Chapter 6
Risk Assessment

"The atomic bomb was the first breach in our innocent conviction of the beneficience of science. My concern is that genetic engineering not become the second."

Robert Sinsheimer
New Scientist, January 20, 1977

"There will be vast numbers of tests going on simultaneously at some point. We'll have to move past the stage when every one of these becomes a focal point."

Allen Dines
Philadelphia Enquirer, May 17, 1987

"I'm drawing up the Whole Risk Catalog. Under D, I have dogs, doctors, dioxin. Where do I put DNA? Very low."

James D. Watson
The DNA Story: A Documentary History of Gene Cloning
W.H. Freeman & Co., 1981

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Chapter 6

Risk Assessment

During the 1970s, public concern about the effects of technology on the environment and human health heightened. As mounting scientific evidence confirmed that many chemical substances produced adverse effects (both acute and chronic) on humans and the environment, the government established programs to control potential hazards. protocols and procedures—methods for the assessment of risks—were developed to enable regulators to evaluate potential hazardous substances. (See ch. 3 for discussion of the regulatory regime and public perceptions of these issues.)

Risk assessment of recombinant DNA technology is not new, nor-is risk assessment of biological products. Nevertheless, questions concerning risk assessment of planned introductions of geneticall$_y$ engineered organisms into the environment recently have become the subject of debate. **Some scientists perceive some risks associated with intentionally introducing these organisms as unique. Others believe introducing recombinant organisms is no different (and probably safer, because scientists constructed them with precision) than introducing nonrecombinant organisms, which has occurred for millennia.**

Are there unique risks in environmental applications of genetically engineered products? Is additional information needed to assess the risks accurately? Can existing assessment methods (e.g., for other biological risks, or for chemical risks) be applied to the planned introductions of genetically engineered organisms? Are there areas where available baseline data are sufficient?

RISK ASSESSMENT V. RISK MANAGEMENT

Risk assessment is the use of scientific data to estimate the effects of exposure to hazardous materials or conditions. Derived from a factual base, risk assessment identifies and characterizes the magnitude of potential adverse affects —either their quality or quantity. It is a separate and distinct process from risk management.

Risk management is the process of weighing alternatives to select the most appropriate regulatory strategy or action. It integrates the results of risk assessment with technical, social, economic, and political concerns. Carried out by regulatory agencies under legislative mandates, risk management is a decisionmaking process requiring value judgments that compare potential risks and benefits, and determine the reasonableness of control costs. Benefits are part of the calculus of risk management. For example, risk management of biotechnological products involves comparing their benefits and problems against those associated with products they are designed to replace.

Risk management must also consider the economic and social costs of regulation. These include the burden of paperwork associated with regulation, and the costs of mitigation and control technologies that channel resources away from production per se (33). The process of risk management depends upon the scientific findings of risk assessment, as well as on public opinion. Chapter 3 describes the significant impact of public opinion, in particular local communities, on environmental applications of biotechnology. A separate OTA report surveyed public perceptions of biotechnology (48).

While recognizing that complex interrelationships between risk assessment and risk management exist, a key to improving the current process is to distinguish between those aspects of the process that are more or less scientific (risk assessment) and those that are matters of policy or value judgments **(risk management).** In fact, a 1983 report by the National Academy of Sciences recommended that regulatory agencies establish and

maintain clear conceptual distinction between the two processes (33).

The domains of risk assessment and risk management of environmental applications of genetically engineered organisms are often blurred in debates on this controversy. This chapter focuses on risk assessment and, more specifically, on the first step in the process of risk assessment: "risk identification." To a lesser extent, issues of risk management are considered when those issues derive from the scientific underpinnings of risk assessment. The role of the Federal Government in managing the risks associated with the environmental release of genetically engineered organisms, an issue presently being analyzed by the General Accounting Office (15), is beyond the scope of this report. This chapter also does not assess the various domains of risk management-e.g., the economic and social benefits that could be derived from planned introductions of genetically engineered organisms.

METHODS TO ASSESS RISKS OF PLANNED INTRODUCTIONS

An orderly process for organizing and interpreting information about the potential health or environmental risks of planned introductions of genetically engineered organisms must be developed and refined. To date, the methods and models proposed for risk assessment of biotechnology have been derived principally from those developed for chemicals released into the environment (13,14, 16,17,45).

