Chapter 11

Regulations

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

Sophocles

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

James D. Watson
The DNA Story: A .Documentary ***History of Gene Cloning***

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INTRODUCTION

Health and environmental regulations aimed at reducing risks associated with a new technology impose direct costs on industry and administrative costs on government. These regulations also result in indirect costs to the public, in the form of higher prices and, perhaps, decreased benefits from innovation. Governments impose regulations, however, to avert the costs associated with mitigating adverse effects that might result from the use of the technology. Ideally, the imposition of regulations results in a net benefit to society. But, balancing the costs of regulation against the benefits of risk reduction through regulation is difficult when a technology is new, and the risks associated with it are uncertain or poorly understood.

Oversight of biotechnology in the United States began in the mid-1970s when concerned scientists asked the National Institutes of Health (NH-I) to implement a set of laboratory-safety guidelines for biomedical research using recombinant organisms (7). Although no evidence existed that these organisms were more harmful than naturally occurring organisms, there was uncertainty about the risk associated with the use of recombinant organisms in the laboratory and concern about rapid, widescale use of the new techniques. Therefore, the NIH Guidelines, published in 1976, outlined conditions for research that would reduce the possibility of recombinant organisms escaping the laboratory or infecting laboratory personnel.

The NIH Guidelines were comprehensive. They detailed proper laboratory procedures for handling various kinds of organisms in different kinds of experiments. They also described systems for containment, using specialized equipment and disabled organisms unable to survive outside the laboratory and, therefore, less likely to transfer deoxyribonucleic acid (DNA) to other organisms (see box 1 l-A). Experiments perceived to entail more risk or uncertainty than others were assigned to higher categories of containment with concomitantly more safety equipment and procedures.

Over the next several years, the guidelines were revised and relaxed as more organisms and experiments were shifted to lower risk categories. The later guidelines also established a graduated oversight procedure. Experiments thought to entail the most risk (e.g., those involving human subjects or the production of highly toxic substances) were reviewed by NIH's Recombinant DNA Advisory Committee (RAC); experiments thought to be less risky (e.g., those using certain pathogens) were reviewed by local institutional biosafety committees. Today, most recombinant DNA (rDNA) laboratory research in the United States is exempt from review and subject to minimal restrictions.

The guidelines are not Federal regulations and cannot be enforced through the imposition of fines or penalties. They are based solely on NIH's contract-making authority. All institutions receiving NIH funding are subject to the provisions of the guidelines, and noncompliance can result in a loss of NIH funding. Other Federal funding agencies have also adopted the guidelines for use by their grant recipients, and the guidelines have been amended by RAC to encourage voluntary compliance by researchers in the private sector. About one-half of all firms conducting rDNA research have voluntarily registered their biosafety committees with NIH, and these firms have been found to follow the guidelines more closely than their public-sector counterparts (70). Because the guidelines are thorough, rational, and relatively easy to implement, they were quickly accepted by scientists and became the standard in most industrialized nations.

In the early 1980s, when new biotechnology-based products approached the marketplace, many of these new products became subject to regulations promulgated by Federal agencies other than NIH, because of the products' intended uses (40). Microorganisms, for example, whether or not they are genetically altered, are subject to Environmental Protection Agency (EPA) regulations if they are to be used as pesticides. Plants and animals used as food are subject to Food and Drug Administration (FDA) and U.S. Department of Agriculture (USDA) regulations.

To coordinate the regulatory activities of the Federal agencies involved, a Biotechnology Science Coordinating Committee (BSCC), recently reorgan-

Box 11-A--Containment

The NIH Guidelines for Research Involving Recombinant Molecules prescribe increasing levels of containment for experiments of increasing risk or uncertainty. The lowest level of containment, BL1, is similar to ordinary laboratory facilities; the highest, BL4, resembles laboratory conditions appropriate for handling deadly pathogens. Methods used to confine organisms to the laboratory are listed in the guidelines; they are based on existing procedures, commonly used in research on pathogens. The methods include:

