Introduction of Recombinant DNA-Engineered Organisms into the Environment: Key Issues

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Prepared for the Council of the
National Academy of Sciences

National Research Council (U.S.)
Committee on the
Introduction of Genetically
Engineered Organisms
into the Environment

NATIONAL ACADEMY PRESS
Washington, D.C. 1987

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Preface

During the past few years, discussions on the introduction into the environment of organisms modified by recombinant DNA techniques have reflected the concerns of the scientific community, the biotechnology industry, and the general public. A wide range of viewpoints has been presented both in scientific publications and in the mass media. During this period, the development of widely acceptable, scientifically based regulations at both the federal and state levels has been greatly delayed. Although progress has been made, there is still a great need to distinguish between real and hypothetical problems. A need also exists to assess in a rational manner concerns about possible adverse environmental effects. To this end, the Council of the National Academy of Sciences issues this paper, "Introduction of Recombinant DNA-Engineered Organisms into the Environment: Key Issues."

A substantial body of knowledge has accumulated on the laboratory use of recombinant DNA-engineered organisms, on organisms that have been modified by traditional genetic procedures, and on the introduction of both genetically modified and nonmodified organisms into agricultural and natural environments. This paper draws upon research and past experience in these areas and applies the relevant scientific principles to the issues surrounding the introduction of recombinant DNA-engineered organisms into the environment.

The paper was prepared by a committee of biologists who represent a broad range of disciplines and experience. In an effort to obtain a balanced review of the issues, the committee sought advice from ecologists, molecular biologists, geneticists, and applied biologists. It is not the objective of this paper to resolve the questions pertaining to the establishment of specific regulations or guidelines governing release procedures. Nevertheless, careful consideration was given to the criteria that are essential in establishing categories of risk.

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Overview

A special committee convened by the Council of the National Academy of Sciences has reviewed key issues in the current discussion on the planned introduction into the environment of organisms genetically engineered using recombinant DNA (R-DNA) techniques. The committee concludes that there is adequate knowledge of the relevant scientific principles, as well as sufficient experience with R-DNA–engineered organisms, to guide the safe and prudent use of such organisms outside research laboratories. Its key findings are that—

- There is no evidence that unique hazards exist either in the use of R-DNA techniques or in the transfer of genes between unrelated organisms.
- The risks associated with the introduction of R-DNA–engineered organisms are the same in kind as those associated with the introduction into the environment of unmodified organisms and organisms modified by other genetic techniques.

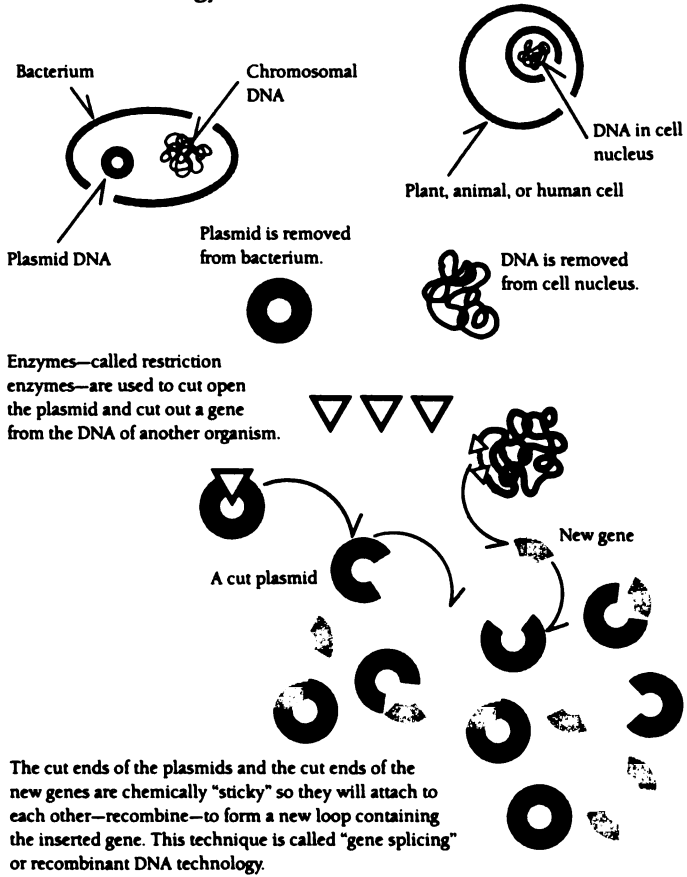
Mounting concerns about environmental degradation, together with the pressing problems of ensuring adequate food and health care for a rapidly expanding global population, provide a compelling rationale for the accelerated study and development of biological organisms for use in agriculture, health care, and biosphere management. The committee concludes that R-DNA techniques constitute a powerful and safe new means for the modification of organisms.