Some aspects of chemical and physical risk assessment lend themselves well to evaluating risks associated with living organisms, particularly containment and mitigation (17). Other aspects of the models do not apply well to living organisms, which reproduce and are subject to selection pressure, or die out (45). Generally the risk assessment process for planned introductions involves:

- **risk identification—identifies the potential risk, designating** its source, mechanism of action, and potential adverse consequences;
- risk-source characterization-characterizes the potential sources of risk, describing types, amounts, timing, and probabilities of harmful events;
- exposure assessment-considers exposure risks, estimating intensity, frequency, and duration of exposure to the risk agent;
- dose-response assessment–analyzes the relationship between amount of exposure and extent of effects; and
- risk estimation—estimates, within a range of uncertainty, the overall risk (14,47).

At present, standardized protocols do not exist for predicting either the kinds of risks or the magnitudes that could be associated with planned introductions of genetically engineered organisms into the environment. Chemical fate models, epidemiological models, and effects models to assess aspects of environmental applications are useful, but not complete. Nevertheless, risk assessment is not an impossible task and conducting a flexible, case by-case, science-based risk assessment (19,36,40) develops and enhances the risk assessment structure Small-scale, experimental field testing will enhance significantly both the basic scientific database and the ability to modify existing risk assessment models Some argue, however, that developing an adequate assessment structure requires substantial new resources beyond those currently obligated for testing and evaluating chemical and other inert hazardous substances (16). In either case, risk assessment raises questions and illustrates data requirements that must be addressed. The implications that many of these questions have for a national research agenda are discussed at the end of this chapter.

CONSIDERATIONS TO EVALUATE IN ASSESSING POTENTIAL RISKS

Identifying and evaluating the array of elements to consider for risk assessment of environmental applications of genetically engineered organisms is one of the issues that must be addressed. Yet underlying this evaluation is the fundamental question of whether or not the entity should be regulated strictly as a product, or as a product that is special because it derives from recombinant DNA processes. Historical considerations of risk assessment and regulation indicate that process-based decisions are not logically consistent with assessments of other biological products.

But are there other important criteria that should be analyzed? Some argue that there are, and one of the first attempts to predict or classify potential environmental impacts of the introduction of genetically engineered organisms described five parameters (l):

Possible Negative Effects.–Before establishing complex risk assessment schemes to address potential problems, this basic question should be examined. If there are none, then no cause for concern exists.

Survival.—Will the engineered organisms survive when introduced? **If not, then there is little likelihood that an ecological problem might arise. If, however, the organism intended for release has been designed to fit a certain role and to survive in the environment, then further assessment is required.**

Reproduction. -Many intended applications do not merely require survival or persistence, but depend on replacement or multiplication of the organism to achieve the desired endpoint. Reproduction of an organism leading to an overwhelming net increase in number could increase the probability of unintended potential effects.

Horizontal Gene Transfer (see ch. 4).–Horizontal transfer of genetic material could be a concern even if the released engineered organisms die after performing their intended function.

Transportation or Dissemination.—If the organisms move beyond the environment in which they were released and were intended to function, they become a potential agent for interacting with other populations or communities. This could have unintended and unpredicted consequences.

Many standards—both positive and negative—exist to gauge the value of each of these **criteria, and in** particular the first question. Yet, in assessing risks, uncertainties will always exist because the ability to ask questions or pose problems exceeds the ability to answer them. The risk management process must be designed to assess the value of these and other criteria and, as indicated earlier, to weigh the benefits and risks of new products against those of old ones. Nevertheless, scientific criteria important to risk assessment (especially risk identification) of planned introductions applications can be identified, and are discussed in the rest of this chapter.

WHAT RISK ASSESSMENTS AND REVIEWS ARE NECESSARY?

Basic to all arguments about the risks of deliberate release of any non-native plant or animal are risk management decisions about the kinds of hazards that are tolerable or intolerable. It is clear that some planned introductions warrant greater concern than others (32). An application with some degree of risk, but with the potential for widespread benefit, would probably be subject to detailed regulatory review. Regulatory review should also, however, be flexible, Thus, for effective and efficient regulatory review, certain applications of genetically engineered organisms could be identified as having negligible risk (e.g., see Coordinated Framework for Regulation of Biotechnology, 51 F.R. 22302). Such applications could be processed through an abbreviated review or be exempt from review.

