Risk Assessment for Federal Regulatory Decisions on Organisms Produced Through Biotechnology

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I. Purposes and History of Risk Assessment: Application to Biotechnology

In one of the seminal treatise on risk assessment, **Risk Analysis: A Guide to Principles and Methods for Analyzing Health and Environmental Risks**, by Cohrssen and Covello (1989), risk analyses are seen to have the principal purpose of leading to better decisions. Methods of analyzing risk have been developed to organize complex risk information to lead to help decision makers determine environmental and health problems associated with a variety of activities and substances, compare the effectiveness of different control and mitigation techniques designed to reduce risks of an activity, and set management priorities, include priorities for regulatory action (Cohrssen and Covello, 1989; Lave, 1987; Russell and Gruber, 1987).

There have been recent reviews of the application of risk assessment techniques to the use of organisms modified through biotechnology. The approaches have been quite different and often led to different conclusions. In the preface to **Assessing Ecological Risks of Biotechnology**, Lev R. Ginzburg writes,

> "Risk assessment involves predicting certain outcomes and estimating the probability associated with each of these outcomes, as well as assessing their consequences. Such quantitative estimates can only be made with mathematical models" (1991).

In contrast, in the preface to **Risk Assessment in Agricultural Biotechnology: Proceedings of the International Conference**, James J. Marois and George Bruening suggest a more tentative position with respect to the precision that can be expected in risk assessments,
"Ecology is not an exact science, and often the application of ecological methods is well ahead of advancements in ecological theory. Also many areas pertinent to biotechnology have little or no ecological basis. Although the population biology of many plants and animals is well understood, most general concepts are under constant refinement. For example, ecologists have a very difficult time predicting the eventual impact that an introduced species will have on an ecosystem. Even the quantification of the attributes that make a species invasive is not completely understood" (1991).

To carry out mandates to protect the environment from the introduction of any organism that could be deleterious, regulatory agencies that give approvals for the use of organisms, especially uses that involve release to the environment of organisms which are either new to an environment or which are significantly modified, must ensure that decisions are based on the best information possible and on procedures that lead to good decision making. Given the very different opinions of those expert in risk assessment, what then is an appropriate model for risk assessments to support regulatory decisions? In the following sections of this paper, we will explore the regulatory structure in the United States for review of organisms modified by biotechnology. Compare approaches to risk assessment, and describe a framework for assessment based on principles of biology and ecology.

II. Framework in the United States for Decisions on Organisms Produced Through Biotechnology

The U.S. Federal policy has been, and continues to be based on several conclusions: (1) the products of biotechnology will not differ fundamentally from unmodified organisms or from conventional products; (2) the product, rather than the process should be regulated; (3) regulation should be based on the end use of the product and conducted on a case-by-case basis; (4) and that the existing laws provide adequate authority for regulating the products of biotechnology. An important corollary to this policy is the Federal commitment to promoting the safe development of the products of biotechnology. Each Federal agency is committed to ensuring protection for public health and the environment from any potentially harmful effects of the technology.

The policy was developed in response to renewed public concern aroused in the early 1980's by proposals to test and use genetically engineered organisms in the environment. The National Institutes of Health (NIH) Guidelines, which were originally written to deal with NIH grantees doing biomedical research in the laboratory, were increasingly proving to be inadequate to the task of reviewing applications for testing in the environment of the broad spectrum of genetically engineered organisms and commercial products (NIH, 1986).

The policy was published in June 1986 as the "Coordinated Framework for Regulation of Biotechnology" (OSTP, 1986) and contained final policy statements by the U.S. Federal agencies that share a major responsibility for regulating the products of biotechnology. The agencies are the Food and Drug Administration (FDA), the Environmental Protection Agency (EPA), and the U.S. Department of Agriculture (USDA).

