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OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

EPA-SAB-EPEC-LTR-93-012

Honorable Carol M. Browner
Administrator
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, DC 20460

Subject: Review of the Research Program for Environmental Release of
Biotechnology Products

Dear Ms. Browner:

The Biotechnology Research Review Subcommittee of the Science Advisory Board's (SAB) Ecological Processes and Effects Committee met on February 18-19, 1993, at the Gulf Breeze Environmental Research Laboratory to review the Agency's biotechnology research program. The Subcommittee reviewed the draft "Environmental Release of Biotechnology Products Research Plan" (dated May 29, 1992) and other supporting documentation.

We were asked by the Agency to evaluate both the ongoing research and the proposed future direction for the biotechnology research program. Specifically, we were asked to assess the program's scientific productivity, use of extramural research, level of interaction with other biotechnology research programs, proposed research on transgenic plants with pesticidal activity, and whether the research questions and approaches were appropriate and reflected the state of the science. At the time of the review the Agency's biotechnology research effort was in a period of transition to the draft "Environmental Release of Biotechnology Products Research Plan." This 5-year research plan was the primary focus of our review, although we also addressed the productivity and results of previous research efforts. We were pleased to note that the revised plan incorporates several new elements and directions recommended by a previous SAB review panel in 1988.

Previous work by the Biotechnology Risk Assessment Research Program has made significant contributions to the scientific basis for assessing the potential risks associated with the development and release of biotechnology products. The early focus of the Agency's research program was on the development of methods and protocols for determining the environmental fate of released genetically-



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engineered microorganisms (GEMs). The revised research plan proposes to apply those protocols to assess potential risks associated with the deliberate or accidental release of genetically modified organisms and pest control agents. We are impressed by both the amount and quality of the Agency's research in this area, and generally agree that the knowledge base is sufficient to allow this change in program emphasis.

The new research plan is the result of considerable work by individuals from several Agency laboratories. This planning group has done an excellent job of defining the major issues surrounding the release of genetically modified organisms into the environment, and has formulated a comprehensive research plan to address these issues. We encourage the Agency to implement the plan, with the modifications suggested below. However, the plan is very ambitious, and we question whether all aspects defined as important can realistically be addressed given the personnel and funding likely to be available. While the plan does contain a list of seven priority research issues, there is little indication of priorities among the specific projects within each research area. For example, there is no indication of how implementation of the plan would be affected by changing budgets (either increases or decreases). The definition of critical information needs should be done by the Office of Research and Development (ORD), in cooperation with the Office of Prevention, Pesticides and Toxic Substances (OPPTS).

Our specific comments on each of the seven issue areas identified in the plan will be addressed below. However, we would first like to make some general observations on the program as a whole:

- a) Much of the work to date has focused on developing bioassays to measure the impact of GEMs on selected ecological endpoints. While this research has produced useful techniques and protocols, the results have shown that impacts are difficult to detect. We suggest that future research place greater emphasis on: 1) identifying new, more sensitive, ecological endpoints for effects, and 2) understanding the fate of specific introduced organisms or genes.
- b) The research program on release of biotechnology products should take full advantage of relevant non-GEM models for assessing health effects, as well as environmental fate and effects where appropriate. The focus of the current biotechnology research program has been almost exclusively on the fate and effects of GEMs. At the beginning of this effort that focus may have been appropriate. However, past work has shown little reason to believe that the fate and effects of GEMs are significantly different from that of other introduced microorganisms, such as those used for bioremediation.
- c) Biotechnology products are a rapidly expanding field of endeavor with significant research being conducted by industry, academia, and other

government laboratories. In light of the limited budget for research on fate and effects of these products, it is critical that the Agency take advantage of the information and resources that are available from other sources. While the biotechnology research group is in contact with several other government agencies, this interaction has been mostly in the form of sharing information about program goals and objectives. We commend the ORD headquarters and laboratory personnel for the outreach efforts to date, but we encourage greater attention to substantive interaction and coordination with relevant groups. For example, there are significant opportunities for sharing data, joint planning of research projects, and even collaborative studies, with agencies like the U.S. Department of Agriculture (USDA), Department of Energy (DOE), National Institutes of Environmental Health Sciences (NIEHS) and the Food and Drug Administration (FDA). In addition, the Agency should seek opportunities to expand collaboration with industry researchers.