Can categories be identified for which abbreviated review or exemption is appropriate? For example, case-by-case reviews at appropriate levels of scrutiny of planned introductions for cur-

rently accepted agricultural practices that differ only by the method used to generate a product not presently regulated might be unduly burdensome. Likewise, applications that are qualitatively identical to previously approved products, e.g., a new ice-minus bacteria application, pose no unexamined risk and should probably be subject to less review or be exempt.

A priori exclusion from review is problematic for many scientists. On the other hand, many scientists argue that applications should be assessed and classified on the basis of certain criteria, and categories requiring different levels of review be developed (23,32). This section examines risk assessment and review considerations for some types of environmental applications.

Crop Plants and Domesticated Animals

Genetically engineered crop plants and domesticated animals appear to be the most likely candidates for the category of minimal risk applications for planned introductions. Two important questions should be considered, however, before assuming that either type of release is wholly safe:

- Do the engineered crop plants or domesticated animals have relatives that occupy similar ecological niches and are problematic as weed plants or feral or pest animals?
- Are the engineered organisms toxic to nontarget species?

In addition, altering a fundamental metabolic process in plants or animals (e.g, plants engineered to fix nitrogen or mobilize a novel insoluble nutrient) could require special scrutiny. Changing metabolic processes can perturb critical energy and nutrient cycles. For example, augmenting nutrient flows might increase freshwater pollution (see ch. 5).

Finally, changes in mutualistic species of crop plants or domesticated animals should probably be carefully examined. Mutualisms-complex interactions in which both species benefit, such as pollination by insects–are important to ecosystem function (6). Introductions of genetically engineered species that interact as mutualists should be tested carefully to ensure that they are ecologically equivalent to existing partners.

Nevertheless, despite the reservations of some, introductions of genetically engineered crop plants or domestic animals are strong candidates for an abbreviated review process in the near future.

Pathogens and Pests

Pathogens or pests used for genetically engineered products slated for environmental release have the potential to affect the environment adversely. The degree of risk associated with importing *any* genes from pathogens to nonpathogens is also of concern. A distinction, however, can be made between the genes of a pathogen that are involved in the disease process and those that direct basic structural or metabolic functions. While some would argue that *any* genes used from such organisms pose problems, others point out that ***general*** genes **of structure and metabolism are not special in pathogens.**

Pathogenicity is known to involve a number of genes that must be intact and operate in a concerted and coordinated fashion in pathogens **(12,39).** The **kind of** review **that relatives of pathogenic species should be subject to is a topic of much discussion. There are two kinds of relatives of pathogenic organisms: avirulent strains that differ from the pathogen by only one or a few genes, and nonpathogenic relatives that contain none of the disease-causing genes. The effect of genetic change on these two types of relatives has different potential for undesirable consequences. Nonpathogenic relatives probably have little realistic chance of acquiring all of the characteristics necessary to become pathogenic (39). That is, because pathogenicity usually requires the concerted action of several genes, a change in one gene would not be likely to convert a nonpathogen to a pathogen. Thus, nonpathogenic relatives could require less review than pathogenic organisms if all other criteria are equal.**

On the other hand, genetic changes can readily convert some avirulent relatives to virulent pathogens (30,39). In these cases, the relatives are avirulent forms of the disease causing species and

differ from the pathogen by only one or two changes. For example, changes in virulence have been described for viral and fungal pathogens. Temperate viruses that infect bacteria can become virulent with genetic changes at only one or a few loci (29). Certain fungal pathogens of plants can evolve (in response to selection pressure) virulence characteristics against new cultivatable varieties within a few years after the new cultivars have been widely planted (50). Finally, avirulent strains of a pathogen can recombine within an organism during an infection to produce lethal recombinant. Recent experiments demonstrated that two avirulent herpes simplex virus type 1 strains could interact in vivo to produce virulent recombinant resulting in a lethal infection in mice (21).

Changing a pathogen's environment or introducing it into a new one could potentially affect virulence expression or host range—thus arguing against exempting from review proposed releases using pathogens, pests, or avirulent relatives. Artificial and disturbed environments, in particular, seem likely settings for such shifts in expressed virulence of a pathogen. Legionella *pneumophila,* the causative agent of Legionnaire's disease, for example, occurs in natural freshwater habitats, but can also adapt to life in cooling towers and other nonnatural aquatic environments from which it has easier access to humans (43). Similarly, *Endothia parasitic* (chestnut blight) is an opportunistic fungal pathogen of several tree species, In its native Asia, the fungus causes little damage, because forest trees have evolved resistance genes (25). Since its accidental introduction into North America, the fungus has virtually eliminated the American chestnut tree throughout its geographic range in the Appalachian mountains because these trees previously had not been pressed by natural selection to evolve resistance.