It is important to note that the authority of these three agencies for regulatory biotechnology is based on statute, and that the implementing regulations are published in the U.S. Code of Federal Regulations. The NIH Guidelines by contrast are not based on a statutory basis but rather on a contractual basis. In recognition of this fact and to avoid duplication, the NIH adopted amendments of the Guidelines to provide that if certain experiments are submitted to another Federal agency for approval or official clearance NIH review is not required (NIH, 1987). The following discussion, focuses on the activities of U.S. Federal agencies with specific statutory authority for regulating biotechnology products.

FDA

FDA, which is part of the Health and Human Services Department of the U.S. Federal Government, regulates foods, human and animal drugs, cosmetics, and medical devices under the authority of the Food, Drug and Cosmetic Act of 1938, as amended. Key amendments to the Act have given FDA authority to require premarket approval of the food and color additives used in food, and premarket safety and efficacy testing for all drugs.

FDA does not consider that recombinant derived products require a special or unique review procedure based on process. FDA's organizational units review products developed through many different processes, with attention to scientific concerns, specific tests, and "points to consider". "Points to Consider Documents" have been made available on such subjects as interferons, monoclonal antibodies, recombinant DNA-derived products, and use of mammalian cell lines. Some FDA actions are subject to the requirements of the National Environmental Policy Act of 1969, or NEPA, as amended, and require production of an assessment of the risk to human health and the environment before approval is granted for marketing. Such assessments examine the alternatives to a given action and evaluate data on the potential risks of the favored alternatives.

The Food and Drug Administration issued a policy statement on foods derived from new plant varieties, including genetically engineered plant varieties, in May of 1992 (FDA, 1992; Kessler *et al.*, 1992). In short, that document stated that most substances added to food as a result of genetic modification are substantially similar to substances commonly found in food and therefore should not be subject to premarket "food additive" regulation under section 409 of the FFDCA unless "objective characteristics raise questions of safety sufficient to warrant formal premarket review and approval". Although the document suggests liberal consultation with FDA to determine the regulatory status of foods derived from genetic modification, the implication of the document is that most substances added to food as a result of genetic modification would be considered as "generally recognized as safe" (GRAS) and would not require regulatory approval as a food additive. The FDA food policy clearly establishes that substances in plants that properly meet the definition of "pesticide" under FIFRA will be addressed through traditional tolerance setting mechanisms with EPA.

EPA

EPA regulates pesticide products, including those produced through biotechnological techniques, under the authority of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) of 1972, as amended. Under FIFRA, as amended, EPA has the authority to regulate the development, sale, distribution, use, storage and disposal of pesticides. FIFRA broadly defines

pesticide as "any substance or mixture of substances intended for preventing, destroying, repelling or mitigating any pest, or intended for use as a plant regulator, defoliant, or desiccant". The development of pest resistant plants through biotechnology has raised the issue on whether FIFRA applies to substances produced in plants.

Although EPA has not issued an official policy, EPA officials have stated that pest control substances produced in plants are pesticides within the meaning of FIFRA and therefore potentially subject to regulation under FIFRA. Section 3 of FIFRA generally requires that a pesticide must be registered before sale or distribution. However, under 25(b) of FIFRA it is possible to exempt certain pesticidal substances from regulation if EPA determines that they are adequately regulated by another Federal agency or are not of a character to require regulation.

The Toxic Substances Control Act (TSCA) of 1976, provides EPA with the authority to regulate chemical substances, except those used as pesticides, food, and food additives, cosmetics, drugs, and medical devices. The applicability of TSCA to the regulation of microbial products, including those that are produced by genetic engineering technology, is based on the inclusion of "microbes" in the definition of "chemical substance".

Because EPA reviews are considered the equivalent of the environmental assessment required under the National Environmental Policy Act (NEPA), EPA is generally considered exempt from the procedural requirements of the NEPA. Under both FIFRA and TSCA, EPA is required to consider both the potential benefits and risks of a product.

EPA published policy statements in October and December 1984, and in June 1986, that established the interim review procedures for microorganisms subject to FIFRA and TSCA. EPA has not published proposed regulations applicable to microbial products of biotechnology under FIFRA and TSCA, but has operated under the policy in place since 1986 (Rogul and Levin, 1991).