COMMENTS ON SPECIFIC ISSUE AREAS

1. BIOASSAY TECHNIQUES

We support the objectives of the bioassay technique research area, as described in the issue plan; namely the development of test systems to detect ecological effects. However, the research approach does not reflect this focus. Greater emphasis should be placed on determining sensitive environmental processes or endpoints where effects would be expected ("vulnerability assessment"), and then developing bioassays for these sensitive points. Researchers should not be constrained to using GEMs, since the best system to measure perturbations may be non-GEMs. In addition, this research need not be directed totally to providing protocols for the Agency's regulatory programs. The microcosm research should support bioassay and gene survival research elements as outlined in the research plan.

We feel that further refinement of existing bioassays, which have not shown significant effects, will not appreciably improve the Agency's ability to do risk assessment of releases of GEMs or other biotechnology products. Greater emphasis on identifying new ecologically relevant endpoints would be a more productive research area. The Agency has had the tendency to deal with microorganisms as if they were chemicals, with specific, constant properties and environmental effects. Microorganisms may be both more specific, in that their effects may be much narrower than a single chemical, and more diverse, in that they can catalyze many reactions. Therefore, the research group should consider broadening the emphasis from single species to consortia or communities, which are more realistic models of nature. Of course, exposure should be related to expected application methods, dosage, and bioassay organism life stages at the time of release.

2. GENE SURVIVAL

The study of transfer of natural genetic elements under environmental conditions is an important research area which should improve our understanding of the ecological significance of naturally-occurring gene transfer. However, further development of sensitive (and sophisticated) tools to study the transfer of DNA from GEMs could have limited utility from a risk assessment perspective. Past and ongoing research by this team and others has demonstrated extremely limited transfer of DNA between microorganisms under realistic, natural conditions. Further and more complex analysis of this low probability transfer is unlikely to alter the risk evaluation based on DNA exchange. In other words, if we already have the ability to detect gene transfer at ecologically relevant levels, does development of the ability to detect even lower levels add anything to our ability to assess risk?

In contrast, the transfer of modified DNA from transgenic plants by pollen or other mechanisms is not well characterized, and therefore research in these areas could improve the Agency's risk evaluations. We also encourage the Agency to continue work on the mathematical modeling of gene transfer. Although detectable transfer has been found in aqueous systems, microbial gene transfer appears to be rare in soil environments, and modeling may be the most reasonable way to assess the probability of gene transfer and the potential effects. Such modeling will provide focus and direction for micro-/mesocosm research.

3. MICRO-/MESOCOSMS

The Agency has a long and distinguished history of microcosm research and has appropriately adapted that technology to biotechnology product fate studies. The goals of this research area have been largely completed since adequate micro-/mesocosm protocols now exist for most current test systems. Remaining needs may be the development of systems (including micro-/mesocosms with multiple trophic levels) to complement newly developed bioassays, gene survival studies, or ecological endpoints.

The micro-/mesocosm research would benefit from a broader view toward biological risk assessment (microbes are not chemicals) and not being constrained by working only with GEMs. As noted previously, risk assessment is complicated by the difficulty in defining measurable endpoints for studying effects. Therefore, we recommend that test systems be sought where ecological effects can be measured.

4. TRANSGENIC PLANTS

The proposed research on transgenic plants, a new research area for the Agency, is comprehensive in its scope and goals. The subject of transgenic plants, particularly pesticidal plants, is important because of the potential economic significance of this new technology (several transgenic crop plants are close to

commercialization), and the potential effects of food crops containing foreign genes which produce insect toxins. The proposed research goals include a comprehensive assessment of potential impacts on soil organisms (bacteria and invertebrates) from release of genetically engineered plants. The research plan does not address the possible human health risks from consumption of transgenic food crops or toxic effects of pesticidal plants on indigenous plants and animals. These topics should be addressed. It is unlikely that the proposed research can be accomplished with the levels of funding, resources, and staffing that are proposed and likely to be realized in the near future. This suggests the need for greater focus, and especially cooperation with other agencies.