Thus, the use of pathogens and some related avirulent species in environmental applications could pose special problems. Such releases are not likely candidates for exemption from review. However, applications transferring general genes (genes not involved in causing disease) from pathogens to nonpathogens do not present pathogen-specific problems. In the absence of evidence indicating special risk factors, such applications could receive a review less rigorous than one using a pathogen. Finally, although the release of any form of pathogenic organism as a biological control agent is likely to generate controversy, this is an area where a mathematical and genetic framework exists for examining the properties of a pathogen before release (2)3,22). Furthermore, there is extensive experience with biocontrol agents, especially in the use of soil-borne plant pathogens (42).

Molecular Construction of the Organism

A different approach that could be used to distinguish applications requiring different levels of review examines the molecular details of the altered organism's genetic construction. Such an examination could include, but not be limited to:

- whether the genetically engineered organism has been constructed using genetic material from the same genus (intrageneric) or different genera (intergeneric);
- whether the alteration of the released organism involves the insertion or deletion of genetic material; and
- whether the alteration of the released organism involves regulatory (not structural or coding) sequences.

Because applications involving genetically engineered micro-organisms have generated much of the controversy in this area of biotechnology, considerations of these criteria will focus on such applications.

Intrageneric and Intergeneric Constructions

Taxonomic groupings are in a perpetual state of flux, with the classification of organisms into species, genera, and sometimes even higher taxonomic categories often changing as scientists learn more about the phylogeny of all organisms. New molecular techniques have changed prior interpretations of evolutionary relationships—sometimes radically so. Such realignment is true for all organisms, including micro-organisms.

The degree of relatedness of the genetic material used in genetically engineered organisms has generated considerable debate. Are intrageneric organisms so similar to those that already exist in nature that laboratory derived intrageneric constructions can be exempt from review? Or are the risks of intrageneric and intergeneric constructions similar, so that they should be reviewed in a similar manner?

Because the prospects for competition leading to extinction can be greater for closely related species than for distantly related ones (9), some propose that slightly modified organisms should receive special scrutiny. Others argue that the designation of genera in microorganisms, and in bacteria in particular, is often arbitrary and the concern about any single case should not be on taxonomic grounds per se, but rather on the ability or inability to cause harm (12).

Intrageneric and perhaps even intraspecific genetically engineered organisms might be expected to be less affected by any fitness disadvantage arising from changes in the natural balances between the genetic components of individuals in any population. Hence, they would be more likely to persist in the environment than intergeneric recombinant. Persistence of intergeneric recombinant, on the other hand, could be less of an issue than for intrageneric recombinant (27). If persistence is an important criterion, then taxonomic factors should be considered.

Gene Deletions

The deletion of an existing gene from an organism is more likely to arise spontaneously in nature than the de *novo* acquisition of a new characteristic. This class of molecular alterations probably poses the least risk for adverse consequences resulting from survival and reproduction after release of the engineered organisms. Other considerations, however, such as the potential for adverse genetic, physiological, and ecological consequences of the particular application would have to be assessed before such applications could be assumed safe and entirely exempt from review. Nevertheless, some review requirements are less pertinent to this type of molecular construction than for those involving acquisition of new characteristics, and so a modified review process could be appropriate.

Regulatory Genes

Regulatory genes control when and how much structural gene product a cell makes. The levels of gene product can affect the expression of individual characteristics, as well as the overall development, structure, function, and vigor of an organism.

Because gene dosage and timing are important to an organism's development, gene alterations in regulatory sequences are important to changes in structure and function (from an evolutionary and ecological standpoint) (5,20). In one example of tetracycline resistance in the bacterium E. *coli*, changes in a regulatory gene result in a 50-fold difference in the level of resistance to the antibiotic (11). Such changes can also affect the organism's ability to survive and reproduce in competition with related or neighboring organisms (31).

Regulatory gene changes in recombinant organisms could conceivably not only produce different patterns of gene expression, but also enhance persistence in the environment. On the other hand, changes in regulatory sequences that alter the metabolic regulation of an organism can reduce the organism's fitness (and thus survivability or persistence).

A pertinent argument has been made that less concern should be focused on the regulatory gene than on the trait whose expression is controlled—some traits being beneficial, while others have the potential for harm (19). The situations just described illustrate this point. Thus, developing a strategy to review regulatory gene changes based on the trait controlled, rather than on the molecular construction of the application, might be prudent.