USDA

USDA has broad regulatory authority to protect U.S. agriculture against threats to animal health, to protect against the adulteration of food products made from livestock and poultry, and to prevent the introduction and dissemination of plant pests. This authority is applicable to genetically engineered animals, plants and microorganisms (Cordle *et al.*, 1991).

The USDA policy on the regulation of biotechnology, consistent with the overall Federal policy (OSTP, 1992), does not view genetically engineered organisms as fundamentally different from those that have traditionally been isolated from nature and introduced into new environments or that have been produced through programs or breeding and selection. The organisms and products produced through the new techniques of biotechnology are regulated under existing laws that apply to naturally occurring organisms and products of traditional technologies. To address the need for specific information necessary for the assessment of the products of the new technologies, a few new regulations have been promulgated and some old ones have been updated.

In the area of animal health, the Virus-Serum-Toxin Act (VSTA) of 1913, as amended, provides USDA's Animal and Plant Health Inspection Service (APHIS) with the authority to regulate all veterinary biologics that are imported into the United States, shipped or delivered for shipment interstate, intrastate and that are exported. USDA also has enforcement mechanisms such as the

power to detain and seize products. The VSTA is administered by APHIS in the same manner for genetically engineered and naturally occurring organisms and products. APHIS issues U.S. Veterinary Biological Product Licenses after satisfactory completion of all requirements to assure purity, safety, potency, and efficacy. Veterinary biological products produced by recombinant methods are evaluated on a case-by-case basis using the same stringent standards for licensing employed for conventionally produced biologics.

APHIS has responsibility under the Plant Quarantine Act (PQA) of August 20, 1912, as amended, and the Federal Plant Pest Act (FPPA) May 23, 1957, as amended, to regulate and permit the movement of organisms which are or may be plant pests. APHIS published regulations June 16, 1987, that pertain to genetically engineered organisms that are plant pests or that present the potential for plant pest risk (APHIS, 1987). Between the summer of 1987 when the regulations were issued and the fall of 1992, APHIS approved over 350 permits for field trials of genetically engineered plants, with over 650 actual field test sites, involving 20 different plant species. Field trials have been approved for 35 States and Puerto Rico.

Regulations should prevent or at least mitigate risks and not inhibit safe innovation or utilization of new technologies. Regulation and any mandatory review requirements must be balanced and, to the fullest extent possible, commensurate with risk (NRC, 1987; NRC, 1989). The APHIS regulatory structure and its permit requirements are initiated to adequately consider plant pest and environmental risk while facilitating the safe movement for research and other purposes of organisms (McCammon and Medley, 1990; Shaw *et al.*, 1992).

III. Choosing from among potential approaches to Assessment

A. Exposure Assessment does not Equate to Risk Assessment: What are the Hazards?

An underlying assumption to environmental risk assessment that must be dealt with early on in the assessment process is the assumption that hazard exists. Classical risk assessment protocols have been widely developed and used for evaluation of nuclear power installations (Okrent, 1987) and for the use of hazardous chemicals in the environment (Cohrssen and Covello, 1989). In these applications the hazard is often self-evident in that specific dose-response calculations can be drawn to describe the hazard.

A classic formula for characterizing risk assessment for these types of applications is: Risk = Hazard $\times$ Exposure. When the hazard is well understood, most of the assessment then is dependent on descriptions of routes of exposure and determination of potential doses as a result of probable routes of exposure. In this model, as a result that hazard is assumed a priori, identification of routes of exposure leads to the conclusion that there is risk.

When applied to the use of genetically modified organisms this model can greatly overemphasize risk, therefore, because biological interactions are complex and, absent a hazard such as pathogenicity, predation, or competition, exposure may not equate to risk. Analysis for hazard is an important component of assessments for organisms modified through biotechnology. Many of the potential types of changes should be expected to lead to safer rather than more hazardous organisms, especially when genes responsible for pathogenesis or other negative traits are deleted or inactivated, such as in many viruses being developed as vaccines. In fact, exposure may lead to risk to the organism being introduced if the introduced organism serves as a host or prey for the organisms it comes in contact with.

