have
as a counterpoint what is being done in current captive fisheries practices, including shellfish.

D. **What is the risk assessment relative to ornamentals produced to provide new or unusual color or shape combinations?**

That is, are color and shape variants produced by genetic engineering as safe as those generated by breeding? This question could be phrased in terms of the assessment for the attraction or repulsion of microorganisms, insects/arthropods, longevity, gene transfer, etc. Ostensibly, such modifications are safer and are more acceptable to the public. However, data are meager, at least in my view.

E. **Microbe marker genes in plants.**

There is a current controversy over marker genes carrying antibiotic resistance in plants. Antibiotic resistance genes are still a convenient and cheap marker and may be safer than other markers. Thus, risk assessment may need to evaluate the evidence of transfer to microbes, other plants, and animals over what has been reported to date. If there is no evidence to support such transfer, nevertheless a project that may provide negative data should still be considered so that the results will be publicly reported. Industry should be eligible, if industry agrees to publish the results. Such results may have already been reported to APHIS and may be accessible for analysis through mutual agreement or, if necessary, FOIA.

F. **The environmental effects of new pharmaceuticals produced in plants.**

Some new pharmaceuticals may have potent biological activity against non-target organisms, e.g. birds and mammals. Thus, in the environmental effects including the effects on non-target organisms normally would include microorganisms of plants and soils; birds and mammals should be considered as well. In this regard, there are some pharmaceuticals I would not have very much concern about, e.g. vaccines (some tests presumably are done already with such materials). However, compounds that might be potent cardiac glycosides or other compounds could be a different story. Both consumption and residue problems should be addressed.

G. **Long-term studies.**

Even though it is difficult, the agency may be able to convince Congress that a few long-term studies are necessary for such types of plants as trees. That is, it would seem that up to ten years may be necessary to assess the risks of modifications as compared to conventional breeding, for trees.
H. **Natural Disasters.**

The spread of genetically-engineered organisms in natural disasters has been neglected. Yet, floods, earthquakes, and hurricanes can spread such microorganisms, plants, and even some animals over short and long distances. What effects might accrue from such natural spread? Such research or model systems might be done using non-genetically modified organisms, to assess the likelihood and real dangers of such spread.

I. **Specific spread and survival of the genetically-engineered weed, Arabidopsis, in a multi-year study.**

Arabidopsis is a model system, which can be grown in small areas, hundreds of mutants are available, and it can be killed with herbicides. Presumably, a great deal of information could be discerned in a short period of time.

3. Other agencies should have an interest in risk assessment of genetically-modified organisms. Perhaps cooperative agreements with or MOUs with NOAA, EPA, FDA, the Department of Commerce, as well as USDA-APHIS would further the risk assessment evaluations of genetically-modified organisms that are of interest not only to agriculture.
REPORT ON THE USDA BIOTECHNOLOGY RISK ASSESSMENT GRANTS PROGRAM

First, in order to assess the Program to date, I have examined the awards given in its first five years, assigning them as far as I am able, to the 9 categories in the Federal Register. Except for those awarded in 1996, I did this from the titles only, as the grants were not available to me; thus, I could have classified them incorrectly.

1. Development of new methodologies, no awards.
2. Information systems and modeling, one award.
3. Fate of genetically modified organisms in the environment. Plants 6; Bacteria 6, Fish 3; Baculoviruses 4; Insects 1; Nematodes 1.
4. Gene flow in plants, 8 awards.
5. Recombination between plant viruses and transgenes, 9 awards.
6. Changes in plant viral host ranges, one award.
7. Potential for non-target effects of plant defense compounds, 3 awards.
8. Identification of genes which can confer additional pathogenicity to animal pathogens, no awards.
9. Environmental risk analysis of large-scale deployment of genetically engineered organisms, no awards.

In addition, there are 6 proposals which do not seem to fall within the 9 categories. One on viroids, one on viral synergism, one on spread of insect resistance, and three doing work with vaccines.

I feel best qualified to address issues related to plants when appraising the Biotechnology Risk Assessment Grants Program. I am a plant scientist, engaged in work in which I have produced transgenic plants resistant to viruses, and I teach a class dealing with plant biotechnology. Topics include risk and safety issues. Additionally, although I do not work in risk assessment per se, I was chosen as Panel manager of the 1996 Grants Program.