IDENTIFYING RISKS: MICRO-ORGANISMS V. MACRO-ORGANISMS

A staggering array of genetically engineered organisms have been proposed for potential environmental applications (see app. A; 44,46,51). Public concern over this next step in biotechnology appears greater when the release involves micro-organisms. Genetically engineered plants with plant genes have been field tested with little controversy. Genetically engineered plants with bacterial or fungal genes and genetically engineered bacteria, on the other hand, have involved more controversy and have been held up longer in the regulatory system or in litigation (10). Is this perception of differential risk between micro-organisms and macro-organisms realistic? Are there actually different risks to releasing genetically engineered bacteria-, algae, fungi, or viruses (microorganisms) compared with genetically engineered plants or animals (macro-organisms)?

Ecological Impacts

The obvious distinction between micro-organisms and macro-organisms is their size, and size may affect the ecological impact of an introduced organism. For example, larger organisms may move farther, move more biomass, and cycle more nutrients (per individual) through an ecosystem. They are also relatively easier to track and recover and, in general, biologists know more about their natural history than they do about micro-organisms.

Although the introduction of small organisms would probably generate less notice than the release of even a few big organisms in the wrong place, the small organisms are potentially more difficult to control. The generally more rapid reproductive rates of micro-organisms could allow

Photo credit: Peter Forde, Advanced Genetic Sciences

Some of the equipment set up for monitoring survival and dispersal of ice minus bacteria in Advanced Genetic Sciences' first field test.

them to proliferate and spread more rapidly through the environment than larger organisms. Microorganisms are also harder to retrieve and exterminate.

Competition

Competitive interactions between newly introduced engineered organisms—either micro- or macro-organisms-and native organisms are crucial components of ecological impact assessment. Competition occurs if the released and indigenous organisms limit each other's abundance in the environment without consuming each other. Competition with alien organisms can result in extinction of native taxa (9,28)53). Among plants, competition-based local extinction appears relatively common (52). Are genetically engineered micro-organisms better able than macro-organisms to compete with natives?

Most data on this subject have focused on microorganisms. Theories of competition do not suggest any difference between the effects of macro- and microorganisms. Those studies that considered competition of micro-organisms also indicated that the principles of competition are universal for both types of organisms (22).

An important issue affecting the impact of released organisms on competitive interactions in the environment is that the less that is known about an ecosystem and a species, regardless of its size, the harder it is to describe competitors. This factor is not an actual function of the different sizes of micro-organisms v. macro-organisms. At present, more pertinent information for microorganisms exists, Thus, it should be easier to assess competitive interactions (and adverse consequences) for the release of an altered microorganism.

Cascade Effects

One of the more difficult problems in analyzing the environmental impact of intentionally introduced organisms is the possibility of cascade effects-changes in one species that destabilize relationships between other species, leading to changes in species far removed from the original disturbance. Cascade effects are the least predictable potential consequences of a planned introduction. Although ecologists have spent a lot of time examining the structure of communities, it is still rarely possible to anticipate all the ramifications of introducing or removing a seemingly innocuous species. Chapter 5 discusses cascade effects in microbial communities and among macro-organisms.

Genetic Impacts

In addition to considering different ecological impacts based on the size of the released organism, important genetic questions should be examined:

- can the organisms exchange genetic information through sexual mechanisms;
- can the organisms exchange genes between species via nonsexual mechanisms (e.g., viruses or plasmids, see ch. 4); and
- does either mechanism carry greater risk of adverse environmental consequences with macro-organisms or micro-organisms?

The issue of genetic transfer mechanisms is not one of differences between macroganisms and micro-organisms. Instead, it is a question of problems specific to a particular release application, For example, even for applications that use sexual reproduction as the principal mechanism for genetic exchange, another factor–the mating system—must be considered. Species that require two individuals of opposite sexes to establish a breeding population do not as readily colonize distant areas as species in which a single individual can establish a breeding population.

Generalizations about potential genetic impacts, however, are best applied to well-studied species of organisms—small or large. Among wild and little-known species, there are diverse mating systems in both groups, Plants and some vertebrates are known to exchange genes with members of other genera, while bacteria in the field might do little recombining of any sort. Thus, a strategy to generically assess potential genetic risk on the basis of a distinction between macro-organisms and microorganisms would be inadequate.