In order to validate the protocols being developed and ensure credibility for this new research area, rigorous external peer review and use of extramural funding is critical until the Agency is able to strengthen its in-house expertise in plant ecology and plant molecular biology. Because other agencies currently have significant expertise in plant science, food science, etc., we recommend close liaison with agencies such as the USDA and FDA. These interagency interactions should be directed toward true exchange of expertise, joint research planning, and joint research projects in appropriate cases.

5. RISK CONTROL FOR LARGE SCALE RELEASES

We recommend that current large scale release of non-indigenous organisms (non-GEMs) be used as a model system to evaluate potential effects of large scale releases of GEMs. Land application of sludge, bioaugmentation projects and some bioremediation projects all offer potential research sites. Research on the effects of releasing non-GEMs should also be an important reference point for assessing potential non-target impacts from a large scale GEM release. As already noted, we encourage the Agency to develop and test fate methods and models because of the difficulty in choosing appropriate and sensitive endpoints for ecological effects.

While much good science has been achieved under the biological containment project area, we question the use of this approach for large scale commercial applications for two reasons. First, introduction of lethal genes is unlikely to be effective as a containment strategy. When induced, the gene would have to be lethal 100 percent of the time, and when not induced, produce zero gene product. Since this scenario of perfect regulation is unlikely, natural selection will almost certainly overcome any introduced lethal trait with the development of resistance. Second, the risk associated with introducing lethal genes into the environment may exceed risks from the organisms to be controlled. Clearly, other mechanisms of control need to be examined.

6. HUMAN HEALTH EFFECTS

The Agency's research on human health effects has been particularly productive and responsive to previous recommendations of the SAB and the needs of the Agency. The goals outlined in the research plan are reasonable, and the

research questions are particularly relevant to a government agency. However, we believe that little is unique about the biological properties of GEMs which would require their exclusive use in this research effort. Much is known about the infectivity of non-GEMs which is directly applicable to the health risk assessment for GEMs. The focus of research under this project area should be on biotechnology products in general.

We question the value of a new evaluation of toxic intermediates from bioremediation, as proposed in this section of the plan. NIEHS already has such an evaluation as a major research goal, and duplication of this effort is unnecessary. Also, the SAB's Environmental Engineering Committee, in its 1992 review of the Agency's bioremediation program, concluded that this research was not high priority (SAB Report No. EPA-SAB-EEC-92-026). If this work is pursued by the Agency, it should only be in cooperation and coordination with NIEHS.

7. LARGE-SCALE MANUFACTURING FACILITIES

Most fermentation processes using GEMs presently follow cautionary guidelines, such as Good Manufacturing Practices or the NIH/FDA guidelines for large scale containment of microorganisms. The research plan does not adequately justify the need for more defined or stricter controls. The proposed research would benefit from greater input and interaction with potential users (the fermentation industry), other relevant agencies (National Institute for Occupational Safety and Health, and FDA), and industrial associations (e.g., Chemical Manufacturers Association, and Pharmaceutical Manufacturers Association). Information on engineering risk control technologies may be more readily available by transfer of existing data or technology from other organizations or equipment manufacturers.

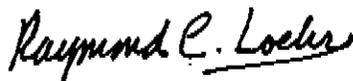
In summary, we find that the Agency's research program on Environmental Release of Biotechnology Products has been extremely productive and is admirably addressing both the science associated with environmental release of GEMs and the Agency's need to assess risk. For continued improvement, we urge the Agency to consider the following recommendations:

- a) establish priorities for research within the seven issue areas;
- b) identify more sensitive ecological endpoints for effects;
- c) assess the fate of specific introduced organisms or genes;
- d) utilize appropriate non-GEM models for assessing health and ecological effects;
- e) increase coordination of research with other agencies and industry researchers; and,

- f) address possible human health and ecological effects of pesticidal plants.

We are pleased to have had the opportunity to review the biotechnology research program. We hope our recommendations will assist the Agency to strengthen and refine this important program, and we look forward to your response.

Sincerely,



Dr. Raymond C. Loehr, Chair
Science Advisory Board



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Ecological Processes and
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Dr. Frederic K. Pfaender, Chair
Biotechnology Research Review
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U.S. ENVIRONMENTAL PROTECTION AGENCY
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February 18-19, 1993

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