Chapter 2

Introduction

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This report addresses some of the genetic and ecological questions raised by the planned introduction of genetically engineered organisms. This introductory chapter provides a context for the report's more technical material by recounting the historical background of the issue and reviewing the types of planned introductions either proposed by industry or otherwise likely in the near future.

Of the many consequences of the commercial development of biotechnology, the most far--reaching will likely result from environmental applications of genetically engineered organisms, if only because their sites of application will often be agricultural lands and products. Commonly called "deliberate release, " planned introductions of these altered organisms may increase agricultural productivity, aid in the cleanup of toxic wastes, enhance the recovery of minerals from low-grade ores in mining, and provide new applications or enhancements of many existing processes. (The term "planned introduction" will generally be used in this report; other synonyms include: ***intentional release, deliberate release, free release,*** and ***environmental application.)***

Some observers, however, warn of the potential for damage through unanticipated consequences of a planned introduction. Although the probability of something going awry maybe very small in any individual case, the possibility of substantial environmental impact if something should go wrong is not trivial (7,16,19). The world's experience with unanticipated problems related to the petrochemical and nuclear power industries plus recent concerns about disruption of global processes by acid precipitation (22), increased levels of atmospheric carbon dioxide (2,10,12), and other results of chronic environmental alteration suggest such cautionary voices should be listened to. Yet the real similarities between such analogies and biotechnology are scant, and fear should not substitute for reasoned discourse on the potential costs and benefits of a new technology.

Chapter 3 outlines the existing mechanism for regulating planned introductions, and discusses the role of public opinion in shaping regulatory policy. It also describes the experiences of a number of the communities in which early field tests have been proposed, completed, or planned, and recapitulates some relevant results of an OTA-commissioned survey by Louis Harris & Associates (26).

Chapters 4 and 5 summarize and synthesize information on some of the potential consequences of planned introductions of genetically engineered organisms, and the problems that face regulators in estimating the likelihood of such consequences. Chapter 6 discusses risk assessment issues, identifying present capabilities and future needs that must be met to improve risk assessment. A number of technical contract reports were commissioned in support of this study; their titles are given in appendix C.

The potential benefits of biotechnology in general, and of planned introductions of genetically engineered organisms in particular, are widely recognized and described in other studies (4,14, 15). Some sense of this potential may be gleaned from appendix A and table 1-1. This report examines hypothetical negative consequences of such applications. In doing so, OTA seeks to establish whether there are areas of potential concern that might be addressed by legislation that would mandate the assessment and management of planned introductions. Most of the possible negative impacts described are more relevant to perturbations of natural ecosystems than to perturbations of the agricultural systems that will host the majority of imminent environmental applications. As such, negative impacts are not likely to be common consequences of planned introductions in the foreseeable future.

In focusing primarily on questions of potential risk, this report leaves a number of important issues unexamined:

- the economics of research and development (R&D) of planned introductions of genetically engineered organisms;
- the economics of different regulatory ap-

preaches;

- the relationship between R&D and regulation; and
- the potential for social changes and economic rearrangements, as well as a broad range of ethical questions and occupational safety considerations.

Some of these issues are examined in other reports, and it is not clear that biotechnology raises unique questions in these areas.

Developing engineered organisms for specific environmental applications is unlikely to be as expensive as developing a broad-spectrum chemical pesticide, which may cost as much as $50 million (to which regulatory costs contribute significantly). But because the introduction of an engineered organism is likely to be more precise and limited than that of a chemical pesticide-indeed, this is perceived by some as one of the advantages of such engineered organisms—the market over which to amortize the costs of R&D and regulation is small. If the costs of regulating engineered organisms are too high, the development of some applications may be economically unrewarding.

It would be ironic if concerns over the potential impacts of planned introductions, which may be safer than the competing chemical technologies they could displace, lead to such astringent and expensive regulatory appreach that economics forced continued reliance on older, less safe technologies% But if risks sufficient to justify restrictive regulation are identified, it would be logical to extend restraints to existing technologies that entail similar or higher risks.