The timely development and rational use of R-DNA–

engineered organisms in such contexts depend on the formulation of sound regulatory policy that stimulates innovation without compromising good environmental management. There is a large body of relevant knowledge on the ecological consequences of biological introductions as well as on the genetic modification of organisms by traditional breeding methods. On the basis of this knowledge, the committee identifies the key biological and ecological parameters that must be evaluated to minimize the probability of damage to valuable ecosystems and maximize the benefits to be gained from biological introductions. These include the biological properties of the organism, the source and target environments, and the scale and frequency of the introductions. The committee further concludes that—

- Assessment of the risks of introducing R-DNA–engineered organisms into the environment should be based on the nature of the organism and the environment into which it will be introduced, not on the method by which it was modified.
- There is an urgent need for the scientific community to provide guidance to both investigators and regulators in evaluating planned introductions of modified organisms from an ecological perspective.

R-DNA Technology



The cut ends of the plasmids and the cut ends of the new genes are chemically "sticky" so they will attach to each other—recombine—to form a new loop containing the inserted gene. This technique is called "gene splicing" or recombinant DNA technology.

Introduction of Recombinant DNA–Engineered Organisms into the Environment: Key Issues

Recombinant DNA (R-DNA) techniques offer exciting opportunities for the development of products in medicine, industry, agriculture, and environmental management (National Research Council, 1984; Olson, 1986). Vaccines are being made safer and produced more rapidly than ever before. Plants are being engineered to resist bacteria and viruses and to produce compounds that are toxic to pests. Bacteria are being modified to protect crops from frost damage and disease, to break down toxic pollutants, to increase the ability of plants to fix atmospheric nitrogen, and to aid in the recovery of metals from ores. To capture the benefits of these and similar developments, however, R-DNA–engineered organisms must be tested and used outside the laboratory, a procedure known as the "deliberate release" or "planned introduction" of genetically engineered organisms into the environment (Halvorson *et al.*, 1985).

As with any intervention in the environment, there may be risks associated with the introduction of certain R-DNA–engineered organisms. There is a perception, however, that R-DNA techniques represent a means of alteration so distinct from other approaches that they will yield organisms that have completely unexpected and possibly deleterious properties outside the laboratory. This perception, along with experiences with certain previous introductions, has fueled public and scientific controversy. The result has been the formulation of regulations more stringent for organisms engineered with R-DNA techniques than for those produced with conventional genetic procedures (Office of Science and Technology Policy, 1986).

This paper examines carefully the issues surrounding the introduction of R-DNA–engineered organisms into the environment. Broadly construed, the term "genetic engineering" encompasses selective breeding, mutagenesis, and fusion of protoplasts, in addition to R-DNA techniques. Although our focus is on the latter, an appreciation of the relationship between R-DNA techniques and traditional genetic methods is essential to the discussion. Therefore we begin with a brief overview of traditional selection and breeding techniques in agriculture. We then consider the concerns voiced most often about organisms engineered with R-DNA and try to distinguish the issues that merit serious attention from those that are not substantial.

Adequate scientific knowledge exists to guide the safe and prudent use of R-DNA–engineered organisms in the environment and to identify the most problematic introductions, but caution is always necessary in environmental management. A considerable body of experience has been accumulated in the genetic manipulation of plants, animals, and microorganisms and in the problems associated with the introduction of such organisms into ecosystems other than those from which they were taken. R-DNA techniques have been in use for more than 15 years in hundreds of laboratories around the world (Watson and Tooze, 1981). During this time, thousands of different organisms have been modified and their characteristics studied. Furthermore, substantial experience has been gained in the oversight of R-DNA experimentation. The Recombinant DNA Advisory Committee of the National Institutes of Health (NIH) has developed procedures for examining and assessing the safety of proposed experiments and has published extensive guidelines on the conditions under which various types of experiments should be done (NIH, 1986). The NIH guidelines, however, were originally formulated exclusively for the laboratory use of R-DNA and do not extend to the introduction of R-DNA–engineered organisms into the environment.

