Chapter 1

Summary, Policy Issues, and options for Congressional Action

"The greatest service which can be rendered any country is, to **add a** useful plant to its culture."

Thomas Jefferson
"The Papers of Thomas Jefferson"
(Accession No. 39161),
Library of Congress, 1800

"one must learn by doing the thing, for although you think you know it you have no certainty until you try."

Sophocles
496(?)-406 BCE

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Chapter 1

Summary, Policy Issues, and Options for Congressional Action

The development in the 1970s of techniques for splicing fragments of DNA from different organisms (recombinant DNA technology) opened up a new science of genetic engineering and a new industry, "molecular" biotechnology. The roots of this new industry lie in practices of animal husbandry, agriculture, and fermentation that extend back for thousands of years. To these ancient practices modern biotechnology adds not only recombinant DNA and cell culture, but also a host of applications using living organisms to make commercial products. These techniques promise to reshape many fields; they are now revolutionizing the pharmaceutical industry and medical diagnosis and treatment.

Commercial biotechnology is advancing into areas that depend on the introduction of genetically engineered organisms into the environment. These applications could improve old tools or produce new ones for many fields, including agriculture, forestry, toxic waste cleanup, mining, enhanced oil and mineral recovery, and others. In some cases, such as pest control or toxic waste management, successful development of biotech - nological tools could reduce or phase out dependence on older, more hazardous chemical technologies. It is widely expected that the application of such biological approaches to many human activities will prove more benign to the environment than traditional technologies.

Planned introductions of genetically engineered organisms into the environment, often called ***deliberate release,*** are not, however, without potential risks, Virtually any organism deliberately introduced into a new environment has a small but real chance of surviving and multiplying. In some small subset of such cases, an undesirable consequence might follow. The complexity of even simple ecosystems makes the precise prediction of such events, and of their consequences, difficult.

This element of uncertainty has led some scientists, public officials, and private citizens to voice concern about the safety of planned introductions. Although there is some consensus in the scientific community that the likelihood of unique or serious problems from planned introductions is quite low, this opinion is not held unanimously. Some scientists cite the beneficial introduction of thousands of species of naturally occurring microbes, plants, and animals that have not adversely affected the environment. Other scientists point out that a small fraction of such introductions have become pests, and suggest that genetic modifications that permit engineered organisms to live in habitats new to them may, in some cases, present similar risks. There is also concern among some scientists that the genetic information newly added to existing species may sometimes produce undesirable changes in their ecological relationships with other species, or, in rare cases, be directly transmitted to other species.

The potential benefits of new biotechnologies have been widely reported. Thus, this report focuses primarily on questions raised by the critics: How do environmental risks from planned introductions of genetically engineered organisms compare to those encountered in the past in agriculture and commerce? How accurately can scientists predict the consequences of planned introductions? What genetic and ecological effects are possible or likely? What scientific and social issues need to be considered in developing risk assessment and mangement procedures? Does the introduction of genetically engineered organisms require new regulatory procedures to protect environmental and public health?

It is important to recognize several conditions that limit generally (though not absolutely) the discussions and conclusions contained in this study:

- **Time Scale**: This study focuses on the near, or foreseeable future, generally within about the next 5 years.
- **Subject Matten** The issues discussed pertain to small-scale field trials more often than to

large-scale, commercial applications. The degree to which these issues are relevant to large-scale, commercial applications should be revealed by the results of small-scale field tests.

- **Definition:** In this study, the term "genetically engineered organism" is used most often to mean an organism to which genetic material has been added or deleted via recombinant DNA techniques. This usage is not, however, absolute, since some regulatory agencies (e.g., EPA) presently define the term more broadly. Some of the genetic or ecological issues discussed in the study might also apply to organisms produced by means not involving recombinant DNA in the strict sense, such as cell fusion.

It is possible that new types of planned introductions not now under development, or the greater scale of some commercial applications, might introduce questions or concerns in addition to those examined in this study.

Foremost among OTA's conclusions is that **there are reasons to continue to be cautious, but there is no cause for alarm.** Significant areas of uncertainty exist, particularly in the realms of microbial ecology and population dynamics. Widespread environmental or ecological problems do not now seem likely, however, though they could emerge in the future. If events develop other than as planned with a particular introduction, it seems more likely that the introduced organisms might become prematurely extinct, and consequently fail to perform as desired. While increased support for relevant research, both fundamental and applied, will reduce uncertainties, **some questions can be answered only with practical experience.**

Even though the range and complexity of applications of new biotechnologies means that the type of general models used for evaluating the risks from chemicals cannot be transferred easily, **adequate review of planned introductions is now possible.** A review process that involves critical study of planned introductions by experts with relevant knowledge and experience offers confidence of being able to anticipate and prevent most potential problems. As the number of such completed reviews increases one may expect some generalizable conclusions about the safety of different types of introductions, This should enable a consequent streamlining of the review process. And although almost any category proposed for exemption from review can be shown wanting through a hypothetical scenario, it is reasonable to expect that, with experience, broader categories will emerge for which less rigorous levels of review could be defended. Categories that could be examined now, at least for abbreviated review, include:

- organisms that could be produced with previously existing methods (e.g., mutagenesis and selection) which, if they were, would not be regulated under existing law;
- an organism substantially identical to one that has already been reviewed and approved for field testing;
- organisms not containing any genetic material from a potential pathogen; or
- organisms whose DNA contains nothing new but marker sequences in non-coding regions.

Regulatory agencies can and should move promptly to establish at least provisional categories for different levels of review. They should act subsequently to modify and streamline these as experience indicates. This will sometimes be a contentious exercise, but the stakes, in terms of economic potential and environmental protection, are sufficient that there can be no substitute for common sense leavened by caution and appropriate flexibility. To guarantee essential public confidence, this also means that such decisions must be accountable, attributable to specific regulatory bodies, and sustainable by defensible and public reasoning.

With adequate review **none of the small-scale field tests proposed or probable within the next several years are likely to result in an environmental problem that would be widespread or difficult to control.** Indeed, greenhouse or microcosm studies are such inadequate predictors of field performance that in many cases **realistic small-scale field tests are likely to be the only way potential risks from commercial scale uses of genetically engineered organisms can be evaluated.** Assuming such small-scale field

tests fail to identify areas of significant concern, there would be no scientific reason not to seek further experience with field tests or applications on a larger scale.

It is important to note that modifying organisms for specific human ends is not new; selective breeders of plants and animals have been transferring genes for millennia, often creating forms through centuries of selection that differ from their original stocks more than the forms produced by recombinant DNA methods. One of the distinguishing characteristics of the new technologies is that they allow scientists to do many of the same things as before with previously undreamed of precision and speed. In evaluating the potential risks associated with these new technologies, the appropriate question is not "How can we reduce the potential risks to zero?" but "**what are the relative risks of the new technologies compared with the risks of the technologies with which they will compete?"** Furthermore, **What are the risks posed by over regulating, or failing to develop fully the new technologies? How do we weigh costs and benefits? How much review is enough?** In most cases the new potential risks will be qualitatively similar to the old risks. Sometimes they will be quantitatively less. The potential benefits to be derived are often substantial.

ANTICIPATED APPLICATIONS

Pending and potential environmental applications of genetically engineered organisms span an enormous range—enormous in terms of engineered organisms, the diverse environments into which they will be introduced, and the functions they are intended to perform (see table 1-1 and app. A).

Many pending or imminent introductions involve minor genetic alterations to modify an existing function in an existing organism. Most involve the activity of the product (protein) of a single structural gene, More than a dozen small-scale field tests have already taken place. Applications for others are pending or anticipated in the near future,

Plants

To decrease crop losses due to weeds, genes have been introduced into several plant species to confer resistance or tolerance to certain herbicides, including glyphosate (Calgene, Davis, CA; Monsanto, St. Louis, MO), sulfonylurea (Du Pont, Wilmington, DE), and atrazine (Ciba-Geigy, Greensboro, NC). Depending on the **particular herbicide,** this practice could increase or decrease pollution hazards by stimulating changes in patterns of herbicide use.

Plants have also been engineered better to resist disease. Tobacco plants (valuable for the ease with which they can be studied) have been transformed to resist crown gall disease (Agracetus, Middleton, WI). Researchers at Monsanto and at Washington University (St. Louis, MO) have also "vaccinated" tobacco and tomato plants against tobacco mosaic virus by inserting a single virus gene into the plant genome. Similar results with the alfalfa mosaic virus suggest that the same technique may protect many plants against virus-caused diseases.

Pest resistance is another promising area. The delta-endotoxin gene of the well known and much used bacterium Bacillus ***thuringiensis*** (BT), which encodes a toxin effective against certain caterpillars, has been inserted into tobacco and tomato plants.

Investigators are pursuing many other applications, including drought or saline resistant plants. Recombinant DNA and cell fusion techniques are being used to create new crop varieties, improve the nutritional qualities of some species, and increase algal production of substances used in the food industry. Future endeavors might include enhancing the ability of certain algae to sequester heavy metals from seawater, and introducing genes encoding compounds that protect seeds against insects. Such engineered seed protection could improve long-term storage of certain crops.

Animals

Most recombinant DNA work on animals focuses on altering livestock, poultry, or fish to improve reproductive performance, weight gain, disease resistance, or (livestock) coat characteristics. The types of alterations being pursued and the confined agricultural settings of most altered animals both provide continuity between modern and historical biotechnology.

Table 1.1 .—Some Representative Pending and Potential Environmental Applications of Genetically Engineered Organisms

MICRO-ORGANISMS

Bacteria as pesticides. "ice-minus" bacteria to reduce frost damage to agricultural crops.

Bacteria carrying Bacillus ***thuringiensis*** toxin to reduce loss of corn crops to black cutworm.

Mycorrhizal fungi to increase plant growth rates by improving efficiency of root uptake of nutrients.

Plant symbionts. Nitrogen-fixing bacteria to increase nitrogen available to plants, and decrease need for fertilizers,

Toxic waste disposal. Bacteria engineered to enhance their existing abilities to degrade compounds found in sludge in waste treatment plants.

Bacteria engineered to enhance their abilities to degrade compounds in landfills, dumps, runoff deposits, and contaminated soils.

Heavy metal recovery. Engineered enhancements possible to several species of bacteria now used to recover metals from low-grade ores (e.g., copper and cobalt).

Pollution control. Possible increased utility of bacteria in purifying water supplies of phosphorus, ammonia, and other compounds.