And while the following chapters suggest that a regulatory system is not strongly grounded in science if it places primary importance on the processes used (e.g., recombinant DNA techniques) rather than the product produced, it cannot be shown that such an approach is entirely without foundation. It is generally agreed that the new techniques will make it possible to do much more quickly many things that were possible before, but only over substantially longer periods. In addition, the new techniques will make it possible to do some things, such as moving genetic material between very different organisms, that would previously not have been contemplated. It will be the challenging task of those who assess and manage risk to determine if these new techniques will eventually bring with them any qualitatively new risks, although it is not now clear that they will.

It is also true that environmental applications of engineered organisms, by increasing yields or productivity in agriculture, may significantly affect economic or social patterns (something that is already taking place independently of biotechnology). Pesticide or herbicide use may be redirected. Growing ranges and seasons of specific crops may shift. Production of specific crops may increase or decrease. The problems and advantages of monoculture and crop diversity may grow or decline. Some of these questions have been studied (25), but none has been approached from the standpoint of genetically engineered organisms in new environmental applications. All these issues could profit from closer examination than is within the scope of this report.

HISTORICAL CONTEXT

Agricultural biotechnology can be traced, some claim, to the earliest domestication of plants and animals in the Middle East, as long as 10,000 years ago (20). Industrial biotechnology is considered by some to follow the prehistoric development of wine making, or the development of brewing in the 11th century. Others see biotechnology dating from the discovery of the structure of deoxyribonucleic acid (DNA) in 1953. Still others date modern biotechnology from the early 1970s, when the tools (restriction enzymes) to move specific pieces of DNA within and between organisms with precision were discovered. These tools greatly increased researchers' ability to intervene in the hereditary processes of plants, animals, and microorganisms. Some individuals see this increase as both a quantitative and qualitative change, affecting not only the amount of intervention possible, but also the kind of effects that can be produced. Regardless of the date chosen as the dawn of biotechnology, the new genetic engineering techniques open possibilities unimagined as recently as two decades ago.

The development of modern biotechnology began, predictably, in research laboratories, where scientists used the techniques to study the structure, function, and organization of genetic material. As technology improved, it became possible to investigate increasingly precise questions about the function of physiological systems and the regulation and interactions of biochemical pathways. Eventually, work with the powerful new tools turned naturally to practical applications, giving rise to the commercialization of biotechnology, a subject examined in an earlier OTA study (23).

The broad applicability of the new techniques is illustrated in the range of industries affected by the emerging biotechnologies. The pharmaceutical industry felt the earliest large effects, with the newly acquired ability to produce significant amounts of such rare or difficult-to-isolate compounds as human growth hormone, insulin, and compounds to dissolve blood clots. Logical extensions of these technologies may result, eventually, in the repair of defective genes in living individuals to cure or ameliorate human genetic diseases (24). The use of monoclinal antibodies (a biotechnology which does not involve recombinant DNA) is expected to revolutionize the diagnosis and treatment of some forms of cancer.

Areas such as specialty chemicals, food additives, commodity chemicals, food processing, waste disposal, mining, and energy production will also experience the effects of biotechnology. Molecular biology and microelectronics may one day meet in a powerful fusion and synthesis, thanks to the new techniques. But agriculture is the next area likely to feel dramatic impacts from biotechnology. Many of these impacts will result from the planned introductions of organisms (mainly plants and microbes) genetically modified to serve precise purposes.

Some observers of these new applications foresee the environmental use of organisms tailored to perform a host of functions. They envision the production of plants that will resist insect pests, disease, and drought; make their own fertilizer; or use nutrients or energy more efficiently. They point to microbes altered to protect crops from frost damage or insect pests; to metabolize toxic wastes contaminating soil or sludge; or to extract rare minerals or compounds more efficiently.