To proceed prudently with environmental introductions of R-DNA–engineered organisms, it is essential to add an ecological perspective to their evaluation (Gillett *et al.*, 1986). In this paper, we identify the properties of the organisms, the source and target environments, and the issues of scale and frequency of introductions that must be considered if the environmental risks are to be minimized and their benefits maximized.

Genetic Engineering:

Past and Present

For thousands of years, humans have modified the organisms around them to meet practical needs. The development of agriculture included the selection and breeding of plants, animals, and microbes that provide greater yields of food and fiber or have other desirable traits. Such selective breeding was repeated many times to produce strains with strong expression of the desired traits; examples include corn with high oil content and dairy cattle with high milk yields. Artificial selection has been applied to thousands of traits in a vast array of organisms, ranging from the yeasts used in baking and wine making to the livestock and plants that constitute a major part of our diet.

Although the mechanisms of heredity were unknown to early breeders, their procedures for selective breeding were a form of genetic engineering. Some agriculturally important traits, such as yield and most forms of disease and insect resistance in plants, are determined by many genes, each with a small effect; others, such as a few forms of disease resistance in plants, are governed by just one gene or at most a few, each with a large effect. Breeders introduce desirable genes into crop plants by appropriate genetic crosses, followed by many generations of further crossing and selection to produce improved marketable strains. Such traditional types of genetic manipulation are limited to organisms that can crossbreed and are therefore quite closely related to each other.

The accumulated experience in plant and animal breeding allows some generalizations. Although a breeder's genetically modified organism is useful in the managed ecosystem for

which it was created, such as a farmer's fertilized and weed-controlled field, it is usually changed in such a way that it is not as fit as its natural progenitor to survive in "the wild"—its original, nonmanaged environment. For example, some plants, like corn, have lost their ability to disseminate their seeds; other plant varieties have a high requirement for fertilizers; and domesticated animals are often dependent on people for feed. Moreover, the genes of an organism do not function independently, but rather constitute a system of interacting components. Organisms that carry genes introduced from other species tend to be at a competitive disadvantage. With a few exceptions to the general pattern (such as the establishment of feral pigs and dogs), the conventional genetic manipulations done by human beings to increase an organism's utility are detrimental to the organism's survival outside the special environments provided.

The R-DNA technology developed over the last 15 years has permitted a new and more precise kind of genetic manipulation. These techniques make it possible to isolate genes, to change the genes and how they are expressed, and, together with other techniques, to insert the genes into whole organisms. R-DNA techniques are unique because they permit genes isolated from almost any organism to be modified to function and be introduced into almost any other organism, regardless of the sexual compatibility of the organisms or the distance of their evolutionary relationship. Breeders who use traditional techniques change (or mutate) genes and move them, but they cannot change or move just one gene or a few at a time. Their methods are much less precise and controlled. A mutation made by traditional techniques may be accompanied by many unknown mutations, which often have deleterious effects on the organism. Furthermore, when genes are moved by traditional sexual crosses, unwanted genes may go along; thus, many cycles of selection are necessary to obtain the desired traits. The power of R-DNA techniques lies in their ability to make extremely precise alterations in an organism rapidly and to overcome the barriers of sexual incompatibility that have hitherto stymied breeders' efforts to move genes. It is precisely these features of genetic engineering with R-DNA techniques that have caused concern.

The Potential Hazards of R-DNA–Engineered Organisms in the Environment: Separating Real from Hypothetical Problems

The ability of R-DNA techniques to expand the range of organisms among which genetic exchanges can be made and to increase the rapidity and precision of genetic manipulations has raised the number of practical applications for genetically modified organisms. But concerns have been expressed about the use of these techniques and about the possibility that their very availability will increase the frequency and scale of introductions of modified organisms into the environment. The two broad categories of concerns are whether distant genetic transfers and the use of R-DNA technology for genetic manipulations are inherently hazardous and whether the widespread introduction of organisms containing R-DNA can cause major ecological disruptions.