Viruses as pesticides. insect viruses with narrowed host specificity or increased virulence against specific agricultural insect pests, including cabbage looper, pine beauty moth, cutworms, and other pests.

Myxoma virus modified so as to restore its virulence against rabbits (which became resistant during early biocontrol efforts in Australia).

Viruses as vaccines. Vaccines against human diseases including:
- —hepatitis A and B
- —polio
- —herpes simplex (oral and genital)
- —malaria
- —acquired immunodeficiency syndrome
- —rabies
- —respiratory syncitial virus

Vaccines against animal diseases including:
- —swine pseudorabies
- —swine rotavirus
- —vesicular stomatitis (cattle)
- –foot and mouth disease (cattle)
- —bovine rotavirus
- —rabies (cattle, other mammals)
- —sheep foot rot
- —infectious bronchitis virus (chickens)
- —avian erythroblastosis
- —sindbis virus (sheep, cattle, chickens)

Muitivalent vaccines. Vaccines possible for antigenically complex diseases such as:
- —malaria
- —sleeping sickness
- —schistosomiasis

PLANTS

Herbicide resistance or tolerance to:
- Glyphosate
- Atrazine
- Sulfonyiurea (chlorosulfuron and sulfometuron) imidazolinone
- Bromoxynil
- Phosphinotricin

Disease resistance to:
- Crown gall disease (tobacco)
- Tobacco mosaic virus (and related viruses)
- Potato leaf roll virus

Pest resistance
- BT-toxin-protected crops, including tobacco (principally as research tool) and tomato.
- Seeds with enhanced anti-feedant content to reduce losses to insects while in storage.

Enhanced tolerance to environmental factors, including:
- **Salt**
- Drought
- Temperature
- Heavy metals

Nitrogen-fixation enhancements
- Nonlegumes enhanced to fix nitrogen, independent of association with symbiotic bacteria.

Engineered marine algae
- **Algae enhanced to increase production of such compounds as B-carotene and agar, or to enhance ability to sequester heavy metals (e.g., gold and cobalt) from seawater.**

Forestry
- **Trees engineered to be resistant to disease or herbicides, to grow faster,** or to be more tolerant to environmental stresses.

ANIMALS

Livestock and poultry
- **Livestock species engineered to enhance weight gain or growth rates, reproductive performance, disease resistance, or coat characteristics.**
- **Livestock animals engineered to function as producers for pharmaceutical drugs, especially of mammalian compounds that require post-synthesis modifications in the cell.**

Fish
- **Triploid salmon produced by heat shock for use as game fish in lakes and streams.**
- **Fish with enhanced growth rates, cold tolerance, or disease resistance for use in aquaculture.**
- **Triploid grass carp for use as aquatic weed control agents,**

SOURCE: Office of Technology Assessment, 1988.

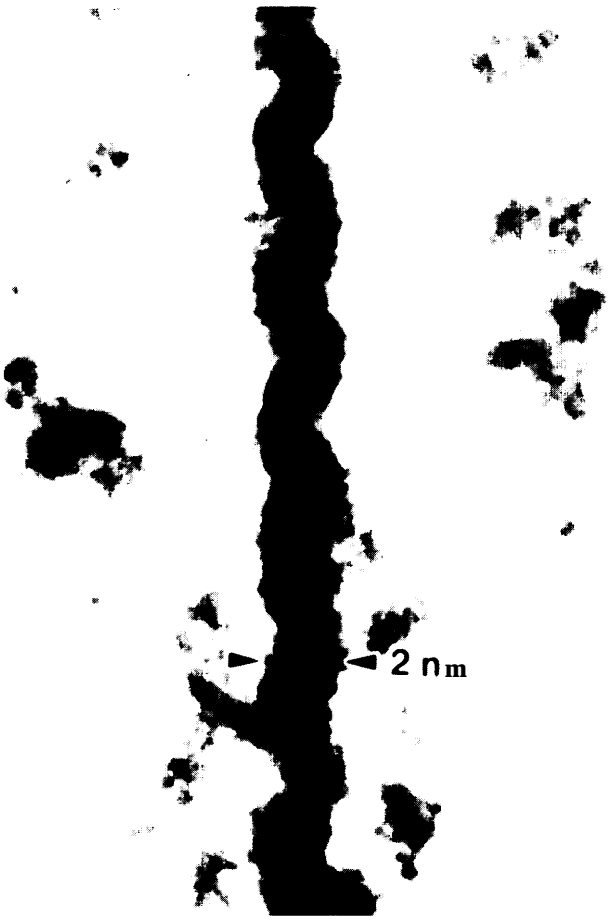

Photo credit" Hideo Yamagishi, Kyoto University

Electron micrograph of DNA double helix, "rim" ⁼nanometer= one-billionth of a meter.

Transferring animal growth hormone genes or exposing fish embryos to abnormally high temperatures to change chromosome number are other successful techniques. Genetic engineering also holds promise for altering insect pests for use in integrated pest management schemes which rely on biological as well as chemical controls.

Micro-organisms

Bacteria, viruses, and fungi offer the molecular biologist some of the best candidates for genetic engineering. Molecular genetics originated in experiments with certain species of these organisms: Of greatest use in this research is the common inhabitant of the human gut, *Escherichia coli.* Other bacteria of medical importance include *Salmonella, Streptococcus,* and *Bacillus.* Yeast, *Saccharomyces cerevisiae,* and other fermenters such as *Lactobacillus* have also been important in the evolution of molecular genetics, as have several bacterial and plant viruses. The genetic structure and functioning of these micro-organisms are among the best understood. Microbes are small and easy to handle in the laboratory, and they reproduce rapidly. Enormous numbers can be examined in a short time.

But the special qualities of microorganisms also present some unique problems. Because they are microscopic, special techniques are required to monitor their survival or dispersal. Their rapid growth rates under favorable conditions and the ability of some species to exchange genetic material make transfer of altered genetic material among some microbes less predictable than among larger organisms.

The ubiquity of microbes (they are literally everywhere; a gram of soil will commonly contain a billion microbes) and their key roles in the fundamental ecological processes of energy flow and nutrient cycles have led to some concerns about the potential for disruption of these processes if large-scale introductions of genetically engineered microbes take place. Some scientists, however, point to the high degree of functional redundancy among members of microbial communities, which acts as a buffer against far-reaching perturbations. They also cite the lack of negative consequences in considerable experience over the last century, during which large numbers of microbes have been introduced into the environment for agricultural and pest control purposes, and for pollution and waste treatment, and conclude from these observations that problems are not likely.

Many promising environmental applications of engineered micro-organisms are being developed. One bacterial application deletes the gene for a cell membrane protein that acts as a nucleus for frost formation. The resulting so-called ice-minus bacteria, derived from species that normally live on plant surfaces, could help reduce crop losses from frost. In other applications, the BT toxin gene has been inserted directly into some bacteria. In

one case researchers hope the transformed bacteria, adapted to live on the surfaces of the roots of corn plants, will help reduce corn crop losses to insect larvae. In another, the transformed bacteria are killed and treated to produce a particle containing BT toxin that can then be applied as a topical insecticide. Other bacteria are being engineered to degrade specific toxic compounds found in industrial waste or sludge. Many bacteria can break down toxic compounds naturally, and there is the potential of enhancing their ability to consume petroleum, solvents, benzene derivatives, or halogenated hydrocarbons like polychlorinated biphenyls, polybrominated biphenyls, or dioxin, although these applications are likely to be some years away.

One important application that has received a great deal of research attention is enhancing or transferring the capacity to make atmospheric nitrogen biologically usable, or to "fix" nitrogen. If managed well, this holds significant potential for reducing the amount of nitrogen fertilizer required in agriculture, thus reducing the costs and the problems associated with nitrate contamination of runoff water. BioTechnica International, Inc. (Cambridge, MA) is preparing to field test a variety of a naturally occurring bacterium with enhanced nitrogen-fixing ability. It is likely that the more ambitious goal of transferring nitrogen-fixing capacity directly to plants is many years from realization.

Viruses, especially those that affect insects, have potential as pesticides as well as vaccines for both animals and humans. Recent efforts have been directed toward engineering vaccinia viruses to produce vaccines for hepatitis B, herpes simplex, influenza, and hookworm as well as vaccines against such animal diseases as rabies, vesicular stomatitis (a disease of cattle), and others. These are usually produced by using recombinant DNA methods to separate the virus genes that will evoke immune responses in the infected organisms from the genes encoding the proteins responsible for disease. When the latter are removed, a number of the problems historically associated with attenuated or live virus vaccines in common use today are eliminated. Multivalent vaccines, which could be effective against several diseases at once or against complex diseases, are also being developed.

THE ROLE OF PUBLIC PERCEPTION AND THE REGULATORY REGIME

In many ways, the wide range of organisms and potential uses complicates the regulatory picture for the new industry of modern biotechnology because the **critical issues differ from application to application.** Policy makers need to rely on sound scientific review and weigh carefully any potential risks against anticipated benefits of each new planned introduction. **A flexible review process, founded in critical scientific evaluation and adaptable to the requirements of particular cases, can serve industry and the public interest well without being unduly burdensome.**

The Effects of Public Perception

Public perception of the benefits and risks of biotechnology is as likely to influence future industry developments as is formal risk assessment by scientific groups and public officials. When proposing to field test genetically engineered organisms, scientists—whether in academic institutions or industry–must be prepared to work with local citizens and officials. Recent experience in several communities and an OTA-commissioned survey have shown that public opinion is ambivalent and can be vocal with respect to planned introductions of genetically engineered organisms. In several cases public opinion has thwarted or delayed proposed field tests. In other communities opposition has been minimal, and in some cases vocal elements have been supportive. (Ch. 3 includes descriptions of the role of public perception in about a dozen local communities where field tests have been proposed or carried out.)

As in science and technology generally, public interest in the new biotechnologies is high. Al-

though people are concerned about the morality and safety of genetic engineering, they believe that research should continue. Most say they believe the benefits will ultimately justify the risks. Indeed, the public claims to be willing to accept relatively high probabilities of risk to the environment (provided oversight is sufficient) in exchange for the benefits that might accrue from environmental applications of genetically engineered organisms.