Others point out that we know so little about how our environment actually functions, of how its components interact (or sometimes, even, what those components are), that it is difficult if not impossible to produce a comprehensive, quantitative assessment of the potential risks to the environment from a particular introduction. They dispute the lowest risk estimates of the strongest proponents, and claim that the closest analog to experience with deliberately introducing genetically engineered organisms into the environment is the introduction of exotic plant or animal species into habitats where they were previously unknown. Although more such introductions have been beneficial, or neutral, than harmful, the European starling, gypsy moth, kudzu, Russian thistle (tumbleweed), and cheat grass are well-known examples of negative consequences that can follow when new species are introduced into environments lacking natural checks. If planned introductions could cause similar problems, then potential ecological effects must be scrutinized closely (see ch. 5).

An examination of the pending and potential planned introductions of genetically engineered organisms suggests, however, that **in most cases engineered organisms are not new to the environment in which they will be used.** Almost invariably, either the same organisms or very close relatives already exist in the ecosystem where the proposed application would take place. The major difference between the existing and introduced organisms lies in the addition or alteration of a specific gene or set of genes regulating some aspect of a biochemical pathway.

Instead of likening deliberate release to the introduction of organisms into a new environment, a more reasonable comparison might be the entrance of new genes into existing organisms. There is a long history of selective breeding in plants, animals, and microbes, much of it carried out with no specific knowledge of the mechanisms of heredity or the nature of the hereditary material. Selective breeding has produced organisms that have surely changed environments and ecosystems, but few that are generally agreed to have been deleterious, much less ruinous. Fewer still have been both runaway and drastically negative. These reassuring points were also cited in a recent paper by the National Academy of Sciences (13). But it remains true that most cases of severe environmental trauma seem to have been the logical consequences of intentional activities initially felt to have been unrelated to their eventual effects.

PENDING AND POTENTIAL ENVIRONMENTAL APPLICATIONS OF GENETICALLY ENGINEERED ORGANISMS

How can the potential environmental effects from planned introductions be anticipated? Perhaps by considering the nature and range of a representative sample of anticipated applications. Even the cursory review in this chapter of the pending and potential planned introductions of genetically engineered organisms illustrates that most areas of human life will be touched by these new technologies. (These applications are also referred to throughout the report in the discussions of issues in ecology and genetics that might be of concern.) Microbes, plants, and animals all stand to be affected directly. Most of the pending or potentially near-term applications involve minor alterations to enhance an existing capability or function. Those that do impart genuinely new capabilities are few in number, but even these are fairly simple or straightforward. Most are controlled by only one structural (i.e., protein-producing) gene.

Plants

Applications of genetically altered plants could be numerous and early, and among the least contentious because plant dispersal is comparatively easy to monitor. The genetic changes being made to plants are constrained primarily by technological difficulties peculiar to plants: the relative paucity of methods for inserting DNA, and the peculiar requirements for culturing different plant cell lines. Despite these constraints, numerous companies and researchers are making progress (see app. A).

Genes have been introduced into numerous plant species to confer resistance to herbicides including glyphosate, atrazine, phosphonitricin, the sulfonylureas, and imidazolinones. Some field tests have already been concluded. Other, similar work has transformed different crop plants with genes conferring resistance to one or another antibiotic, a genetic tag that makes the engineered plants easier to monitor.

In addition to herbicide resistance genes, disease resistance genes have been used to transform tobacco plants. The first field tests of plants made resistant to crown gall disease were carried out in 1986.

In a related development, a long known (but incompletely understood) phenomenon has been exploited to provide protection against some plant viral infections. Plants inoculated with mild strains of certain viruses or viroids acquire some protection from more virulent strains that cause severe disease. A collaborative effort between researchers at Washington University in St. Louis, MO, and Monsanto Co. has resulted in this “cross protection” against tobacco mosaic virus being engineered into tobacco plants. In that work, a single viral gene encoding a viral coat protein was inserted into the plant genome. Preliminary indications suggest that the same process might be useful in protecting other plants against a variety of viral diseases.