Some of the concerns are substantial; others are not warranted. To avoid the two extremes of paralyzing overregulation and inattention to significant potential hazards, the issues must be assessed in the light of scientific knowledge and accumulated experience. This section deals only with those questions that can be answered on that basis. It draws on our experience, largely in laboratory and agricultural applications, although future uses of R-DNA–engineered organisms will include the leaching of ores and degradation of pollutants, as well as agricultural applications outside our current experience (Gillett *et al.*, 1986). Nonetheless, for all applications the appropriate focus of concern should be the properties of the engineered organism, not the method by which it was produced.

Some argue that all possible genetic combinations have occurred during evolutionary history and that organisms with

novel traits therefore cannot be produced by R-DNA manipulations. However, it is probable that only a small fraction of genetic combinations have ever arisen, and most would have appeared in environments unfavorable to the survival of the organism. It is quite likely that R-DNA techniques will permit the introduction of genes that will confer traits novel to a given organism in a contemporary environment. Therefore, evolutionary arguments cannot be used to assert categorically that engineered organisms are risk free. Rather, the evaluation of the risks associated with a particular introduction should be based on the properties of the engineered organism and its target environment.

Is It Inherently Dangerous to Use R-DNA Techniques to Move Genes Between Unrelated Organisms?

Are R-DNA technologies inherently hazardous? They have been used in hundreds of laboratories for more than a decade to produce R-DNA–engineered organisms on a small experimental scale and more recently on a large commercial scale in industrial fermenters. During that time, the transfer of innumerable genes between very different kinds of organisms has created untold numbers of individual transgenic organisms. No hazard peculiar to the use of R-DNA techniques has yet surfaced, and there is a broad consensus among biologists that R-DNA techniques are safe.

Considerable concern is voiced over the use of R-DNA techniques to move genes between organisms that do not generally exchange genes in nature. But are such transfers truly novel? Genetic exchanges brought about by unconventional, nonsexual means occur often in nature. Recent advances in molecular biology have revealed that the cells of most organisms can assimilate and incorporate genetic material from almost any source, and there is evidence that such exchanges have sometimes occurred naturally. They are usually unproductive because the genetic signals for gene expression function only when the recipient organism is closely related to the donor. To solve this problem, researchers have learned to alter the signals that enable a gene to be expressed in the recipient organism. Nature has done this too. For example, strains of the crown gall bacterium (*Agrobacterium tumefaciens*) carry genes that can be expressed only in plant cells. The bacteria have developed a mechanism for transferring certain genes to plant cells and for directing the plant cells to express the genes to make compounds that the bacterium can use as a source of food and energy. Thus, gene transfers among different types of organisms do occur in nature.

Are genetic transfers between unrelated organisms more likely to give rise to problem organisms than genetic transfers between closely related organisms? Also, is there scientific justification for designating as "novel" an organism containing a gene, or a small number of genes, from another species? Many thousands of distant genetic transfers have been carried out with R-DNA techniques, and the organisms with the new genes have the predicted properties: they behave like the parent organism, but exhibit the new trait or traits expected to be

associated with the introduced gene or genes. Thus, an R-DNA modified organism is not a "novel" organism; rather, it is like a breeder's new variety of a flower. Occasionally, unexpected changes occur, but these have been detrimental to the organisms, making them less able to survive.

No evidence based on laboratory observations indicates that unique hazards attend the transfer of genes between unrelated organisms. Furthermore, there is no evidence that a gene will convert a benign organism to a hazardous one simply because the gene came from an unrelated species. The strong implication is that neither the source of the gene nor the method by which it is introduced warrants concern in assessing R-DNA–engineered organisms.

Are R-DNA–Engineered Organisms Like Nonnative Organisms?

An analogy is frequently made between the potential consequences of introducing R-DNA–engineered organisms into the environment and the serious ecological disruptions that have been caused by the introduction of certain nonnative or alien organisms, such as the gypsy moth, the starling, and the kudzu vine. This comparison is based to some extent on the assumption that R-DNA modifications can change the properties of an organism in a wholly unpredictable way that will increase its ability to affect the environment adversely. As discussed in detail in the preceding section, experience to date indicates that this is extremely unlikely. Engineered organisms, whether produced by traditional or R-DNA manipulations, resemble the parent organism in their reproductive and growth characteristics, and they are often at a disadvantage with respect to their parents in their ability to survive and to reproduce. Thus, it is not valid to regard all R-DNA–engineered organisms as nonnative.