The Existing Regulatory Framework

Shortly after recombinant DNA technology appeared and began to be more widely used during the 1970s, concerns were raised about its safety. In an unprecedented move, scientists developing the new techniques met in 1975 at the Asilomar Conference Center (Pacific Grove, CA), and agreed to control stringently their own research until the safety of the new technology could be assured. In 1976, the National Institutes of Health (NIH) issued the first formal guidelines for recombinant DNA research. As research continued, and as scientists learned more about the safety of genetically engineered organisms, initial fears proved excessive, the guidelines were repeatedly revised, and the controls on recombinant DNA research in the laboratory were relaxed.

Some of the safety concerns that have surfaced over the planned introduction of genetically engineered organisms are about issues quite different from those associated with research confined to a laboratory. Numerous ecological issues not relevant to laboratory work become important when applications move beyond the laboratory and into the environment, Assuming regulation is appropriate (an assumption challenged by some), who should regulate planned introduction experiments? How should regulatory agencies assess potential risks? As more and more products reach field-test stage, the need to answer these questions becomes more pressing.

The White House Office of Science and Technology Policy published the Coordinated Framework for the Regulation of Biotechnology in June 1986. This document identifies the agencies responsible for approving commercial biotechnology products (table 1-2) and their jurisdictions for regulating field tests and planned introductions (table 1-3). It describes the regulatory policies of the Environmental Protection Agency (EPA), the U.S. Department of Agriculture (USDA), and the Food and Drug Administration (FDA), as well as the research policies of the National Institutes of Health (NIH) the National Science Foundation (NSF), EPA, and USDA. The purpose of the Framework is to enable the agencies to ‘(operate in an integrated and coordinated fashion [to] cover the full range of plants, animals, and micro-organisms derived by the new genetic engineering techniques. ”

At present, FDA relies on its existing policies for regulating biotechnology products. EPA regulates biotechnology under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Toxic Substances Control Act (TSCA). USDA relies on the Plant Pest Act and related statutes, while the Occupational Safety and Health Administration has regulatory authority over certain aspects of biotechnology that relate to workplace safety.

Table 1-2.—Agencies Responsible for Approval of Commercial Biotechnology Products

Biotechnology products	Responsible agencies
Foods/food additives	FDA, * FSIS[a]
Human drugs, medical devices, and biologics	FDA
Animal drugs	FDA
Animal biologics	APHIS
Other contained uses	EPA
Plants and animals	APHIS,[c] FSIS,[a] FDA[b]
Pesticide micro-organisms released in the environment	EPA,[d] APHIS[c]
Other uses (micro-organisms):	
Intergeneric combination	EPA,[d] APHIS[c]
Intrageneric combination:	
Pathogenic source organism	
1. Agricultural use	APHIS
2. Nonagricultural use	EPA,[d] APHIS[c]
Nonpathogenic source organisms	EPA Report
Nonengineered pathogens:	
1. Agricultural use	APHIS
2. Nonagricultural use	EPA,[d] APHIS[c]
Nonengineered nonpathogens	EPA Report

● Designates lead agency where jurisdictions may overlap,
[a] FSIS, Food Safety and Inspection Service, under the Assistant Secretary Of Agriculture for Marketing and Inspection Services, is responsible for food use.
[b] FDA is involved when in relation to a food use.
[c] APHIS An/real and Plant Health Inspection Service, is involved when the micro-organism is plant pest, animal pathogen, or regulated article requiring a permit.
[d] EPA requirement will only apply to environmental release under a “significant new use rule” that EPA intends to propose.

SOURCE: 51 Fed. Reg. 23339.

Table 1-3.—Jurisdiction for Review of Planned introductions

Proposed research	Responsible agencies
Contained research, no release in environment:	
Federally funded	Funding agency,[a]
Nonfederally funded	NIH or S&E voluntary review, APHIS[c]
Foods/food additives, human drugs, medical devices, biologics, animal drugs:	
Federally funded	FDA,[b] NIH guidelines and review
Nonfederally funded	FDA,[b] NIH voluntary review
Plants, animals and animal biologics:	
Federally funded	Funding agency=, APHIS[c]
Nonfederally funded	APHIS[c], S&E voluntary review
Pesticide microorganisms:	
Genetically engineered:	
Intergeneric	EPA[d], APHIS[c], S&E voluntary review
Pathogenic intrageneric	EPA[d], APHIS[c], S&E voluntary review
Intrageneric nonpathogen	EPA[d], S&E voluntary review
Nonengineered:	
Nonindigenous pathogens	EPA[d], APHIS
Indigenous pathogens	EPA[d], APHIS
Nonindigenous nonpathogen	EPA[d]
Other uses (micro-organisms) released in the environment:	
Genetically engineered:	
Intergeneric organisms	
Federally funded	Funding agency=, APHIS[c], EPA[d]
Commercially funded	EPA, APHIS, S&E voluntary review
Intrageneric organisms	
Pathogenic source organisms	
Federally funded	Funding agency,[a] APHIS,[c] EPA[d]
Commercially funded	APHIS[c], EPA[d] (if nonagricultural use)
Intrageneric combination	
Nonpathogenic source organisms	EPA Report
Nonengineered	EPA Report*. APHIS[c]

● Designates lead agency where jurisdictions may overlap.
[a]Review and approval of research protocols conducted by NIH, S&E, or NSF.
[b]APHIS issues permits for the importation and domestic shipment of certain plants and animals, plantpests and animal pathogens, and for the shipment or release in the environment of regulated articles.
[c]EPA iurisdiction for research on a plot greater than 10 acres.
[d]EPA reviews federally funded environmental research only when it is for commercial purposes.
Abbreviations: NIH = National Institutes of Health; S&E = United States Department of Agriculture Science and Education, APHIS = Animal and Plant Health Inspection Service; EPA = Environmental Protection Agency

SOURCE: 51 Fed. Reg. 23305

Several problems—virtually none of them new or unique to biotechnology-face regulators, particularly in the area of planned introductions of genetically engineered organisms:

- **Scope:** Should regulation be product-based, or is there a foundation for basing it on the processes used in producing the products?
- **Definitions:** Common definitions of critical terms such as *deliberate release* into the environment, and *pathogen,* need to be established.
- **Risk Assessment and Management:** Decision makers must perform a complex balancing act—weighing the known risks and benefits of existing technologies against the potential risks and likely benefits of new technologies.
- **Jurisdiction of Federal Agencies Regulating Biotechnology:** Potential conflicts between overlapping jurisdictions of Federal agencies should be prevented from interfering with appropriate regulation.
- **Role of State and Local Governments:** Local zoning and environmental statutes are important determinants of policy that may affect future tests and applications.
- **Public Perception:** Whatever the scientific and regulatory judgments, public perception

will strongly affect the conduct of field tests and the final outcome of commercial applications of biotechnology.

The Coordinated Framework appears to provide means for dealing with most of these problems and others (discussed in ch. 3). As of May 1988, it had been in use for 23 months, and will soon need to be formally evaluated to determine if there are problems it does not cover adequately.

GENETIC CONSIDERATIONS

The planned introduction of genetically engineered organisms that can survive and multiply raises a variety of genetical questions, many of which are relevant only if there is a reasonable probability that the introduced organisms could have a deleterious impact on the environment or public health. The likelihood of such a consequence depends on the nature of the organism and on the new genetic information it carries. It also depends on whether the new genetic material in the altered organism remains where it was inserted, performing as designed, or is transferred to a new location in a nontarget organism, possibly performing in an unanticipated manner. It may therefore be important to consider, where such occurrence is plausible, the probability that novel genetic material will spread beyond the engineered organisms at the release site. The migration of genetic material from one organism to another by means other than germ cells is called horizontal transfer. In bacteria, horizontal transfer is the transmission of genetic information from one contemporaneous bacterial cell to another by whatever means.

What are the potential outcomes of such transfer? Are they beneficial, harmful, or of no consequence? How can the movement of genetic material be observed? What techniques or constraints can limit the frequency or mitigate any potentially adverse consequences of gene transfer? Special considerations exist for each set of organisms.

What Researchers Know About Gene Transfer

Gene transfer between species takes place via a limited number of means, including:

- **Hybridization:** also known as sexual outcrossing, in plants and animals. In animals this is generally impossible except with closely related species; it is common in many groups of plants.
- **Transformation:** the incorporation by bacteria of DNA fragments from the immediate environment.
- **Plasmids:** circles of DNA that are separate and replicate independently from the chromosome within cells. Some are self-mobilizable, and can transmit themselves between compatible cells. Others require the assistance of mobile plasmids to be transferred.
- **Viruses** nucleic acid (DNA or RNA) packaged in a protective protein coat (unlike plasmids). To reproduce, a virus must infect a cell and take over the host cell's metabolic machinery. Viruses can transfer genetic material between species via "transduction" (see glossary),
- **Transposons (Transposable Elements) and Insertion Sequences:** DNA sequences carrying one or more genes, and flanked by insertion sequences—short DNA fragments that are able move to different places within the cell on the same or a different DNA molecule.

Some of these mechanisms are shared by several classes of organisms, while others are unique to particular groups. Gene transfer is more likely in some groups of bacteria, and less easy to control or predict than hybridization in plants or animals. Except where indicated, the following discussion of gene transfer is more relevant to bacteria than to higher organisms.

Much of what investigators know about gene transfer comes from laboratory experience. Gene transfer between bacteria, for example, is well studied among laboratory populations. Although the frequency of transfer may be relatively low, rapid reproduction and large populations mean that genes can be transmitted into some bacterial populations quite rapidly, if coupled with the

appropriate selection pressures. Among insects, evolutionary evidence indicates transfer can occur via transposable elements and viruses, but how often is not known. Similarly, it seems that some horizontal transmission between disparate mammalian families may have taken place in the past, but little evidence exists for transfer in recent times or at appreciable frequencies. Gene transfer among plants by mechanisms other than hybridization has not been well studied, and if it occurs in nature it seems to be quite rare.

The systems of genetic transfer that have been studied were chosen largely for their amenability to laboratory research. They represent only a small sample of what actually occurs in nature. It is clear that with a few exceptions (i.e., between some closely related animal or insect species, between many higher plants, and between some bacterial species), **significant natural obstacles block most gene flow between species.** It is logical to assume, and data support the conclusion, that natural populations of bacteria (generally less dense than laboratory populations) experience lower rates of gene transfer than do laboratory populations. Questions that remain include:

- How extensively do gene transfer mechanisms observed in the laboratory operate in nature?
- What are the genetic and environmental conditions under which novel information could be incorporated into a foreign genome and subsequently expressed?
- How do populations of organisms limit incursion of new genetic material?