Many other genetic manipulations to tailor plants for specific environmental applications are being pursued now, or are likely to be pursued in the future. Tolerance to drought, irrigation water salinity, extremes of temperature, and variation in soil conditions all are subject to different degrees of genetic control, making them susceptible to directed manipulations. Because plants engineered for increased tolerance to these fac-

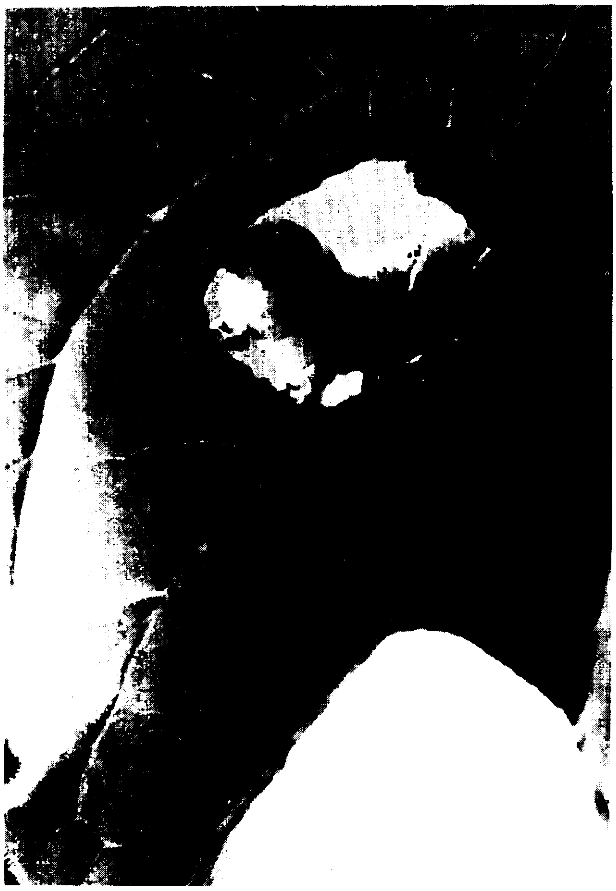

Photo credit: Rohm & Haas Co.

Manduca sexta (tobacco hornworm) larva at work. The moth will consume 95 percent of its entire life cycle's **food supply while in** the larval stage of development. Moth larvae are the most destructive insects to world agriculture and forestry.

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Photo credit: Monsanto Co.

Monsanto and Washington University researchers begin field test of tomato plants carrying BT ***toxin gene*** in test plot in Jersey County, Illinois, summer of 1987. Examining experimental plants in foreground are Robert Fraley, Director, Plant Science Technology, Monsanto Co., and Roger Beachy, Professor of Biology, Washington University in St. Louis, Missouri.

tors maybe grown in habitats new to them, some of the precautions taken to assess the risks of introducing exotic species may apply. Researchers also report substantial progress in the development of recombinant DNA techniques to alter or improve the nutrient qualities of crop plants (9).

Researchers may also explore the possibility of increasing the concentrations of "antifeedants" in seeds. Such compounds (e.g., canavanine), toxic to seed-eating insects, occur naturally in some seeds. Their production is under genetic control, and concentrations vary in seeds from different plant populations and species. This natural variation has already been exploited to reduce losses from insects, particularly in some developing countries. It would be relatively simple to transfer the capacity for producing such compounds to plants that are not naturally able to protect their seeds in this way. Care must be taken, however, that such added compounds do not have negative consequences for the intended consumer, as are known with brown sorghum (6).

In the future, scientists maybe able to alter nonleguminous plants to enable them to extract usable nitrogen from the atmosphere (to '(fix" nitrogen). However, the technical problems associated with transferring this capability are greater than those posed by almost any of the other applications so far mentioned. While most of those applications involve a single gene, or at most a small number of genes, nitrogen fixation involves as many as 17 different structural genes with associated regulatory elements. To transfer such a gene complex from the parent bacterium into a plant and ensure its proper function in the new genetic background is a challenging task beyond the reach of present techniques. Studies of plant gene regulation are progressing, however. And the first plants with symbiotic bacteria engineered to increase their fixation of nitrogen were ready for testing in 1987, and slated for field tests in 1988.