Species invasions are among the most serious problems confronting environmental managers, and the nonnative or alien species model of introduction does provide a sound basis for extrapolation when the introduced species is not native to its target environment. But many of the currently proposed agricultural applications of R-DNA–engineered organisms will involve reintroducing modified organisms into the same or a similar environment from which they were taken, so they are not analogous to the introduction of a nonnative species.

Will the Use of R-DNA Techniques Accidentally Create New Plant Pests?

It has been suggested that the genetic engineering of crop plants might increase the potential for creating new pest plants, or "super-weeds." Weeds differ from crop plants in a number of traits. These include vigorous growth, production of large numbers of seeds, production of seeds that are long-lived and germinate readily, the capacity for either self- or crosspollination, and a mechanism for rapid dispersal. One published summary of the characteristics of an ideal weed includes 12 traits, most of which are determined by many genes (Keeler, 1985). Although few weeds possess all these traits, most successful ones have a cluster of several. A single mutation can signifi-

cantly enhance the potential of a given plant to become a weed, but the plant must already possess a number of the characteristics conducive to weedlike behavior. Moreover, although the mechanisms by which weeds have evolved will continue to operate, there is no evidence that plants engineered with R-DNA will behave differently from plants produced by traditional breeding procedures.

Care must be taken when genes conferring traits such as herbicide resistance are introduced into plants that can outcross with closely related wild and weedy species. Caution must also be exercised in the genetic manipulation of weeds, but the probability that R-DNA modification can inadvertently convert a crop plant to a noxious weed is negligible and warrants little concern.

Can R-DNA Accidentally Convert a Nonpathogen to a Pathogen?

Among the dangers envisioned in R-DNA genetic engineering of microorganisms is the inadvertent conversion of a nonpathogen into a new, virulent pathogen. How valid is this concept? It is important to recognize that virulent pathogens of humans, animals, and plants possess a large number of varied characteristics that in total constitute their pathogenic potential. The traits contributing to pathogenicity include the ability to attach to specific host cells, to resist a wide range of host defense systems, to form toxic chemicals that kill cells, to produce enzymes that degrade cell components, to disseminate readily and invade new hosts, and to survive under adverse environmental conditions outside the host. Together with the need to compete effectively with many other microorganisms for survival, these traits form an impressive array of requirements for pathogenicity. The possibility that minor genetic modifications with R-DNA techniques will inadvertently convert a nonpathogen to a pathogen is therefore quite remote.

In dealing with a pathogen or with properties related to pathogenicity, different considerations apply. For example, an avirulent (nonpathogenic) strain of a pathogen can be converted into a virulent strain by a small genetic change, because the transition can be controlled by either a single gene or a small number of genes. A change in a single gene in the fungal pathogen that causes black stem rust of wheat, for instance, can alter the range of wheat varieties it can attack. However, this is a genetic change in a pathogen that is able to infect some varieties, but is nonpathogenic to others; it does not represent the conversion of a nonpathogen into a pathogen.

Can Introduced Genes Spread in a Microbial Population?

Concern has been expressed over the possibility that an introduced gene could move from a harmless microorganism to a weak pathogen by natural mechanisms and increase the pathogenicity of the latter. Many studies have indicated that populations of bacteria characteristically do not exchange chromosomal DNA (Selander *et al.*, 1987). Yet it must be recognized that certain mobile genetic elements can spread widely among unrelated populations in the presence of a specific selection

pressure. It is not the introduction of a microorganism with a special genetic trait that results in population explosions, but selection for that special trait, often as a consequence of the application of manufactured chemicals or drugs. Movement of plasmids that carry genes for antibiotic resistance is a well-recognized example of such gene mobility.

Transfer between microorganisms of plasmids, transposons, and other mobile genetic elements has been central to the evolution of pathogenic traits. The pathogenic types within the common bacterial species *Escherichia coli* all carry genes for pathogenicity on mobile plasmids or bacteriophages. It might be surmised from these observations that the wide-ranging spread of genetic information is proceeding at a high rate in natural populations of microorganisms. But the fact that certain components essential for pathogenicity are carried on plasmids and bacteriophages does not mean that genetic traits for virulence spread indiscriminately in populations of nonpathogens, converting them to pathogens. On the contrary, transfer of a plasmid with the genetic information that codes for an enterotoxin is not adequate to convert the majority of normal *E. coli* strains to pathogens. The reason is clear: pathogenicity depends on many genes, as indicated earlier. Even though many determinants of pathogenicity are on plasmids, only a small subset of bacteria in natural populations have all the traits essential to the "pathogenic personality." That is true not only for the major pathogenic genera in the enteric group of bacteria, but also for most of the other bacteria of medical and agricultural importance.