- *Good microbiological practice, as described in a number of standard texts.* At the lowest levels of containment, these practices include: restricting access to the laboratory; cleaning and decontaminating the lab daily or after a spill; forbidding eating, drinking, or smoking in the lab; wearing lab coats; decontaminating wastes; controlling insects and rodents; and instructing laboratory personnel in aseptic techniques-to lower the risk of contamination and infection. Good practice appropriate for experiments entailing more risk, such as experiments using human pathogens, may include serological monitoring of lab personnel or vaccination, if such vaccination is available.
- *Laboratory design or equipment that prevent physical exposure.* At the lowest levels of containment, for example, labs should be equipped with sinks, window screens, and sterilization equipment; and the lab should also be easy to clean. At higher levels of containment, labs might be designed to be separate from traffic flow, with windows sealed shut, and special ventilation systems installed.
- Biological containment *of micro-organisms. Experiments use* micro-organisms unable to grow outside the laboratory and limited in their ability to transfer DNA to other organisms.

These containment procedures are complementary; standard practices can be combined with various combinations of physical and biological barriers.

The containment principles outlined in the NIH Guidelines have formed the basis for most regulations in the United States which govern the use of genetically modified organisms. They have also been adopted by other countries. Combining physical and biological containment is also possible and appropriate for higher organisms. Plants and their pollen, for example, may be contained by removing reproductive organs (detasseling corn); using plant mutants that do not form reproductive organs (cytoplasmic male sterility); using herbicides and insecticides; geographically, isolating experimental plants from similar plants, by staggering planting dates, or physically separating plants by growing them indoors or in a greenhouse.

SOURCES: 51 Fed. Reg. 16958; 52 Fed. Reg. 31848; 53 Fed. Reg. 43410; 54 Fed. Reg. 10508; 55 Fed. Reg. 7438; National Research Council, *Field-Testing Genetically Modified Organisms: Framework for Decisions (Washington* DC: National Academy Press, 1989).

ized and renamed the Biotechnology Research Subcommittee (BRS) (see box 1 l-B), was established under the aegis of the President's Office of Science and Technology Policy (OSTP). Many questions of agency jurisdiction were settled with OSTP's 1986 publication of the "Coordinated Framework for Regulation of Biotechnology." The document describes how new biotechnological products will be regulated under existing law. Although it can be argued that products made using biotechnology are not always treated exactly as their nonengineered counterparts are treated, in general, an effort has been made to base regulations on the intended use of the products, rather than on the method by which they are produced.

Many other countries have adapted existing laws and institutions, originally developed for the oversight of chemicals and to protect agriculture and the environment, to accommodate advances in biotechnology. However, it is no simple matter to base scientifically sound biotechnology regulation on legislation written for other purposes. New legislation specific to the regulation of biotechnology was enacted in Denmark, Germany, and the United Kingdom (U.K.). Existing legislation has been amended in The Netherlands, and further legislation is under consideration (31). The European Community (EC) has also enacted two new directives regulating biotechnology: one concerns the contained uses of genetically modified organisms and the other regulates deliberate releases of such organisms.

An exhaustive description of these evolving biotechnology laws and regulations is not appropriate here. Instead, this chapter offers a broad view of national regulatory policies. Scientific assessments of risks associated with different applications of biotechnology are summarized, along with the U.S. approach to regulating these applications. Finally, international trends in regulation are outlined. These

differences in approach from nation-to-nation, particularly through their effects on investment and innovation, will influence the ability of the United States to remain competitive in biotechnology on the international scene.

BIOTECHNOLOGY RISK AND REGULATION IN THE UNITED STATES

The first step in conventional risk assessment is hazard identification, that is, analyzing the specific threat to health or the environment associated with a substance or process. Much of the controversy surrounding the regulation of biotechnology has focused on hazard identification, as agencies attempt to evaluate the type of hazard posed by this new technology (53,68). Because there have been no examples of adverse effects caused by biotechnology, projecting potential hazards rests on extrapolations from problems that have arisen using naturally occurring organisms. The consensus among scientists is that the risks associated with genetically engineered organisms are similar to those associated with nonengineered organisms or organisms genetically modified by traditional methods, and that these risks may be assessed in the same way (18,34,49,50,53).