Predicting Potential Effects

Several questions are posed by the introduction of a recombinant organism into the environment: What are the conditions that encourage transfer or maintenance of the inserted genes, and how likely is it that genes could be transferred beyond the target site? If transferred, will the new genetic material be expressed? If transferred and expressed, will there be any environmentally significant consequences, positive or negative? (The last question is considered more fully in the section on *Ecological Considerations.)*

Some observers maintain that if it is known that the gene in question will not move about, the potential consequences of gene transfer should not be a concern. Others argue that if the modified organism or gene will cause no problems if it does spread, then estimating the probability of transfer is unnecessary. Both issues must be addressed for a balanced evaluation of the potential consequences of a proposed introduction experiment. A very low probability of transfer multiplied by a moderate probability of hazard if transfer occurs produces a different situation than if both probabilities are very low. Of course, a significant probability of benefit could also offset all or part of any potential risk.

Other observers argue that it should be assumed that any introduced genetic material will eventually be transmitted to nontarget species, and that any consequences should be anticipated. Predicting the consequences and evaluating the risks of deliberate release requires information about intrinsic and extrinsic factors influencing the magnitude, frequency, and stability of gene transfer. **At a minimum, an analysis of the magnitude of gene transfer in those cases where it might be important must address two questions:**

- **How frequently is the genetic material likely to be transferred** to nontarget organisms, especially in comparison to natural background rates?
- **What is the degree of genetic relationship** between the original organism and the nontarget species?

Intrinsic Factors

Intrinsic factors, which are elements of molecular biology, include characteristics of the host organism such as the gene involved, the vector for transferring the gene, and the engineered system itself. Ideally, the biology and natural history of at least these elements would be well described and understood. **The life cycle, natural history, and genetic repertoire of the organism from which a gene is deleted or into which a gene is inserted should be well understood, and the gene itself and the mechanisms controlling its expression in the new host cell should be examined.** Substantial "natural history" needs to be

understood before proceeding with planned introduction experiments. Reviewers should be sensitive to the possible expression of novel properties of the host organism.

Because a vector can shuttle genetic material between organisms, familiarity with its host range and behavior is critical. Some vectors transfer genetic material by themselves, but some require outside help. It is important to establish whether the new gene is mobile or immobile in its new host cell. Last, **the whole construct of the introduced gene, new host, and vector material needs to be considered. The intracellular configuration of the new gene in the host organism—where it finally resides in host DNA—is a prime determinant of its potential for movement to new hosts.**

Extrinsic Factors

Extrinsic factors are imposed by the environment. The environment where the engineered organism will be released should be analyzed along with other environments the organism could encounter. Factors to be considered include:

- **Receptivity of Habitat**: Will the engineered host survive to do its job and reproduce once introduced? Natural variation in crucial environmental factors is great. Soil systems, and other natural habitats, may not be sufficiently fertile to support the addition of large numbers of engineered organisms. Engineered bacteria will often beat a selective disadvantage when competing with natural populations.
- **Potential Nontarget Recipients**: The most likely nontarget recipients of engineered genetic material are genetically similar organisms; the probability of transfer declines with decreasing similarity or relatedness. If the engineered gene is already present in the recipient environment, concern about transfer beyond the intended host is reduced.
- **Density**: The higher the densities of engineered organisms and potential nontarget recipients, the more likely gene transfer is, although in the absence of selection pressure it will have no consequence.
- **Selection Pressure**: Environmental conditions will determine whether an engineered gene or organism will persist in a population, be expressed, or increase in frequency after introduction. Strong selection for a particular trait-e.g., the presence of an antibiotic—increases the frequency of a gene or genes coding for that trait. Selection pressures vary with each application and depend on the gene involved, how it is regulated and expressed in the host, and its interaction with the environment. While it can be expected that many introductions will be selected against, or at best be selectively neutral, those introductions favored by selection are likely to be most successful.

Monitoring Gene Transfer

Convenient, economical, and effective methods of tracking engineered organisms or the engineered gene(s) they contain are being developed. These can be divided broadly into selective and biochemical methods.

Selective tracking methods work by marking the host chromosome with antibiotic resistance genes or nutritional markers that confer a competitive advantage under specific conditions. When exposed to selection pressure exerted by the antibiotic, for example, organisms carrying the resistance gene survive and can be easily detected,

Such markers must be carefully screened, however, because those that confer an unintended competitive advantage-or that mutate to confer resistance to a whole family of antibiotics-could lead to problems (see box A). On the other hand, resistance genes are already present in many naturally occurring soil micro-organisms (a valuable source of new antibiotics), and antibiotic resistance markers have long been used in studies of root ecology with no apparent ill effects.

When using nutritional markers the host chromosome can be marked with a metabolic gene (e.g., one coding for the production of an enzyme) not normally found in that organism, Monsanto researchers have produced such a system with their insertion of genes for metabolizing the sugar lactose into the soil bacterium they are studying.

Box A.—The Power of Selection Pressure: Antibiotic Resistance Genes in Bacteria

The bacterium responsible for gonorrhea, Neis***seria gonorrhea,*** was once highly vulnerable to penicillin. About 30 years ago, penicillin-resistant strains began appearing. Today, local populations of highly resistant bacteria have become common. These resistant populations are most often centered in places where low doses of ampicillin (a penicillin derivative) are administered continually and indiscriminately as a prophylactic. The resistance is carried on a plasmid that has been transferred between bacterial species; the identical plasmid has also been found in the intestinal bacterium ***Escherichia coli.***

Responding to the decline in effectiveness of penicillin, many physicians have switched to newer, more effective antibiotics. Spectinomycin is an important one that has been used widely to treat sexually transmitted diseases among U.S. military personnel in the Republic of Korea since 1981. There have been increasingly frequent reports, however, of disease strains resistant to this antibiotic. Tests have revealed that most of these strains are susceptible to penicillin as well as to some other antibiotics.

The key factor in this story is selection pressure. Indiscriminate and widespread use of one antibiotic exerts strong and consistent selection pressure on the target populations (in this case, bacteria), favoring survival of organisms resistant to the antibiotic. Substituting a selection pressure caused by one agent for a similar selection pressure caused by another evokes a similar response to the new agent. [n the meantime, selection pressure caused by the First agent (penicillin) having been released, the response (which is energetically expensive for the cell to maintain) is likely to be dismantled by selection pressure against energy consumption unnecessary for survival.

The spread of antibiotic resistance factors is the sort of adaptive response any population will manifest in response to strong selection pressure. In bacteria, the rapid, worldwide spread of the initial penicillin resistance was enhanced by highly active vectors—a conjugative plasmid and a transposon. Such combinations of intense selection pressure and actively mobile vectors should be avoided whenever possible. Responses to such problems should take advantage of existing, natural selection and capitalize on it.

SOURCE: Office of Technology Assessment, 1988

As with antibiotic resistance gene markers, however, this may not always reveal if or how widely the engineered gene or construct may have traveled to other organisms. The movement of genes does not always correspond completely to the movements of the original host organism. To track the engineered gene itself, a selectable marker gene must remain where it is inserted, close to the gene to be tracked; the two would most likely be transferred together (depending on how closely they were linked), making it possible to locate the engineered gene by selecting for and isolating any cells with the marker gene.

Biochemical methods often rely on gene probes made with recombinant DNA techniques. A gene probe is a segment of DNA whose nucleic acid sequence is complementary to the gene of interest, or to a portion of it. The probe is labeled with radioactivity or marked with a dye that can be easily detected in the laboratory. A gene probe will track a gene even if it is separated from a tightly linked selection marker or in an organism that cannot itself be cultured. But to quantify gene transfer would require general tests of all microbes or DNA in the release environment; processing large numbers of samples would be difficult and expensive.

Inhibiting Gene Transfer

As with detection and tracking, techniques to prevent or reduce horizontal gene transfer are not yet well developed. Researchers can either choose or modify the host and/or the vector so that introduced organisms have a low probability of persisting in the environment, of transferring genetic material, or both. Specific choices and modifications will depend on the characteristics of the organisms involved and the purpose for which they are engineered.

Whereas gene transfer may be a legitimate concern in planned introductions of some bacteria, it is unlikely to be a general concern with plant DNA vectors even when the most active plant vectors are used. Nor is gene transfer a concern in organisms engineered by gene deletion, though other traits may then be important.

Reducing or eliminating the use of mobile plasmids and transposons could also help minimize horizontal transfer. A disarmed transposon with its engineered gene could no longer separate and move independently from the chromosome where it was inserted. This approach of "crippling the vector" has been successfully used in transferring the gene for *Bacillus thuringiensis* toxin into another common bacterium, *Pseudomonas fluorescens;* it has also been used to make an immobile vector for insect genetic engineering.

In another approach, an EPA research group is working to construct a "suicide" bacterium designed to persist in the environment only as long as it is needed. The bacterium contains a plasmid carrying a gene that functions only in the presence of the toxic substance the bacterium is designed to clean up; when the toxic substance is no longer available, the plasmid self-destructs. The technique is intended to destroy the plasmid DNA before it can transfer to another host. However, if the host bacterium were killed before the plasmid were degraded, and the plasmid remained intact with its inserted gene, the plasmid DNA could theoretically reinfect another host. But maintaining this assembly costs the cell energy, and any natural mutation that inactivated the system would be favored by natural selection.

As advances in nucleotide chemistry make other techniques possible, new ways of immobilizing vectors and creating restricted and escape-proof hosts are being explored. Fundamental research might be most productive if directed toward increasing understanding of the ecology of different traits. Meanwhile, the genetic implications of introducing any particular organism into the environment are best considered on an individual basis.

ECOLOGICAL CONSIDERATIONS

The major ecological concern over planned introductions of genetically engineered organisms into the environment stems from the potential for unforeseen or long-term consequences. **Although there are enough uncertainties that introductions should be approached with cau-**

tion, a large body of reassuring data, derived chiefly from agriculture, supports the conclusion that with the appropriate regulatory oversight, the field tests and introductions planned or probable in the near future are not likely to result in serious ecological problems.

The results of most planned introductions are likely to be either beneficial, as planned, or neutral. If only because most planned introductions are likely to be agricultural, any negative consequences would most likely involve an agricultural problem, one that might be controlled or mitigated by crop rotation, introduction of new crop strains, or other agronomic practice. In those rare circumstances of a negative impact on a natural community, the consequence seems most likely to be a transitory disturbance of plant or animal community structure, evidenced by fluctuation in numbers or relative abundance.