Evolutionary Impacts

The risks of evolutionary lability in the deliberate release of either micro-organisms or microorganisms should be considered. Neither group

is perfectly adapted to its environment. Given real space and finite populations, any organism is likely to evolve if presented with an environmental opportunity or challenge (7). An analysis of the environmental risks (including genetic and ecological risks) would be inadequate if the released taxa evolved characteristics that were lacking when the organisms were introduced. The potential for evolution is a function of both population size and, most importantly, the selection pressure applied. Do microorganisms differ from macro-organisms in their potential to evolve?

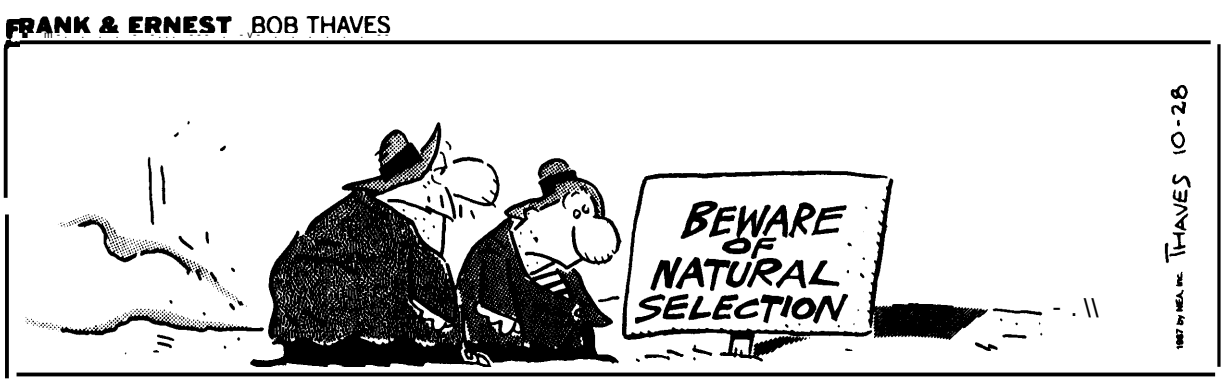
Number of Organisms

The number of organisms to be introduced is a key component in the consideration of evolutionary potentials and impacts. Micro-organisms and macro-organisms include diverse types with different potential for invasion and establishment. In general, the number and the density of organisms involved in a given environmental application will be greater in a release of microorganisms. This difference in numbers makes the probability of an evolutionary response higher in an introduction that involves micro-organisms. Other things being equal, the evolutionary risks associated with the environmental release of microorganisms will be greater than those for released macro-organisms. For example, if mutation occurs at a rate of one in 10^7 organisms and if one in 10^3 of these mutations has an evolutionary impact, the net probability of an environmental impact is one in 10^{10}. Therefore, a release of 10^{12} bacteria in a field trial (e.g., 1 liter of 10^9 organisms per milliliter) could result in an evolutionary impact in that population. However, such a consequence is unlikely to occur among a release of only $1O^9$ organisms.

Selection Pressure

Selection pressure is the most critical component in estimating the probability of adverse evolutionary consequences. In the face of selection pressure, a trait that favors survival and reproduction (i.e., differential reproductive success) will increase in frequency in the population. Traits conferring disadvantages will be selected against. Natural selection appears to operate on microorganisms and macro-organisms by the same mechanisms. But the larger number of microorganisms (by as much as six orders of magnitude) can allow more rapid adaptive responses since they have shorter generation times and more genetic variation can be screened in a given amount of time,

Some applications are more sensitive to selection pressure than others, and this difference stems mainly from the various uses of engineered organisms. Again, however, sheer numbers of released organisms could play an important role. For example, strong selection that eliminates 99 percent of a species will leave behind 10 survivors of a population of 1,000, and 10,000 survivors of a population of 1 million. The survivors of such selection would probably be better adapted, and a population of 10)000 is more likely to reproduce itself than is one of 10. Thus, larger populations (in this case a larger number of released organisms) increase the probability of evolutionary response to selection pressure. The larger numbers of released organisms that would be associated with microorganism applications could more readily evolve in response to environmental selection pressures than the smaller macro-organism populations.