Several authors have analyzed exposure assessment. Kareiva (1990) has examined mathematical models of population spread for analyzing results of field releases and has applied these to spread of pollen in crops such as cotton.

Supkoff (1990) has developed a model for air transport of microorganisms when those microorganisms are sprayed on vegetation in a field, and Upper and Hirano (1991) have examined aerial dispersal of bacteria in a broader context. Similarly, models of water transport of microorganisms on the soil surface have been developed by Moore (1991), and the transport of microorganisms in soil and groundwater has been considered (Berry and Hagedorn 1991).

The discussion treating these studies and exposure assessment, or in some cases a theoretical approach to exposure assessment, is not meant to minimize their proper role in risk assessment. They are essential when a hazard from an organism has been identified, to estimate risk. They are, however, inappropriately used when, absent a hazard, a prediction of exposure leads to the assumption of risk.

B. Setting Risk Assessment Priorities

If risk assessment is to be used as an effective decision making tool, some mechanism must be used to focus the analysis on the higher risk areas or, with the growing number of uses of organisms, the risk assessment effort will be diffused and wasted on analysis of low risk applications. In the United States, William Reilly, Administrator of the Environmental Protection Agency, has proposed a national debate on risk and priority setting, and several science advisory committees have examined priority setting at regulatory agencies (EPA, 1991).

At the USDA we have been examining the priority setting on the basis of risk with respect to the organisms we regulate. We have put forward to the Agricultural Biotechnology Research Advisory Committee the concept that most field crops, modified with a number of the safer traits, if grown under an appropriate set of conditions based on performance standards, could be presumed to be safe and not require a formal assessment before field testing. The committee has endorsed the scientific basis for that approach and will provide detailed comments that we will take into account when implementing that approach. The use of simple notification, rather than more formal assessment and permitting of the safer applications of organisms modified through biotechnology would allow resources to be focused on those with relatively more risk.

C. "Quantitative" Environmental and "Quantitative" Ecological Risk Assessments

There have been a proliferation of concepts for risk assessment of research in the environment. An environmental risk assessment has been described as a "scientific enterprise in which facts and assumptions are used to estimate the potential for adverse effects on human health or the environment that may result from exposures to specific pollutants or other toxic agents" (Thomas, 1987). As is suggested by the previous definition, the emphasis of environmental risk assessments has often been human health with much of the discussion being devoted to various environmental routes of exposure to humans of toxic materials. When the emphasis is on potential impacts to the environment or its component parts, rather than impacts on humans, the term "ecological risk assessment" has been used (North and Yosie, 1987). Ecological risk assessment has been characterized as "the development of a formal approach to characterize the scientific knowledge of the risk to ecological systems following exposure to environmental contaminants" (Thomas, 1987).

When ecological risk assessment has been described by some who approach it from a background in environmental risk assessments of chemicals, they have often described ecological risk assessments as being analogous to a series of additive environmental risk assessments. In other words, the approach would be to develop a numerical dose-response curve for each organism in the ecosystem that might be significantly affected. When we consider the great difficulty that has been expressed in developing this type of data for most most ecosystems for even well-studied chemicals (Silbergeld, 1987; Cohrssen and Covello,, 1989), the lack of success for this type of additive, organism-by-organism numerical model seems evident (Tiedje *et al.*, 1989).

As discussed earlier, an underlying assumption to environmental risk assessment that must be dealt with early on in the assessment process is the assumption that hazard exists. Many recent analysis of environmental and even ecological risk assessments have provided elaborate models for exposure assessment, and purport to thereby measure risk, without carefully assessing what traits in the organisms could logically, let alone be demonstrated, to result in hazard.

When the chemical model for risk assessment is used for ecological studies, as it has been described above, ecological risk assessments are often equated to being analogous to a series of additive environmental risk assessments. That approach sometimes leads to a quantification of a few well-studied interactions rather than identification of likely interactions; the reasons being several. There is in the chemical model an over-reliance on quantifiable measures. Since much of the data base for biological interactions is qualitative and qualitative discussion does not fit into the model, it may be overlooked or under-utilized.