Photo credit: Peter Forde, Advanced Genetic Sciences

Advanced Genetic Sciences Researcher Julianne Lindemann spraying "ice-minus" bacteria on strawberry plants in test plot on April 24, 1987. Protective clothing was required by the California Department of Health Services. Note reporters and onlookers in immediate background where coffee and donuts were consumed without hesitation.

The worst possible ecological impact a planned introduction could have would be to disrupt a fundamental ecosystem process, e.g., the cycling of a mineral or nutrient, or the flow of energy in an ecosystem; such disruptions are not, however, among the credible consequences of any introduction that seems likely within the next several years. The high degree of functional redundancy among species (particularly microbes) involved with such processes (e.g., nutrient cycles or energy flow) and the resilience and buffering in natural ecosystems are persuasive arguments against the likelihood of such consequences.

Although predicting ecological consequences of planned introductions is complex, researchers and regulators are addressing the questions raised by such introductions. Five criteria have been laid out for evaluating the likelihood of environmental impact:

1. **Potential for Negative Effects** If it is known that a recombinant organism will have no neg-

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ative effects, there is no cause for concern. But predicting ecological effects, their probability, and assessing whether they are negative or positive is not always straightforward.

2. **Survival:** If a genetically engineered organism does not survive, it is unlikely to have any ecological impact. It is also unlikely to fulfill the purpose for which it was engineered (unless brief survival was all that was required).
3. **Reproduction:** Some applications require not only survival of the recombinant organism but its reproduction and maintenance. Increasing numbers could, in some settings, increase the possibility of unforeseen consequences.
4. **Transfer of Genetic Information:** Even if the engineered organism itself dies out, its environmental effects could continue if the crucial genetic material were favored by selection and transferred to and functioned in a native species, as described in the preceding section.
5. **Transportation or Dissemination of the Engineered Organism:** A recombinant organism that moves into nontarget environments in sufficient numbers could interact in unforeseen ways with other populations or members of other communities.

Genetically Engineered Organisms and Exotic Species

Although there is much disagreement, some scientists hold that the historical experience presented by introduced exotic species, though imperfect, offers some useful examples of potential problems to guard against in the planned introduction of genetically engineered organisms.

Every environment contains organisms that have originated and evolved elsewhere and arrived in their new habitats either independently or with human assistance, These are called exotics. Some lessons can certainly be learned from experience with exotics, but important differences exist between them and most genetically engineered organisms.

Most engineered organisms being studied with planned introduction in mind will differ from naturally occurring counterparts in only one or a few genes. Scientists already have a great deal of experience with introductions of new agricultural crops or cultivars that differ from previously existing varieties by a small number of genes. And while one or a few genes can have a major impact on such things as host range or pathogenicity, they more often do not. The USDA's Plant protection Office has recorded over 500,000 introductions since 1898, mostly from outside the United States, including large numbers of plants, insects, and microbes. Although the proportion that has actually become established is not known, there have been occasional negative consequences, sometimes severe or far-reaching. Few, however, have been lasting, and fundamental ecosystem processes and ecological relationships remain intact. Serious consequences have almost invariably been associated with introduced exotics. Table 1-4 summarizes some of the major differences between planned introductions of genetically engineered organisms and exotics.

Most ecologists agree that successful introductions of exotic species, almost by definition, usually exert some effect, even though only a small fraction of all introductions actually result in the establishment and maintenance of a breeding population. Data for insects suggest that perhaps 41 percent of the species successfully introduced in

Table 1-4.—Comparison of Exotic Species and Genetically Engineered Organisms

	Exotic organism[a]	Engineered organism[b]
No. of genes introduced	4,000 to >20,000	1 to 10
Evolutionary tuning	All genes have evolved to work together in a single package	Organism has several genes it may never have had before. These genes will often impose a cost or burden that will make the organism less able to compete with those not carrying the new genes,
Relationship of organism to receiving environment	Foreign	Familiar, with possible exception of new genes

a 'Exotic organism' is used here to mean one not previously found m the habitat
b "Engineered Organism" is used here 10 mean a slightly modified (usually, but not always, by recombinant DNA techniques) form of an organism already present in the habitat

SOURCE Office of Technology Assessment 1988

the United States between 1640 and 1977 have turned into minor pests, even though they had no known detrimental effects in their original habitats. But not all species behave invasively when introduced into a new habitat, and data on introductions are most likely to overestimate impacts, given that organisms not producing an impact are more likely to be overlooked. Experience with exotics suggests that introductions most likely to result in negative consequences include:

- exotics introduced into an environment they can colonize and where they have no potential natural predators or competitors, e.g., herbivores such as goats or rabbits introduced to an island;
- ecological generalists or species that can survive and flourish on many different foods, e.g., insects that can lay eggs on a variety of host plants or parasites that include a wide spectrum of species in their host range; and
- exotics introduced into disturbed ecosystems where natural relationships and constraints have been disrupted.

Although no planned introductions actually reflect any of these scenarios, close analogs can be found in agricultural systems, which are, in an ecological sense, "disturbed." This may make agricultural systems seem especially susceptible to perturbations from unanticipated consequences of a planned introduction. However, as noted earlier, different strategies for managing agricultural systems provide many flexible control and mitigation techniques. Furthermore, the better analogy with experience from introduced agricultural varieties provides additional reassurance.

Potential Impact on Populations or Communities

Local populations or communities can be affected by the introduction of organisms (engineered or not) that are:

- slightly modified forms of resident types,
- forms existing naturally in the target environment but requiring continual supplements to function,
- forms existing naturally elsewhere that have not previously reached the target environment, or
- genuine novelties.

Most anticipated introductions will be slightly modified forms of resident types. Few are likely to be forms existing previously in the target environment that require supplements, since the need for continual supplementation of existing crops (e.g., with fertilizers) is one of the forces impelling development of engineered varieties free of such requirements. Forms existing elsewhere that are new to the target environment bear the greatest similarity to exotic organisms, and thus carry a higher risk of leading to problems. These also promise great benefits, however, as with the introduction of predators to control introduced insect pests. Few genuine novelties are likely in the foreseeable future.

Plant Communities

At present, most plant genetic engineering focuses on introducing into crop plants genes that confer resistance to herbicides or pests, and these alterations are technically among the easiest to accomplish. The market for herbicides and pesticides is profitable and flexible. Modifying other commercially important traits, such as yield components, overall protein production, taste, nutrition, or photosynthetic rates, lies farther in the future.

A prominent concern is that herbicide-resistance genes may spread into weedy relatives of crop plants, most likely by sexual reproduction. If the genes spread to weeds against which the herbicides are targeted, the herbicides become less effective. Such a development would most likely lead to changes in herbicide use patterns or management practices.

One considerable genetic engineering effort against a specific pest involves the insertion into plants of genes coding for toxins from *Bacillus thuringiensis* (BT). These bacterial compounds are highly effective pesticides against the young larvae of butterflies, moths, and some beetles. Farmers have applied BT to their fields in large quantities for decades. Rohm & Haas (Philadelphia, PA) and Monsanto (St. Louis, MO) have already carried out successful field tests in which engineered tobacco and tomato plants to which

BT toxin genes were added gained protection from predation by caterpillars.

The simple presence of large quantities of BT toxin in the environment is not worrisome because it is not toxic to humans or animals, and it decomposes in a relatively short time. Produced inside crop plant tissues, however, BT toxin is protected from environmental degradation, thus extending its persistence as it provides season-long pest control. However, this might introduce a problem of a different kind: such an approach also lengthens the time that less susceptible individuals (e.g., late larvae and adults) of the target species may be exposed to the toxin, and thus subjected to selective forces that can be expected to lead to evolution of resistance in those populations.

How severe this potential problem might be is unclear. BT accounts for only a minor portion of total pesticide use. While forestry and home garden use has increased in recent years, its market share in agricultural use has declined, losing ground to such promising new compounds as synthetic pyrethroids. But if the evolution of resistance to BT is judged to present more than just a problem for product longevity, evolutionary biology offers several possible solutions.

Because resistance will most quickly evolve in pest populations if the toxin is chronically present, distribution of the toxin could be strictly limited to the times and places it is needed. This could be done by limiting the expression of the BT toxin gene to those plant tissues that pest insects habitually forage on, or by inserting regulatory gene sequences that would induce expression of the BT gene only in response to tissue damage caused by the target pest. With progress in understanding gene regulation in plants, such measures may soon be practical.

Another, immediately practical solution is based on the observation that pathogens and pests adapt more quickly to the defenses of prey species in a genetically homogeneous community, such as a cultivated field, than in a genetically diverse one. Increasing the variation in the genes controlling defenses against pests should slow the pests' adaptive response. Genetically pest -resistant crop plants could be mixed, for example, with unprotected plants. A smaller proportion of protected plants will exert lower selection pressures on the insect populations, slowing their evolution of resistance. Yet they would still offer enough protection to preempt the growth of swarms of herbivorous insects that cause the most crop damage. This approach is based on a strong theoretical and experimental foundation, and is well within the capability of existing technologies.

Insect Communities

Because they inflict so much damage on agricultural products, insect communities have become the target of recombinant plants, microorganisms, and insect predators engineered to check them. Two representative examples are the bacterium *Pseudomonas fluorescent,* which has been altered to enable corn to resist the black cutworm, and a class of viruses that parasitizes certain pests.

The black cutworm feeds on the roots of corn plants, causing significant corn crop losses. It is vulnerable to BT toxin. Monsanto scientists have used a special vehicle called a transposable element to insert the gene for BT toxin into ***Pseudomonas fluorescent,*** which lives among corn roots, The transposable element has been altered to make it unlikely that the inserted gene can move beyond its insertion point or leave its ***Pseudomonas*** host. Preliminary tests suggest that the bacteria do not move beyond the roots they colonize initially, nor are they likely to persist in a field from season to season.

Baculoviruses, rod-shaped viruses that are specific pathogens to one or a few closely related insect species, are being developed to target insect pests, including the cabbage looper and pine sawfly in the United Kingdom. Initial tests involved inserting a marker DNA sequence into the virus to enable scientists to track it. Researchers hope this work will produce a better understanding—and therefore better control—of the dispersal of such altered viruses, as well as of the genetics of host specificity.