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IMPLICATIONS FOR A RESEARCH AGENDA

Planned introductions of genetically engineered organisms are the new frontier in biotechnology. The techniques for exploiting this frontier (e.g., recombinant DNA technology and plant cell culture) are well-developed and continue to be refined. But specific data and basic, broad-based information about many areas necessary to develop capabilities for generic risk assessment and management strategies are lacking. In many instances, much of this information can only be obtained by small= scale, experimental field testing. Still, controversies surrounding initial applications to release genetically engineered organisms into the environment have illuminated areas where research efforts should focus.

Current Status

Although nearly all risk assessments—including chemical assessments—are and will continue to be plagued by incomplete data (8), some research efforts have begun to yield information that is crit - ical to the examination of potential risks associated with the planned introduction of genetically engineered organisms. As the data compiled from small-scale field trials increase, regulators can develop and refine the risk management process. The charge of funding research efforts to enhance risk assessment of environmental applications of genetically engineered organisms falls principally to three Federal agencies: the Environmental Protection Agency (EPA); the U.S. Department of Agriculture (USDA); and the National Science Foundation (NSF).

Environmental Protection Agency

EPA funds biotechnology risk assessment research through the Office of Research and Development. At EPA, all biotechnology research projects—intramural and extramural—involve risk assessment. Funding in fiscal year 1986 totaled $4.4 million; in fiscal year 1987 it reached $5.7 million (26). Table 6-1 lists some of the types of projects being funded by EPA to develop an adequate scientific database that will allow prediction of environmental risks possibly associated with the deliberate release of genetically engineered organisms. In a recent solicitation for research grant proposals, EPA identified ecological risk assessment, ecosystem structure and function, and ecological and toxicological effects as priority areas (49).

Table 6.1.—Types of U.S. Environmental Protection Agency Biotechnology Risk Assessment Projects

- Methods for assessing the fate of genetically engineered micro-organisms in the soil
- Methods for detecting, identifying, and enumerating genetically engineered bacteria in the soil
- Survival, modification, and effects of genetically engineered micro-organisms in aquatic environments
- Genetic transfer in aquatic environments
- Fate and effects of genetically engineered micro-organisms on ecological processes
- Fate and effects of genetically engineered micro-organisms in simulated natural environments

SOURCE: Office of Technology Assessment, 1988,

Federal law limits the scope of EPA's biotechnology research efforts to those program projects designed to assist other EPA sectors to perform their missions. Nevertheless, the range of research projects that the Agency funds should provide valuable data and should advance in the field of biotechnology risk assessment and risk management generally.

U.S. Department **of Agriculture**

Biotechnology research performed by or for USDA is administered chiefly through the Agricultural Research Service and the Cooperative State Research Service. Direct risk assessment components of research represent only a small fraction of the biotechnology projects at either agency (4,47). No clear direction to increase or promote risk assessment aspects of biotechnology research at USDA exists (4). Recent reports, however, indicate that the Department plans to increase the profile and funding in its research agenda of aspects specific to biotechnology risk assessment (18).

National Science Foundation

From 1 to 13 percent of biotechnology projects funded by NSF relate directly to risk assessment (47). Equally as important as funding for direct biotechnology risk assessment, however, is NSF funding for research projects to develop the fun-

damental scientific database needed for appropriate risk strategies. NSF supports projects in several key areas, including microbial ecology, the ecology of genes and plasmids, evolutionary biology, and systematic. Additionally, NSF has issued a program solicitation to establish Biological Facilities Centers and Biological Research Centers (35), one of which is to be devoted to biotechnology risk assessment (24).

Finally, NSF, USDA, and the U.S. Department of Energy have undertaken a joint initiative for plant science centers beginning in fiscal year 1988 (34). Successful initiatives might involve examining responsible application of genetic engineering to avoid undesirable environmental effects or clarifying ecological processes in agroecosystems and (34).

Research Needs For the Future

Several permits for small-scale field tests of environmental applications of biotechnology are in the regulatory approval process or have been been approved and conducted (see ch. 3 and app. A). While the information and data gained from these experiments will be valuable in designing future risk assessment and risk management protocols, an expansion of basic scientific research to gather data critical to risk assessment is also necessary. Billions of dollars are being invested throughout U.S. industrial sectors to comply with various environmental standards, but comparatively little is being invested specifically to improve the scientific basis for the standards (8). An improvement in risk assessment would be a major step in ensuring that compliance money is well spent (8). Important areas of research include:

- **Taxonomy and Systematics.—gathering data on the classification and evolutionary** relationships of natural populations (especially nontarget microorganisms) should be emphasized.
- Natural History. -collecting data on the life histories of organisms intended for planned introductions and the organisms with which they interact is critical, especially for those with potentially harmful impacts.
- Ecology.—the complex interactions of microbes, plants, and animals need to be better understood so that improved predictive capabilities can be developed. Crop ecology, in particular, is important because agricultural uses will be the majority of early applications.
- Test Systems.—aquatic and terrestrial laboratory microcosms and mesocosms look promising for analyzing ecological processes prior to planned introduction. They need further development and refinement.