Another fault of using quantitative risk assessments for complex interactions of biological organisms is that many of the interactions cannot be quantified with any certainty. In many assessments, when there is uncertainty with a numerical component or the component is expressed as a range, the number used for risk calculation is the most conservative or provides the most risk-averse decision. When several quantitative elements must be estimated in an assessment then the resulting numerical measure of risk may seem to have precision, but has no predictive value or utility to guide informed decisions.

Therefore, we conclude that many of the models for "environmental risk assessment" or "ecological risk assessment" that have been described are not appropriate to provide models for evaluation of the use of modified organisms. Such models are often based on oversimplified models that were developed for use of hazardous chemicals in the environment. Many uncritically assume that hazard exists and seek to characterize the risk from that hazard through exposure assessment. Most do not allow for qualitative data based on experience and observation, instead providing principally for numerical analysis.

At APHIS we have sought to identify review strategies that will provide a mechanism for support of decisions on the use in experimental field testing of genetically modified organisms, the release of exotic biocontrol organisms, and the documentation of those decisions. We have avoided over-reliance on chemical models of risk assessment. The environmental analysis used takes advantage of the more flexible, multi-disciplinary approach of the environmental assessment mandated by NEPA as discussed in the next section. Site-specific, or application specific environmental assessments have proven to be an effective vehicle for ecological risk assessment on decisions for experimental field uses of genetically modified organisms and releases of exotic biocontrol organisms.

D. Ecological Risk Assessments based on Biological and Ecological Principles

The environmental analysis that is developed for a genetically modified organism, rather than being simply a "risk assessment", and "environmental risk assessment", or an "ecological risk assessment" *per se*, may contain one or several risk assessments. The environmental assessment might be characterized as containing a biological assessment in a specific ecological framework. That is, the biology and natural history of the organism that is to be introduced is carefully examined, both data from the behavior of the organism in its natural environment and specific host range (or other biological test) done in contained environments like the laboratory or greenhouse. The environment expected to be accessible to the organism when it is introduced is described. Predictions are then made about the expected behavior of the organism in the environment in which it is to be introduced based on familiarity with the ecology of the recipient organism, taking into account the biological functions that have been introduced or changed. The potential impacts to the accessible environment are described and mitigation procedures for impacts are noted.

It should be clear that this approach is not fundamentally different from the types of review that have traditionally occurred for introductions of exotic biocontrol organisms (Lima, 1988; Coulson and Soper, 1989; Charudattan, 1990). The principal difference is that the questions are posed more formally than they have been in the past so as to provide a structured review and analysis of the organism, and potential impacts that may occur from its introduction, either positive or negative. Additionally, information about the changes to the organisms have been factored into the review. The major difference between considerations for the introduction of genetically modified organisms and biological control organisms new to an environment, is the behavior of the genetically modified organism is usually much more predictable, most recipient organisms that have been engineered tend to be faimilar organisms of agriculture with which we have much experience.

The NEPA is our basic national charter for protection of the environment. It establishes policy, sets goals, and provides means for carrying out the policy. NEPA requires all Federal governmental agencies to prepare a "detailed statement" for major Federal actions significantly affecting the quality of the human environment (Bausch, 1991). This detailed statement is known as an environmental impact statement. An agency determination that the proposed major action would not result in any significant environmental impact must be supported by an environmental assessment.

Two fundamental principles underlie NEPA's requirements: Federal agencies have the responsibility to consider the environmental effect of major actions, significantly affecting the human environment and the public has a right to review that consideration.

Specifically, where appropriate, an environmental assessment (EA) is prepared in accordance with the National Environmental Policy Act (NEPA) of 1969, as an aide to the decision making process. The EA provides a template for ecological risk assessment for the decision, and ensures that the full range of risks associated with release of the organism have been addressed and properly characterized. This decision making model may provide a valuable template for analogous Federal permitting activities requiring ecological risk assessment.