Microbial Communities

Microbes can be and are being altered for many uses. Two of the most useful potential applications involve altering root-inhabiting micro-

organisms to increase the amount of nitrogen they fix (discussed later in this chapter), and inoculating plants with altered bacteria to enable them to resist frost damage.

The introduction of ice-minus bacteria has been a source of some controversy among the lay public (see ch. 3). The cell membrane of some bacteria contains a protein encoded by a single gene that acts as an efficient nucleus for the formation of ice crystals on the surfaces of plant leaves or blossoms where the bacteria live. Without such a nucleus, ice crystals do not form until about 9 'F below freezing. Crop losses to frost damage in the United States average about **$1.6** billion per year. Scientists reasoned that removing the ice-nucleating gene from the bacteria and using them to colonize crop plants could confer a measure of frost resistance on the host plants and eliminate at least a portion of the annual crop loss.

Small-scale field tests of this ice-minus system present little risk: Ice-minus mutants are present in natural bacterial populations. The different strains produced by geneticists have precise genetic alterations, unlike natural ice-minus bacteria, in which any of thousands of genetic changes can produce the ice-minus trait. Nevertheless, some observers of these fieldtests have been concerned about a possible worst-case scenario, albeit one that could only apply to large-scale uses of ice-minus bacteria.

Natural precipitation depends on ice nuclei for ice or water droplets to condense around and grow big enough to fall as snow or rain. Terrestrial and marine plant material turn out to be more effective than dust particles as ice nuclei, and bacteria growing on plant material may account for a portion of this difference. If ice-minus bacteria were widely applied in agriculture, some claim, the atmospheric reservoir of ice nuclei might grow smaller, changing local or perhaps even global weather patterns. Some possible support for this argument comes from Africa's Sahel desert, where overgrazing has reduced already sparse vegetation. In this scenario, the reduction in ice nuclei due to overgrazing may have contributed, in turn, to decreasing precipitation, further reducing vegetation.

Several different studies suggest, however, that even under a long chain of worst-case assumptions (many of which contradict known facts) the alteration of climatic patterns through large-scale agricultural applications of ice minus bacteria is not likely, Many of these assumptions, however, could benefit from being tested by further research,

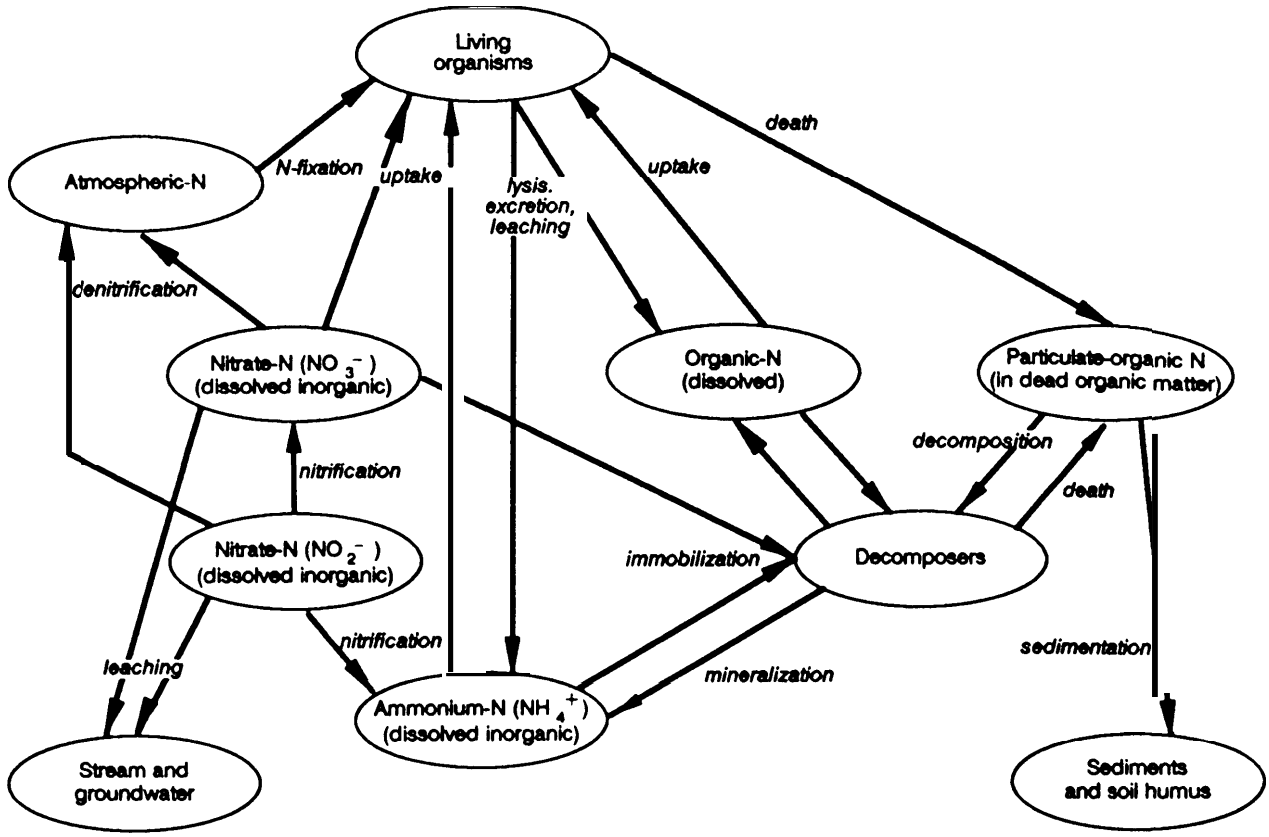
Potential Impact on Ecosystem Processes

Ecosystems are enormously complex and, as a rule, not well understood. Associations of plants, animals, and micro-organisms interact with one another and with their physical environment so as to regulate the flow of energy through the system and the cycling of nutrients within it. The major force driving these processes is capture of the sun's energy by photosynthetic plants and its storage in biologically accessible carbon. Carbon and all other substances vital to living things circulate within ecosystems in biogeochemical cycles. Any major perturbation of these cycles could not only affect living organisms but might disrupt the functioning of ecosystem processes. Much evidence, however, suggests that major perturbation is unlikely.

All organisms require water, carbon, nitrogen, oxygen, phosphorus, and sulfur; carbon and nitrogen are required in the largest amounts, and are usually "rate-limiting." When the biologically available quantity of any of these substances sets an upper limit on the living tissue (biomass) that can be assembled from it and other components, that substance is said to be limiting. When carbon is limiting, as it often is, it puts an absolute upper limit on the biomass a habitat can support. Plants are the primary carbon producers (fixers) in most ecosystems, and decomposes such as insects, nematodes, bacteria, and fungi are the major movers of carbon once it has entered an ecosystem.

The nitrogen cycle (see figure l-l) is equally important, for plants require nitrogen to grow. Although elemental nitrogen is not limiting-indeed, it makes up nearly 80 percent of the atmosphere by volume–biologically accessible forms of it are. Nitrogen fixation, a complex process that trans-

Figure 1-1 .-The Nitrogen Cycle



The nitrogen cycle: processes in terrestrial and aquatic systems. The microbially mediated processes include mineralization, vitrification, denitrification, immobilization, and N-fixation.

SOURCE: Office of Technology Assessment, 19S8.

forms gaseous nitrogen into biologically accessible forms, is thus crucial to life on earth. The most important nitrogen fixers are rhizobial bacteria, those that live closely associated with the roots of certain plants, particularly legumes.

Given the complexity of ecosystem associations, interactions, and processes, it is not surprising that introducing a genetically engineered organism into the environment has raised concerns. Perturbations of any of the fundamental processes sketched above might have significant effects. Ecosystems, however, by the very complexity that makes them difficult to understand, are buffered and often resilient in the face of perturbations. **While fundamental disruptions of ecosystems should be guarded against, historical experience with both accidental and intentional introductions suggests that such risks are not likely consequences of any planned introductions of genetically engineered organisms being considered now or likely in the near future.**

Nitrogen Fixation

Increasing the availability of nitrogen to economically important plants, thus increasing production per unit cost, would clearly benefit agriculure and forestry. But the biochemical pathways of nitrogen fixation, which appear to be similar in all rhizobial bacteria, are controlled by multigene sequences. Research is under way on these control mechanisms and on transferring nitrogen fixation genes into plants themselves.

The symbiosis between nitrogen-fixing bacteria and their host plants is close. Nearly a century of experience with rhizobial inoculants demonstrates a lack of negative consequences from

introductions of such bacteria and makes this a safe system to explore with field tests. Indeed, larger changes to patterns of nitrogen distribution and movement in an ecosystem can generally be achieved by crop rotation than by microbial inoculations.

Larger effects may be possible, however, if the ability to fix nitrogen is transferred to nonleguminous plants. The technical complexity of transferring the large number of genes involved (about 17) and ensuring their effective control are so great that this is not likely within 5 years, and maybe not even in 10.

Microbes and Toxic Waste

Success in enhancing the ability of certain microbes to degrade toxic compounds, including herbicides, pesticides, and industrial wastes, could make a major contribution toward alleviating today's severe toxic waste problem. Naturally occurring microbes with such degradative powers are being used increasingly to help cleanup environmental contaminants. On the other hand, introducing a microbe engineered to degrade several classes of materials might conceivably lead to a cascade effect—trigger a chain of consequences arising from chemical similarities between some toxic wastes and natural compounds. It is most likely, however, that bacteria will be engineered to deal with specific compounds, rather than diverse classes. However, if bacteria were engineered to clear up oil spills or grease deposits in sewers, their potential to attack valuable resources might be of concern. But in most microbial environments, carbon is severely limiting, and competition for it is intense. Competition with naturally occurring microbial populations would likely be severe for most engineered microbes. The technical difficulty of producing such constructs makes any associated potential problems unlikely in the near future.

RISK ASSESSMENT

Most researchers and policymakers agree that although there is no general methodology for predicting and evaluating the risks of planned introductions, a flexible, mechanism for review of those that might pose some risk has, for the time being (the next several years), much to recommend it. It offers a high likelihood of anticipating potentially significant problems that might arise and of revealing the kinds of planned introductions that will merit the closest scrutiny as well as those that might require little or none. Review procedures developed for assessing the risks of toxic chemicals have been proposed as models, but it is not clear how applicable these are. With many commercial applications of biotechnology reaching the field-test stage, however, regulators need clear risk assessment and risk management guidelines.