However, although increased investment in specific research areas is critical, the paramount need is to develop interdisciplinary research programs in order to support biotechnology risk assessment. Research in such programs should be thoroughly integrated, from hypothesis generation to experimentation and interpretation of results. Active research cooperation among microbiologists, geneticists, ecologists, molecular biologists, evolutionary biologists, plant pathologists, entomologists, agronomists, and epidemiologists should be encouraged. The scientific data gained through such collaborations would improve significantly the ability to assess biotechnology risks (37,38)41). Nevertheless, uncertainties and questions in risk assessment of planned introductions will continue to exist. No amount of research funding can answer all questions; tough risk management decisions that weigh benefits against risks will need to be made.

SUMMARY AND CONCLUSIONS

During the 1970s, public concern about the effects of technology on the environment and human health led to the development of methods to help regulators evaluate and control potential hazards. More recently, attention has focused on evaluating risks that might be associated with planned introductions of genetically engineered organisms into the environment. The related issue of managing risk has also received public attention.

Risk assessment, a process distinct from risk management, uses scientific data to estimate the effects of exposure to hazardous materials or other situations. Derived from a factual base, it can be qualitative or quantitative, Risk management, on the other hand, weighs policy alternatives to select the most appropriate regulatory strategy or action, This process depends on the scientific findings of risk assessment, as well as the role of the public. It involves the integration of scientific, social, economic, technical, and political concerns. A key to improving the current situation is to distinguish between those aspects of the process that are scientific (risk assessment) and those that are matters of policy decisions (risk management).

Although risk assessment of recombinant DNA technology is not a new issue, the specific application of risk assessment to planned introductions of genetically engineered organisms has become a matter of debate. Methods developed in the previous decade for chemical risk assessment have been suggested as models for assessment of risks that might result from the planned introduction of engineered organisms. To date, however, generic risk assessment protocols to analyze the impacts of genetically engineered organisms have not been widely agreed upon.

Experiences with historical agriculture applications are pertinent and provide parallel scientific information for many potential applications. Small-scale, experimental field testing is necessary to improve baseline data for risk assessment.

At present, some scientists argue that the expectation of safety can best be met by a scientific review of proposed releases of genetically engineered organisms into the environment on an adaptable, case-by-case basis, and that at this time *a **priori*** exclusion of any application from review is problematic. Other scientists hold that a rigid case-by-case approach could paralyze advances in planned introductions of genetically engineered organisms, and that a proper balance between regulation and safety would involve each organism being assessed and classified (on the basis of scientific criteria) into categories requiring different levels of review. In either case, future experience with the impact of various types of genetically modified organisms on environmental processes should result in a safe, streamlined review process for some applications, or a lifting of the requirement for review.

Categories that could be considered for abbreviated review include: crop plants and domesticated animals, and organisms involving nondisease-associated genes or gene deletions. Applications in which the genetically engineered product is substantially identical in its properties to naturally occurring genetic variants; that could be produced with previously existing methods and without being subject to regulation under existing law; that are already available and approved for field testing; or that contain no new genetic material except marker sequences in noncoding regions probably could warrant abbreviated review or possibly even exemption.

Ecological, genetic, and evolutionary impacts that could result from planned introductions of micro-organisms or macro-organisms are important in assessing risks of an introduction. In general, existing knowledge of macro-organisms (plants or animals) exceeds information available for micro-organisms (bacteria, algae, fungi, or viruses), so less scrutiny might be required to yield an evaluation of the risks associated with the release of a macro-organism.

Controversies surrounding the initial applications to release genetically engineered organisms into the environment have illuminated areas where fundamental knowledge of many systems is currently lacking. In particular, active research cooperation among microbiologists, geneticists, agricultural scientists, plant pathologists, entomologists, agronomists, ecologists, and evolutionary biologists should be encouraged. Interdisciplinary research is critical to developing adequate risk assessment and risk management for planned introductions of genetically engineered organisms. To dispel speculation, increasing the general knowledge base about organisms intended for environmental applications is paramount.

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