Other, more tractable plant applications involve the genetic engineering of marine algae to increase their production of food additives (carrageenan, betazarotene, and agar). Someday algae may even be altered to sequester rare minerals or metals found dissolved in sea water, providing an intriguing fusion of the agriculture and mining industries.

Animals

Because animals are generally larger than microbes, and relatively easy to track, animal applications of genetic engineering have met with less controversy. Most biotechnology work aimed at animals is focused on veterinary products for animals, such as vaccines, or on hormonal supplements like bovine somatotropin. Much of the work that is directed at altering animal genomes per se is geared toward altering farm stock to improve reproductive performance, weight gain, disease resistance, or coat characteristics. Since such organisms (indeed, and many crops, as well) will be restricted to agricultural settings, it will often make more sense to consider them "contained", rather than as introduced into the environment in the way that microbes are. Work is also being done to develop cattle or sheep as '(factories" for such substances as human blood factor IX, and other pharmaceuticals.

In work that may be relevant, researchers in Michigan and in Washington are developing strains of fish (salmon) that should live longer and grow larger than average. The procedure involves exposing early fish embryos to abnormally high temperatures. The ensuing shock causes a peculiar chromosomal abnormality (a doubling of one of the chromosomal sets, a condition called triploidy) that disrupts the fish's normal sexual development. The results include infertility as well as longevity and increased size. The altered fish avoid the usual fate of spawning followed by death. Sterile, triploid grass carp are produced in a similar manner, and being used to control some aquatic weeds in Florida. Other researchers (primarily in foreign countries) are working to introduce specific genes into different fish species to increase temperature tolerances or growth rates. Because fish engineered for increased tolerance to such environmental stresses may thrive in habitats new to them, some of the precautions taken to assess the risks of introducing exotic species may apply.

Microbes

Genetically engineered microbes present more uncertainties and generate more concern and opposition than engineered plants or animals. Their small size complicates the task of monitoring and tracking dispersed microbes (5). The genetic promiscuity of some microbes also makes horizontal transfer of genetic material more likely. And microbes are involved inmost fundamental ecological processes. But this same involvement, together with the ubiquity of microbes, makes them the choice for many environmental applications of genetically engineered organisms contemplated at present. **An enormous amount of past experience with microbes introduced for biocontrol or agricultural purposes suggests that most in-**

productions of engineered micro-organisms are likely to be without noticeable ecological consequence% Although most such introductions can be expected to be safe, a few instances of problems with biocontrol microbes used in agriculture suggest the need for some caution (17).

Bacteria are being studied for a host of innovative pesticidal applications. Of great interest is Bacillus ***thuringiensis*** (BT), a bacterium that produces a protein that is toxic to the larvae of many Lepidoptera (butterflies and moths); different strains produce proteins toxic to some other insect pests, primarily some flies and beetles. A protein known as the delta-endotoxin is produced by a gene that has been inserted into a bacterium (Pseudomas fluorescens) that lives on the roots of corn plants. Scientists hope this will protect corn crops against losses to the black cutworm, which can be substantial in infested fields. Other researchers have inserted the same BT gene directly into plants to exploit its pesticidal properties. In yet another application, the gene has been inserted into a different bacterium that is then killed and preserved in a novel way to increase the toxin's persistence. Under normal circumstances, the ultraviolet-light-sensitive toxin degrades very quickly in the environment; by protecting it from ultraviolet light inside the killed bacterium, the toxin's efficacy as a pesticide is extended.