Thus, the weight of evidence indicates that the transfer of large segments of genetic material rarely leads to its persistence in a population unless strong selection pressure is applied. Furthermore, even when some of the genes required for pathogenicity are on mobile genetic elements, they have a low probability of dissemination to related bacteria with a complementary array of genes for pathogenicity, and an even lower probability of transfer to unrelated species of bacteria.

Will R-DNA–Engineered Microorganisms Alter Soil Microbial Communities?

Nonpathogenic soil microorganisms from different regions might be used in managed ecosystems, and there is concern about potential negative consequences for the native microbial community. Such concern is not necessarily unique to the use of R-DNA–engineered organisms, but is enhanced by the prospect that R-DNA techniques will result in the production and introduction of many more soil microorganisms than in the past.

It has been suggested that little or no experience with such introductions is available to provide guidance. In fact, although little has been done with aquatic microbial communities, a substantial body of data exists on the worldwide use of nitrogen-fixing soil bacteria in the genus *Rhizobium*. These bacteria have been used since the 1890s, and more recently nitrogen-fixing organisms in the genus *Frankia* have also been used. To our knowledge, their widespread use has not resulted in detectable adverse effects on the microbial balance in the

diverse soils into which they have been introduced, even when the soils have been quite different from those from which these bacteria were originally isolated. Similarly, improved strains of some soil fungi that establish a symbiotic relationship with the roots of many species of pines and other trees (mycorrhizae) have been introduced into forest nurseries without evidence of damaging effects.

This record reflects the stabilizing or buffering capacity and resistance to change that have been attributed to the tremendous abundance and diversity of life in soils, as each gram of soil includes nematodes, protozoa, fungi, and insects, as well as 10 million–100 million bacteria, belonging to many different genera. It should also be noted that seeds, cuttings, and propagative material such as seed potato tubers with their attendant microflora and microfauna have been and are constantly being moved from one region to another with no evidence of major problems affecting the soil microbiology. Thus, nonpathogenic soil microorganisms from diverse environments have been introduced on a large scale without evidence of negative impacts.

Microorganisms have also been widely used as insect control agents. For example, *Bacillus thuringiensis,* a bacterium that produces a protein toxic to some insects, has been used on a large scale to control gypsy moths and other insects, and no adverse effects on indigenous microorganisms have been attributed to this procedure. Nonetheless, major shifts in microbial communities have occurred under certain circumstances. The recent rapid rise in antibiotic-resistant microorganisms in human populations is a familiar example, as are algal blooms in polluted waters. Such major population shifts are generally attributable to selection by environmental factors, such as an increase in chemical nutrients or the widespread use of fertilizers, insecticides, pesticides, or antibiotics. Thus, observed major shifts in microbial communities in soils mainly reflect alterations in environmental factors rather than solely the biological or ecological characteristics of the introduced organisms. In the case of introduced pathogens, the prevalence and susceptibility of hosts are also of major importance. Thus, when considering the introduction of a microorganism, not only must the biological and ecological properties of the organism be weighed, but also the environment into which it will be introduced.

Classification of Risks Associated with the Introduction of R-DNA–Engineered Organisms into the Environment: What Factors Need to Be Considered?

Legitimate concerns exist about the biological and ecological consequences of introducing new or altered organisms into the environment on a large scale. Although these concerns are not restricted to organisms altered with R-DNA techniques, they have been brought into focus by the possibility that genetically altered organisms will be used more extensively in the future, in both traditional and altogether different ways. Some risks are associated with the introduction of certain organisms, regardless of the method by which they were produced. Therefore, society's task must be to classify and manage the risks appropriately.