The complexity and uncertainty of ecological risk assessment as compared to assessment of human health risks; and compliance with the intent and procedural requirements of NEPA as a mechanism for documenting ecological risk assessments and assuring informed decisions.

The structure of the environmental analysis provided for the following types of questions and considerations:

1. What is the organism and how was it modified?
2. What is the biology of the unmodified (or recipient) organism in its natural environment?
3. What is the biology of the donor or vector genetic sequences or gene products?
4. What are the characteristics of the environment?
5. What other organisms is it expected to significantly interact with in the new environment and what are the potential outcomes of this interaction?
6. What procedures or controls are available to mitigate any negative impacts identified?

It is important to note that the questions are of a form that would allow the use of valid qualitative information as well as quantitative data to provide the answers. The use of these types of questions are then analyzed as described in more detail below.

The environmental assessment is a key component in the review process. It contains a thorough accounting of the Agency's analysis leading to a decision. It is a public document, made available to anyone who requests it, free of charge. Each environmental assessment is made up of a summary describing the purpose of the document, Departmental regulations, the conditions under which the permit is issued or denied, the background biology of the organisms, and the possible environmental consequences of the field test. The environment that could be affected by the field test is described and the precautions developed for protecting that environment, including field plot design, field inspection and monitoring, test plot security, and termination plans are analyzed. The environmental consequences of the test are examined from all possible perspectives. Consideration is given to the biology of the recipient, donor, and vector, and to the potential for biological containment based on knowledge of this biology. Any possibility of risk to native flora or fauna is evaluated, with special consideration of organisms which are threatened or endangered. Any potential impact on human health is examined. It is through the environmental assessment that the public can be assured that APHIS has fully considered the possible consequences of releasing the regulated article into the human environment.

The use of the NEPA environmental assessment as the mechanism for this environmental analysis provides the necessary structure for decision making without imposing inappropriate chemical-based models of risk assessment. It avoids the over-emphasis on data that can be expressed numerically that is a fault of some traditional approaches to risk assessment.

IV. The Bases for Good Regulatory Decisions

We conclude that, for risk assessments to support fully informed decisions, that they must be based on the best available data and should be based on the method that has the best predictive power. It is important that hazard should be carefully identified and separated from more generalized concerns that may be based more in emotion than fact.

Given the level of the characterization biological and ecological interactions, and their complexity, quantitative systems are usually not feasible for prediction of risk from organism based systems. In biological systems, strictly quantitative systems of assessment tend to be over-conservative, leading to risk averse decisions. Strictly quantitative systems tend to cause information useful to risk assessment to be ignored or under-utilized in decision making.

Assessments that are based on careful evaluation of the biology of the organism with the application of ecological principles, and that use comparison with experience with similar

organisms has proven to be the most useful approach to risk assessment for biotechnology. Biological assessments in the context of an environmental assessment allow the use of both quantitative methods and qualitative measures as they are available or appropriate.

Environmental assessment also allows a discussion of what can be called "risk concerns", those concerns which have been expressed with regard to organisms modified through biotechnology that may be based on hypothetical scenarios or other than scientific experience. These concerns may fall outside risk assessment *per se*, but it is important that in risk communication that all concerns, whether endorsed by experts or not, that are expressed by the general public are appropriately addressed. This allows for communication of relative lower risk of many of these concerns as a basis for discussion.

Regulatory Agencies must ensure that the decisions it makes are based on the best information and utilize appropriate procedures. The use of the structured environmental assessment process as a component in the review of organisms modified through biotechnology provides an appropriate structure for the informed and responsible decision making. This pre-decisional tool allows for flexibility of inputs, including qualitative information as well as quantitative data. The environmental assessment provides a template for ecological risk assessment for release decision, and ensures that the full range of risks associated with release of the organism have been addressed and properly characterized. This decision making model should provide a valuable template for analogous Federal permitting activities requiring ecological risk assessment.

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