An important element in approaching the current regulatory framework for regulating planned introductions is to distinguish risk assessment from risk management. Risk assessment is the use of scientific data to estimate or predict the effects of exposure to hazardous materials or situations; the process may be qualitative or quantitative. Risk management, on the other hand, is the process of weighing policy alternatives to select the most appropriate regulatory strategy or action. Risk management depends on the scientific findings of risk assessment, but also takes into account technical, social, economic, and political concerns. It is influenced by public opinion and requires value judgments: How acceptable are the potential risks of genetically engineered organisms in the environment relative to their benefits and the costs of controlling them?

Must All planned Introductions Be Reviewed?

Some scientists and public officials hold that without an adequate, general database for risk assessment of deliberate release experiments, safety can best be ensured by comprehensive scientific review of all proposed releases case-by-case. Others believe that some applications pose such negligible risks that comprehensive review of every proposed field test would be unnecessary as well as burdensome. It is clear that not all planned introductions offer the same potential for

undesirable consequences. **It should be possible now, or become possible in the near future, to sort planned introductions into broad categories for which low, medium, or high levels of review are appropriate.** All proposals for field tests will require a certain, minimum level of scrutiny in order to assign them to one of these three levels. What criteria can be used to determine whether an application is inherently safe? Some that are relevant include:

- The engineered organism duplicates the phenotype (appearance and function) and community relationships of naturally occurring organisms or those produced with conventional methods.
- The engineered organism will not survive and reproduce after release into the environment.
- The engineered genetic material will not be transferred to any other organism.
- The engineered genetic, physiological, and ecological functions will have-no excessive adverse effects on the environment, or the effects will be unambiguously positive.

As more of the above conditions are met, the level of review might be appropriately reduced. More specific questions also need to be considered. Are there certain categories of organism that are safer to release than others? Are there particular genetic alterations that pose fewer risks than others? Some that have been suggested for abbreviated review include:

- organisms produced by recombinant DNA techniques that are functionally identical to organisms that could be produced by other methods (e.g., mutagenesis and selection, or hybridization) and, if so produced, would not now be subject to regulation;
- organisms containing no genetic material derived from any potential pathogen; or
- any organism identical in function to one that has already been reviewed and approved for field testing.

Genetically engineered domesticated animals and crop plants are widely (though not universally) considered to be relatively safe for release. Given the relative containment of such introductions and the relative ease of controlling them, review of introductions involving agricultural plants and animals might well be kept separate from reviews of introductions involving microbes. Before assuming that a particular animal or plant is safe, however, it is important to ask whether the engineered trait would have any harmful potential in wild populations, and, if so, whether gene flow to related natural populations is possible. The latter will be tightly dependent on whether or not the engineered plant or animal is closely related to and can hybridize with any weedy or otherwise problematic species. In addition, animals or plants that have been altered in a fundamental metabolic function (e.g., a plant made capable of fixing nitrogen) or are partners in mutualisms (interactions that benefit all species involved) also require careful scrutiny.

Engineered organisms that are derivatives of pathogens or pests, differing from the pathogen or pest by only one or two gene changes or organisms engineered to receive from pathogens or pests those genes that are associated with a destructive or disease process, constitute categories likely to require extensive prior review. Most of these are viruses, bacteria, or fungi whose virulence can sometimes shift via simple genetic changes or in which a single gene can determine the difference between a benign and harmful form. Such potential pathogens and pests are unlikely to be exempted from review even though here, too, most genetic changes can be expected not to have effects of this sort. Considerable reassuring experience indicates that many pathogenic organisms can be handled and tested safely (e.g., human and animal vaccines).

In another approach, the molecular details of a genetically engineered organism could be examined to determine whether it could be exempted from review. Such an examination should include but not be limited to these questions:

- Does the introduced organism contain inserted genetic material from a donor of the same genus, or from a different genus? A slightly modified organism might be more likely to persist in the environment into which it was released, leading to greater potential for long-term effects. It is also, however, more likely to have occurred naturally.
- Is the alteration an insertion or a deletion of

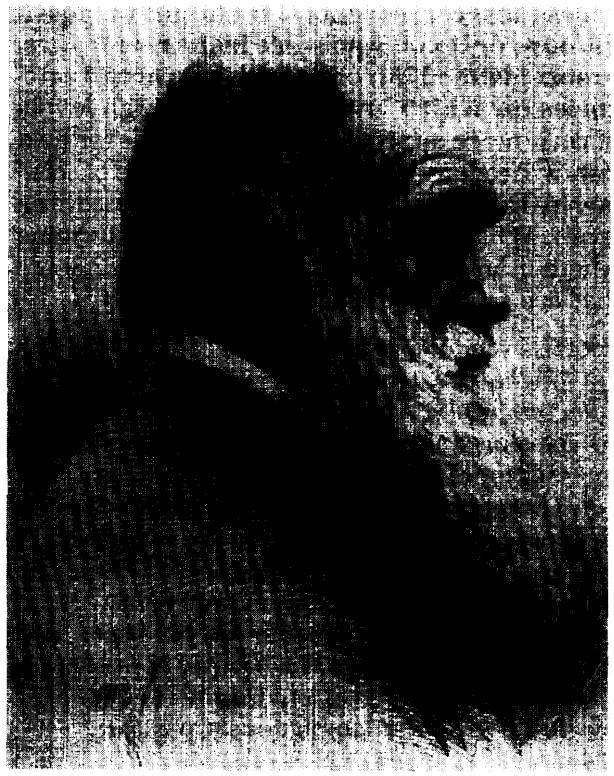
genetic material? Deletions generally present less potential than insertions for long-term survival of the organism, or reproduction, and horizontal transfer of an introduced gene.

- Does the alteration involve a regulatory or a structural gene(s)? Regulatory genes control the time, rate, and quantity of production of proteins encoded by structural genes. Changing regulatory sequences could significantly alter an organism's overall structure or functioning, including its ability to survive and reproduce.

In sum, although the characteristics of engineered organisms make certain kinds less likely than others to cause problems, it is not now possible to describe any broad categories that could be completely exempted from review. **Counterexamples can be provided from existing experience to negate almost any proposed category for exemption from review. A review procedure that involves the flexible, adaptable, case-by-case review of proposed planned introductions deemed to involve significant risk is most prudent at present.** Such "case-by-case" language does not imply, however, that each field test should be reviewed de novo. Experience with reviewing proposals for planned introductions is rapidly being accumulated. It is reasonable to expect this experience will provide a data base to justify establishing or broadening categories for abbreviated review, eventually to include some exemptions.

Micro-Organisms v. Macro-Organisms

Ecological, genetic, and evolutionary impacts resulting from size differences among organisms must be considered in assessing the risks of their release. Particularly from ecological and evolutionary standpoints, microorganisms present greater uncertainties than do macro-organisms, though it is not clear this means they present greater risks. Although most macro-orrganisms are large, and thus relatively easy to track, many insects, weeds, and vertebrates that were introduced have been impossible to exterminate. Most investigators agree that microbes are more difficult to track and control than macro-organisms, though not all agree this means microbes pose



Charles Robert Darwin, 1809-1882. Discoverer of the Principle of Natural Selection.

greater problems. On the other hand, the life history and population models now available to researchers often fit micro-orrganisms better than macro-organisms, making them in some ways easier to study.

Although their large size means macro-organisms can move more biomass or cycle more nutrients through an ecosystem per individual than micro-organisms can, they are not as numerous. The rapid reproductive rates and easy dispersal of small organisms could allow them to proliferate and spread faster through the environment than large ones. And although micro-organisms play key roles in fundamental ecosystem processes, functional redundancy among members of microbial communities seems to provide a greater degree of resilience to environmental perturbations than macro-organisms enjoy.

Evolutionary lability is an important consideration in biological risk assessment: Any assessment of risks, no matter how thorough, would be inade-

quate should the engineered organisms evolve traits they did not have when released. The potential for a population to evolve depends in part on the numbers of individuals in that population, but most importantly on the selective forces involved. **Therefore all reviews of planned introductions, particularly those involving microbes, should carefully scrutinze the selective forces that will be involved and the likely consequences of selection on the introduced organisms.**

Implications for Research

Some of the controversies surrounding the initial attempts to release genetically engineered organisms into the environment have pointed out gaps in knowledge about ecological systems. Current and proposed small-scale field tests will undoubtedly begin to fill some of these gaps and contribute to the development of better risk assessment protocols, but more than this is needed. Active research cooperation—intellectual, financial, and political—is vital.

Taxpayers are investing much to develop science and technology, but relatively little to develop means for ensuring the safe and wise application of such knowledge. Funding for science and technology, and the resulting research, is very uneven across fields, The National Science Foundation and the National Institutes of Health are major sources for funding in biological research, but the basic knowledge necessary to assess the performance of a technology often remains undeveloped, even as the technology is being refined for use. Research on the ways in which biotechnology may influence natural and managed ecosystems, how to assess its risks and benefits, and how to manage it as a technology, should perhaps be viewed as part of the cost of developing the technology, Research areas that need to be stressed include:

- test systems, such as aquatic and terrestrial laboratory microcosms, where ecological interactions can be analyzed before actual release—although such tests are not sufficient substitutes for field tests, they provide *essen*tial information needed in considering the potential consequences of planned introductions;
- the classification and relationships of organisms in natural populations (taxonomy and systematic)) especially the genetic relationships of colonizing species or those organisms related to candidates for engineering and planned introductions;
- natural history of organisms planned for genetic alteration and release;
- . interactions within natural and managed microbial communities (microbial ecology and population dynamics); and
- . more efficient and convenient monitoring and tracking techniques for use in microbial studies;

Interdisciplinary programs involving microbiologists, geneticists, ecologists, evolutionary and molecular biologists, epidemiologists, and risk assessors managed by universities, industry, and government agencies are critical to developing the scientific foundation for setting adequate risk assessment and risk management policies for biotechnology.

POLICY ISSUES AND OPTIONS FOR CONGRESSIONAL ACTION

Three policy issues related to the planned introduction of genetically engineered organisms into the environment were identified during the course of this study. The first involves the development of scientifically founded criteria for the review of planned introductions of engineered organisms. The second concerns actions that Congress might take to shape or direct regulatory policy toward the review and regulation of planned introductions. The third relates to actions Congress might take to affect the development of information and trained personnel that will be needed in the future to ensure that planned introductions continue to be carried out safely.