Human beings have moved many organisms from the ecosystems in which they evolved into different ecosystems, for a variety of reasons. Almost all our food crops and animals have been introduced from other ecosystems, as have many of our ornamental plants and our pets. Bacterial and fungal parasites have been introduced to control harmful insects. Microorganisms have been added to seed and soil to increase crop growth by improving nitrogen fixation. Although we have less information about nonpathogenic microorganisms than about pathogenic microorganisms, plants, animals, and insects, we know that only a very small fraction of all the attempted or accomplished introductions have led to destructive invasions (Simberloff, pp. 152–161, in Halvorson *et al.*, 1985). Large-scale plantings of genetically modified nonnative crops, such as wheat, soybeans, and corn, have generally not resulted in the escape of plants from cultivated fields into unmanaged ecosystems as weeds. Furthermore, the biological control of certain

insects and pest plants by introduced, nonnative parasites and predators has had negligible negative environmental impact.

Nonetheless, a small fraction of introductions of nonnative organisms have gone awry, and these have been the subject of considerable concern (Mooney and Drake, 1986). Japanese beetles, gypsy moths, the kudzu vine, and starlings provide familiar, frequently cited examples of uncontrolled, destructive invasions of nonnative organisms. Introduced nonnative fish species have driven many indigenous freshwater fish populations in the western United States and elsewhere to the brink of extinction. And large shifts in species composition have occurred throughout subtropical areas of North America, where introduced fish species have largely displaced native fish species. Thus, introductions of nonnative organisms are associated with risks, and these must be weighed against the benefits. Moreover, the capacity to alter organisms to carry out specific chemical tasks, such as the recovery of metals from ores or the degradation of toxic organic chemicals, will make it possible to use organisms in new ways in environments not previously subjected to such alterations.

Yet even a casual enumeration of the organisms that have been and will be engineered makes it clear that some kinds of engineered organisms warrant greater concern than others. For some, sufficient knowledge of their ecological characteristics permits us to alter them in various ways and introduce them into the environment with little or no risk of adverse consequences to either the human population or the target ecosystem. In contrast, there are others about which we are relatively ignorant or whose properties demand greater concern about ecological consequences.

If we are to proceed prudently with the use of R-DNA–engineered organisms, we must create categories that permit us to classify relative risks associated with environmental introductions, so that levels of containment and environmental assessment will be appropriate to the intended use. This section of the paper identifies and discusses the scientific considerations that must underlie the effort to categorize risk.

Source and Target Environments

Although introductions that have caused major ecological disturbances can be cited, most (such as the chestnut blight fungus) have involved the movement of an organism from one environment into another. These are inappropriate models for R-DNA–engineered organisms being reintroduced into the environment from which the organisms were taken. For crop species and other organisms being reintroduced into the source environment, traditional experience in the breeding and testing of new strains of plants and microbes is the most appropriate model. However, for introductions involving R-DNA–engineered organisms taken from quite different environments or geographic locations, the accumulated experience with introduced species is most appropriate for risk assessment.

Many of the currently proposed introductions are in agriculture, and the organisms are unlikely to become widely established outside the field to which they are applied. For most crop species, the chance of proliferation as weeds is remote.

That depends, however, not only on the recipient environment but on the organism, because a number of species survive as weeds in some, but not all, noncropland habitats. For introduction into unmanaged ecosystems, the characteristics of the existing ecological community must be considered along with the environment. For the introduction of nonnative organisms, it cannot be said that all ecological communities are stable and resilient to perturbation, in light of considerable evidence to the contrary. Some communities are more likely to be invaded than others, and such differences are critical in determining the success of any introduction.

The Biological and Ecological Characteristics of the Organism

For the determination of ecological risk, the biological properties of the R-DNA–engineered organism are paramount. For example, if the organism is a pathogen or if the R-DNA modification affects pathogenicity or invasiveness, appropriate safeguards are essential. Yet strict and rigid controls for all organisms are not justified. It is inappropriate to treat every microorganism as though it were a potential pathogen, because the likelihood of converting a nonpathogen into a virulent pathogen by a small genetic change is extremely slight.

The ecologically important characteristics of an organism include survival, reproductive potential, dispersal characteristics, pathogenicity, competitiveness, and the manner in which it is involved in essential processes in the ecosystem. Each organism has unique patterns of reproduction and survival, and these depend on its environment, which in many cases is created or influenced by human beings. For example, modern corn is largely a creation of humans, selected over thousands of years for its usefulness as a food plant. Today's high-yielding hybrid corn varieties depend completely on people for propagation and culture and cannot become widespread weeds in nonmanaged areas. Hence R-DNA–engineered corn plants are not likely to cause problems. In contrast, plants with broad dispersal capabilities or weedy relatives merit more careful attention.