First, I wish to address issues relating to plant viruses, my own specialty. The Federal Register notice has indicated that there are several ideas of concern to which proposals may be addressed. Those who suggest potential risk in the plant virus field have raised a number of issues. The principal proponents for more risk assessment have been Rissler and Mellon, in their publication "The Ecological Risks of Engineered Crops." For plant viruses they feel we need more research to address the possibility that new viral strains may arise, viral host
ranges may be broadened, viral diseases may be made more severe, and that weed species may be made virus resistant.

The Program has made awards which address these issues, in particular dealing with recombination and host range. It is conceded by all that recombination between a virus and a transgene can occur, but the main consideration is whether the outcome is bad. To date, there has been no suggestion that new, and more deleterious strains or viruses have arisen. The same argument can be made with respect to the broadening of the host range. I feel that the only grants which should be considered in the plant virus area in the future should deal with large-scale field trials to see if there is credence to the genesis of bad viruses or expanded host ranges. This may well be done for us by the entry of virus-resistant plants into commerce. The experiences of Asgrow with virus-resistant squash, and Monsanto with virus-resistant potato could serve this purpose.

The same arguments could be made for gene flow experiments, between plans and between microorganisms. In plants, it has been shown that it is possible for genes to flow between transgenes and other species. The question now is what are the consequences? Are we seeing problems? Are movements from transgenic plants more of a problem than from non-transgenics? Once again, we are at the stage where only field experiments on a significant scale will be appropriate to answer these concerns.

No awards were made for new methodologies, and I'm not convinced that we don't have the tools already to do adequate risk assessment. Retaining this category would be benign, but I suspect the response from applicants will be minimal.

I am not a big fan of modeling for risk assessment. Only one award has been made, and I don't know if useful information was generated. There were a number of modeling proposals submitted in 1996, but the Panel was not sufficiently impressed with this ultimate utility to give them an award. Some were interesting academic exercises, but little else.

As far as Category 8 is concerned, do such genes exist? Have there been any applications in this group?

In summary, I should like to see an emphasis on experiments in Category 9. I feel we need this information, which is the ultimate in risk assessment.

Although you did not ask for the following information, I feel that what I said in my final report as Panel Manager is relevant to the future of the Program, as is my recent experience at the annual symposium sponsored in part by the Program.

**PROPOSALS:** The instructions to the applicants should be tightened to get proposals which would have a common format. In particular, the length of the summary should be specified, perhaps by providing a page similar to NRI proposals. In fact, some used that page; others rambled on with as many as three pages. Also, some applicants played games with a progress report. Even though they were renewing a project closely related to their current one, several chose to consider it a new submission, and did not give a progress report. The section on progress report should indicate that they provide a progress report on any project supported by the
Risk Assessment Program. This is a policy the NSF follows. The instructions should also require a table of contents.

PANEL: The Panel was small (6) and their expertise covered the research areas of the Program more or less adequately. For the future, I feel that if an APHIS or other regulatory person be appointed to the Panel, that person should only be asked to look at all of the proposals with respect to their relevance to risk assessment. Thus, the Panel would have six members with scientific expertise in disciplinary areas plus the extra person dealing with risk assessment. As constituted this year, the APHIS person had problems with the science of some of the proposals to which he was assigned.

CONFERENCE: I was pretty disappointed in several aspects of the conference I attended last summer in Ottawa. Parts of it were good; there were a few nice papers presented by the grantees. However, even though they were expected to attend, very few did! My principal problem, however, was its lack of attention to assessing the field. Many of the questions you are asking of your panel now, should have been addressed in the conference. They should have summarized where we are in the various research areas. They should have assembled some focus groups of grantees and others to summarize. They should be asking the questions I raised above about when we have sufficient information in some of the areas to enable us to move on to others. Additionally, if the conference is to have impact, it is important to have a timely report; the report from the 1995 conference was published just in time for the 1996 conference. That is unacceptable in my view.

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APPENDIX C
APPENDIX C

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