Viruses also offer potential for exploitation as pesticides. In particular, different baculoviruses (so named for their rod-like shapes) are specific for many insect pests. Genetic engineering to enhance their virulence and limit or alter their host ranges promises to increase their usefulness (2 I). Early applications of viruses that are pathogenic to insect pests of cabbage plants or pine trees are at or near the field test stage in the United Kingdom, where larvae are serious pests to agriculture and forestry. Research is being carried out on similar systems in several universities and industrial laboratories in the United States.

Other viral applications involve the production of vaccines for both animals and humans. Separate research programs are aimed at tailoring the vaccinia virus to produce vaccines against such diseases. A recombinant vaccine has already been developed for hepatitis B, a major Third World health problem. Other vaccines are being developed for herpes simplex, influenza, hookworm, and AIDS (acquired immunodeficiency syndrome). Animal applications under development include vaccines for vesicular stomatitis (cattle), swine pseudorabies, mammalian rabies, and others. Some of these animal vaccines have undergone field tests, which have generated varying degrees of controversy (see ch. 3).

A number of different groups in the United States and Europe are working on multivalent vaccines designed to protect against several diseases with one vaccination, or against one disease that is antigenically complex (e.g., malaria, sleeping sickness, or schistosomiasis). These programs aim to exploit the large capacity of the vaccinia virus to carry genetic information. This large capacity enables the virus to carry several genes encoding different proteins that will each stimulate an immune response. One of the difficulties in developing vaccines for antigenically complex diseases has been the different antigens the disease agents express at different stages of their life cycles. Traditional vaccines may stimulate an immune response that will protect against infection at one stage in the parasite life cycle, but not another. Vaccinia-based vaccines may overcome this obstacle. Clinical experience with traditional vaccines against many virulent diseases gives excellent reason to suppose that engineered vaccines will be at least as powerful and safe.

Bacteria are also being genetically altered to metabolize specific toxic compounds found in waste or industrial sludge. In recently reported work, scientists have tailored metabolic pathways in bacteria to enhance their ability to metabolize: benzene derivatives (18); the halogenated hydrocarbons (polychlorinated and polybrominated byphenyls (PCBs and PBBs), and dioxin); and oil spills (3)8). The past 5 years have seen much significant progress in this area, using enrichment cultures and naturally occurring bacteria that are then applied to environmental problems. Many naturally occurring bacteria can degrade complex organic compounds, and some are being harnessed to keep closed ecosystems clean, as in the soil bed reactors planned for Biosphere II (1) or in wastewater treatment facilities that must cope with activated sludge.

"Ice-minus" bacteria, the altered bacteria for which the first field test permission was requested, have received the most publicity. These bacteria are expected to reduce frost damage to crops, a problem that costs U.S. agriculture an estimated $1.6 billion annually. Ice-minus bacteria differ from unaltered bacteria in that a single gene has been deleted, one that normally encodes specifications for the construction of a protein normally found in the cell membrane. This protein acts as a potent nucleator for the formation of ice crystals. In the absence of such a nucleator, ice does not commonly form until the temperature drops 5 to 10 "F below freezing. Researchers at the University of California at Berkeley, and at Advanced Genetic Sciences in nearby Oakland, reasoned that the gene for this ice-nucleating protein could be deleted from the bacteria. These altered bacteria—virtually identical to bacteria that can be found in nature-could then replace the normal, ice-nucleation positive (INA +) bacteria living on the leaf surfaces of crop plants, thus providing some protection to frost-sensitive crops. Collaborative work between these groups of researchers has produced early systems designed to protect such crop plants as potatoes and strawberries. Successful field tests of both were conducted in 1987.

An important new marker system called "lac ZY" is being developed to track engineered microbes in the environment. Researchers from Monsanto Co. and Clemson University are developing the system through a collaborative effort (11).

SUMMARY

Planned introductions of genetically engineered organisms span an enormous range in terms of the altered organisms, the diverse environments in which they are to be applied, and the types of functions they are intended to perform. There are difficulties in estimating precisely the potential environmental hazards, and in assessing the risks and benefits for any particular application. But there is also a substantial body of relevant experience that can be used as a guide.

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