Following each policy issue several options **for** congressional action are listed, ranging from taking no specific steps to taking major action. Some of the options involve direct legislative action. Others are oriented to the actions of the execu-

tive branch but involve congressional oversight or direction. The order in which options are presented does not imply their priority. Furthermore, the options are not, for the most part, mutually exclusive: adopting one does not necessarily preclude adopting others in the same category or within another category. A careful combination of options might produce the most desirable effects.

ISSUE: What criteria should be used to review applications for permission to field test planned introductions of genetically engineered organisms?

Scientists do not now agree that there is a clear scientific need for a review process by different mechanisms or according to different criteria for engineered organisms intended for environmental introduction than are now being applied to nonengineered organisms.

Option 1: *An organism engineered for planned introduction into the environment should not require pre-release review simply because it was produced via recombinant DNA techniques.*

With this approach, planned introductions of engineered organisms would not be reviewed according to criteria or mechanisms any different than would be required for the same introduction if it did not involve an engineered organism. A review process organized in accord with this option would have the advantage of focusing exclusively on the product and its characteristics, rather than the process used to produce it. This approach could be most easily adapted to existing regulatory authorities and the mechanisms through which they are administered. One disadvantage is that some potential problems associated with engineered organisms are different than most of the problems existing regulatory authorities handle, e.g., problems stemming from the ability of living organisms to grow, reproduce, or transmit genetic material to nontarget species. It is also possible that some engineered organisms will raise significant, new questions that regulators would overlook, absent special review. However, such problems are not entirely new; some are familiar, already regulated aspects of existing practices, especially in agriculture. Nevertheless, even if there is no clear need for a new regulatory approach, planned introductions of genetically engineered organisms could benefit from some review at least for the foreseeable future, even if only to provide public reassurance that field tests of engineered organisms are not unduly hazardous.

Option 2: All proposals to introduce genetically engineered organisms into the environment should receive the maximum possible pre-release scrutiny.

The advantage of this approach is that it is most likely to ensure that potential hazards associated with field tests of any planned introduction will be discovered and eliminated. The disadvantage is that very few planned introductions, at least for the foreseeable future, seem likely to present significant hazards. Substantial resources could be committed to unnecessary review; the personnel and resources of regulatory agencies would be strained or swamped, and significant impediments would be placed in the path of researchers attempting to develop products.

Option 3: Planned introductions should be reviewed on an adaptable, case-by-case basis, according to scientific criteria that are agreed upon and consistent, and tailored to the specific questions posed by particular applications.

Any specific set of criteria is likely to be somewhat contentious. This will be especially true of any criteria intended to apply to separate proposals that would be reviewed by different agencies. However, the broad outlines of a regulatory approach that should be generalizable are clear: **it should be possible to sort all applications for permission to field test engineered organisms into broad categories for which low, medium, or high levels of prior scrutiny will be appropriate.** Assigning an incoming application to a level of review must, of course, be done on a case-by-case basis. This does not mean that all applications for permission to field test will require the same level of scrutiny: they should not. Nor does it mean that the review of each application should begin *de novo,* without regard to past experience with engineered organisms or relevant knowledge gleaned from the study of nonengineered organisms. Such background information is essential to expeditious review.

As experience accumulates, assuming no untoward developments, since the majority of planned introductions are not expected to generate problems, the presumption of low level review might be extended to a broader range of proposed field tests. Conservative standards that could be useful in sorting proposals into the appropriate review category might include criteria like the following:

- Low Review:
  - —Product is functionally identical to one already reviewed and approved for field testing.
  - —Product is functionally identical to others that can be produced with nonrecombinant DNA techniques.
  - —Product will entail lower levels of risk to the environment or to public health than existing products with which it will compete.
  - —Product differs from naturally occurring organisms only by the addition of noncoding marker DNA sequences to noncoding regions of the DNA of the recipient.
- Medium Review:
  - —Product is different in some ways, but generally similar to previously existing products in general use.
  - –Product entails substantial probability of new genetic material being transmitted to nontarget organisms in application environment or beyond.
  - —product entails significant probability of altering community into which introduced.
- High Review:
  - —Product involves the transfer into a new host organism of disease genes derived from a pathogenic donor.
  - —Product is a genuine novelty with which there is little or no previous experience that can serve as a guide to risk assessment and management.
  - –Product entails substantial probability of disrupting community into which introduced.

ISSUE: **What administrative mechanisms can regulatory agencies use to apply such criteria to the review of applications for permission to field test planned introductions of engineered organisms?**

Option l: Allow regulatory agencies independently to develop and apply criteria for reviewing applications for permission to *field* test planned *introductions of engineered organisms.*

This would permit regulatory agencies to develop criteria for sorting and evaluating planned introductions of engineered organism with exclusive attention to applications falling within their separate jurisdictions (e.g., engineered plants by USDA or engineered microbes by EPA). The advantage to this approach is that agencies need not consider issues that would be important only to applications under the jurisdiction of another agency. The drawback to this approach is that different agencies might regulate according to disparate standards or criteria, leading to inconsistent levels of review, regulation, or enforcement.

*Option 2: Direct the regulatory agencies to de-*velop, in *coordination with one another, **but not** by any particular process, specific criteria for classifying and reviewing applications for permission to field test planned introductions of engineered organisms.*

This was the original intent of the Coordinated Framework established by the Administration on June 26, 1986 (51 Fed. Reg. 23301). In order for this option to function well, however, effective leadership is needed from a coordinating authority. Under the Coordinated Framework, it was intended that this role be fulfilled by the Biotechnology Science Coordinating Committee (BSCC). As it is presently constituted, the BSCC lacks the power to impose its decisions upon the regulatory agencies, or to eliminate disparities in approach by different agencies. Criteria for review that have emerged under this framework to date have not been entirely consistent among agencies. In addition, basic tasks, such as the adoption of commonly agreed upon definitions for "deliberate release)" have not yet been accomplished.

Option 3: Provide an interagency group with the power to direct the coordinated development of criteria for classifying and reviewing applications for permission to field test planned introductions of genetically engineered organisms.

This would produce a system similar to that embodied in the Biotechnology Science Coordinat-

ing Committee and outlined in the Coordinated Framework, except that the coordinating body would be created by Congress and would have specific powers. Such a body, created by Congress, could be composed of the same or different members as the BSCC, organized within the Office of Science and Technology Policy, or created elsewhere. It would have the authority to direct the preparation of review standards to be used by regulatory agencies according to consistent criteria, and to standardize regulatory approaches as much as possible among different agencies. It could develop such standards independently or in conjunction with the relevant agencies.

ISSUE: Is research supporting the planned introduction of genetically engineered organisms adequate?

Option 1: Take no action.

A significant amount of research is now funded by the Federal Government in areas that contribute to the knowledge base required for sound review and regulation. Principal agencies now sponsoring or conducting such research are NSF, NIH, USDA, and EPA. Such research will likely continue in the absence of additional, targeted appropriations. An example of the type of research likely to be productive is the recent OSTP sponsored initiative, jointly funded by NSF, USDA, and DOE, to fund interdisciplinary, fundamental research in several targeted areas of plant science.

Option z: Establish an interagency task force to coordinate interdisciplinary research.

Whether or not funding is increased, the different agencies funding relevant research (NSF, USDA, NIH, and DOE) could increase their coordination in the sponsoring of new research initiatives. The recent collaboration between NSF, DOE, and USDA in the establishment of an initiative for research in plant science might be an appropriate model.

Option 3: Increase research funding to selected target areas.

If funding is increased to selected areas, it could most profitably be directed to the divisions of funding agencies sponsoring most of the relevant research. These include, at NSF, the Directorate for Biological, Behavioral, and Social Sciences, and its components, the divisions of molecular biosciences, biotic systems and resources, information science and technology, and others; the National Institute of Environmental Health Sciences and the National Institute of General Medical Sciences at NIH; components of the Division of Science and Education at USDA; and at DOE, the Office of Health and Environmental Research in the Office of Energy Research.

Particular value is likely to be derived from funding earmarked for interdisciplinary studies, or collaborations between scientists in the various disciplines important to understanding and predicting the consequences of environmental perturbations. **Emphasis should be given to studies focusing on the single most important factor affecting the fate and consequences of planned introductions: natural selection,** or the selective interactions between competing organisms, and the selective pressures on organisms due to environmental factors. Other promising areas include basic research in molecular and developmental biology, studies of gene regulation, microbial ecology, community interactions and processes, and evolutionary and ecological relationships.

The disadvantage of such targeting is that it assumes the specific areas where the most important research should be done can be accurately predicted. The results of research are, by nature, unpredictable; this may be especially true of the interdisciplinary research important to planned introductions. Administrative flexibility and adaptability would therefore be important in any such programs, along with the avoidance of undue specificity in the targeting of funds.

Risk assessment and management are vital areas that will increase in importance with the numbers of planned introductions. They lack, however, a strong, vocal constituency to argue for increased funds. The primary agency now funding such studies is EPA, and much of the sponsored research is applied in nature. Both EPA and NSF could be encouraged to enhance their support for basic research relevant to biotechnology research assessment. In the absence of a strong, organized, vocal constituency to help advise on the most effective program, progress might be driven by

allocating for risk assessment and management research a fixed proportion of the funding designated for research in other relevant areas.

Public education specific to biotechnology is another important area presently lacking a strong constituency to argue for improvements. They could be achieved through actions taken by the Science Education divisions of both NSF and USDA. Specific measures might include brochures and pamphlets, newsletters, public conferences and debates, yearbooks and annual reports, and extension service activities.

Option 4: Increase personnel education and training.

Because they already have similar programs, the primary agencies to administer any new training programs would logically be NSF, NIH, and USDA. For the near future, the most effective investment would be in programs to provide mid-career training for established investigators. Other valuable programs could include funds for graduate student and postdoctoral training.

There is an urgent need for scientists who are neither molecular biologists nor ecologists, but investigators comfortable with and competent in the techniques and background knowledge of both areas, able to use whichever tools are appropriate to the task. Interdisciplinary training is vitally important to the production of such investigators. Part of the reason there is not more research now being done to develop methods of predictive ecology and risk assessment has to do with historical neglect of these areas by funding agencies, since recognition of their importance has been slow to emerge, But as funding availability has increased in the recent past there has been a relative shortage of investigators applying for or trained to carry out such research.