The different meanings of the term "introduction" must be considered for various organisms. Although testing live vaccines in farm animals, planting R-DNA–engineered crops, and releasing R-DNA–engineered insects all constitute introductions into the environment, the extent to which the various organisms can become established varies widely. The classification of organisms on the basis of such characteristics should make it possible to proceed with many experiments either without significant risk or with no greater risk than we already accept as part of traditional breeding, biological control, and vaccine development.

Scale and Frequency of Introductions

Growing evidence indicates that the establishment of many species, such as those used for biocontrol, is unpredictable and depends on the confluence of such factors as favorable weather, favorable sites, and suitable vectors or other means of transport. Although the data on accidental introductions do not permit

the same level of quantitative analyses as for introductions related to biocontrol of insects or weeds, the conclusions are similar. Some introductions will not succeed no matter how often they are repeated. More generally, success depends to some extent on the scale and frequency with which organisms are introduced. This applies both to the difficulty of establishing organisms that we want to succeed and the ease of establishment by those that may create problems. Experience in biological control has shown that success is enhanced in some instances if the scale or frequency of application is increased, and thus the scale and frequency of a given introduction are of central importance. The implication for R-DNA–engineered organisms is that large-scale or sustained applications might have consequences different from small-scale or single applications.

The attractiveness of R-DNA genetic engineering methods lies in the specificity and efficiency with which they allow genetic manipulations. In turn, this may increase the frequency of introductions. Thus, the cumulative probability of undesirable effects resulting from repeated applications or frequent introductions must be considered, although if care is exercised in the preliminary analysis of environmental risk, most introductions will pose a low risk of environmental damage.

Conclusions

Several conclusions can be drawn from this review of the relationship between traditional genetic manipulation techniques and the R-DNA techniques developed during the last 15 years, and of the experience gained from the application of each.

- There is no evidence that unique hazards exist either in the use of R-DNA techniques or in the movement of genes between unrelated organisms.
- The risks associated with the introduction of R-DNA–engineered organisms are the same in kind as those associated with the introduction of unmodified organisms and organisms modified by other methods.
- Assessment of the risks of introducing R-DNA–engineered organisms into the environment should be based on the nature of the organism and the environment into which it is introduced, not on the method by which it was produced.

To realize the potential benefits of genetic engineering with R-DNA methods, we must strike a wise balance between the thrust of innovation and the restraint of regulation and oversight. Such a balance must rest on accumulated experience, scientific knowledge, and the judgment to discriminate among organisms and introductions that differ in their potential to cause ecological problems. Basic and applied scientists generally agree that many contemplated introductions are either virtually risk-free or have risk-to-benefit ratios well within acceptable bounds. To avoid inhibiting the development and

testing of low-risk organisms for environmental use as an inadvertent consequence of a justifiably cautious approach to high-risk organisms, such as pathogens and noxious weeds, we must create risk categories. A classification scheme must rest on considerations of several types, including the nature of the biological function affected or introduced by genetic engineering, the environment from which the organism was taken, the ecological characteristics of the R-DNA–engineered organism itself, the characteristics of the recipient environment, and the scale and frequency of the proposed introductions. Moreover, the regulatory process must be cognizant of previous experience in the regulation of R-DNA and maintain flexible mechanisms for the continuing modification of regulations based on accumulated information and the deeper understanding of the scientific principles involved.

Intensive use of traditional genetic techniques has been central to the improvement of nutrition and health throughout the world. Although the problems of managing the planet and its growing human population are not all subject to scientific and technological solutions, the intelligent and thoughtful application of scientific advances must constitute a major part of any rational approach to health, nutrition, and biosphere management. Our discussion of R-DNA technology and the environmental use of modified organisms leads to the following conclusions:

- R-DNA techniques constitute a powerful and safe new means for the modification of organisms.
- Genetically modified organisms will contribute substantially to improved health care, agricultural efficiency, and the amelioration of many pressing environmental problems that have resulted from the extensive reliance on chemicals in both agriculture and industry.
- The timely development and the rational introduction of R-DNA modified organisms into the environment depend on the formulation of sound regulatory policy that stimulates innovation without compromising good environmental management.
- The scientific community urgently needs to provide guidance to both investigators and regulators in evaluating planned introductions of modified organisms from an ecological perspective.

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