Many uses of biotechnology are similar to classical technologies or extend these technologies. Micro-organisms, plants, and animals that have been genetically altered through selective breeding or by treatment with chemical mutagens are widely used in U.S. agriculture and in the fermentation industry. The newer techniques also result in genetic alterations, but genetic engineering enables researchers to make more precise, well-characterized changes than are possible using classical techniques. The new techniques are unique, however, because they allow the transfer of genetic material across species.

Where similar technologies have been used extensively, past experience can bean important guide for risk assessment. The most familiar application of biotechnology is its use in the production of biochemical, especially proteins. Safety procedures developed for protecting chemical production workers can be adapted to biotechnology, and most countries have no special regulations governing the use of biochemical produced using biotechnology. Wide experience with the introduction of new varieties of plants has also helped scientists pinpoint potential problems in introducing genetically engineered plants.

In other cases, however, experience is uneven. Although certain micro-organisms-for example, the nitrogen-fixing bacteria ***Rhizobia—have*** been widely used in agriculture, experience with many other micro-organisms is more limited. The smaller research base has made planned introductions of engineered micro-organisms into the environment more controversial than the introduction of new plants. Information on the structure and function of microbial communities is often lacking, making it difficult to assess the effects of environmental introductions. In addition, micro-organisms are relatively difficult to confine and track (50,68).

Because experience with similar technologies and applications can be useful in assessing risk, it is reasonable to regulate biotechnology-derived products under existing legislation via established agencies that have experience in regulating specific applications. This policy, usually referred to as "product-based regulation," has often been repeated in U.S. agency and interagency policy statements.

Biochemical Products

Biotechnological processes can be used to produce proteins that are found in small amounts in nature and that can be difficult to isolate and purify. Instructions for making proteins are contained in the genetic material, the DNA, of each cell, and a set of DNA instructions for making a protein can be transferred from one organism to a single cell of another organism. From that cell, the new organism, usually bacteria or cultured mammalian cells, can be grown in large quantities in a production facility and their protein products isolated. These products can be enzymes, which are specific catalysts produced in cells to speed up intracellular chemical reactions, proteins with other life-sustaining properties, or other biochemical. The commercial product is a purified biochemical, not a living organism.

Some of these genetically engineered products are substitutes for commercially available products. Biotechnology, however, provides a faster, safer, or more economical means of obtaining comparatively large amounts of the product. Before the development of genetic engineering for example, human growth hormone isolated from human cadavers was scarce. Ultimately, it was withdrawn from the

Box 11-B-Federal Coordination

The Biotechnology Science Coordinating Committee (BSCC) was founded by the Office of Science and Technology Policy (OSTP) in 1985 to:

> . . . serve as a coordinating forum for addressing scientific problems, sharing information, and developing consensus; promote consistency in the development of Federal agencies' review procedures and assessments; facilitate continuing cooperation among Federal agencies on emerging scientific issues; and identify gaps in scientific knowledge.

The committee consisted of the Commissioner of the FDA, the NIH Director, the Assistant Secretary of Agriculture for Marketing and Inspection Services, the Assistant Secretary of Agriculture for Science and Education, the Assistant Administrator of the EPA for Pesticides and Toxic Substances, the Assistant Administrator of the EPA for Research and Development, and the Assistant Director for Biological, Behavioral, and Social Sciences of the National Science Foundation.

Rather than being a forum for discussion, however, BSCC became the center of interagency disagreements about regulatory policy. Internal dissension reached a climax in 1988, when EPA sent its proposed rule for regulation of genetically modified micro-organisms under TSCA to the Office of Management and Budget (OMB) for review before publication in the Federal Register. The chairman of BSCC wrote to OMB requesting that OMB withhold clearance until BSCC could consider the proposed rule. A series of interagency meetings and memoranda resulted in deadlock. The chairman informed OMB, and OMB refused to approve EPA's draft rule. In response, the EPA representative to BSCC stopped attending meetings and placed the draft rule and interagency memoranda in a public docket. As of mid-1991, no proposed rules for EPA regulation of micro-organisms under TSCA and FIFRA had been published.

One major area of disagreement was the precise definition of organisms that would be subject to EPA regulations. In 1989, various approaches to this problem were discussed by BSCC and by the agencies' scientific advisory committees. Not surprisingly, BSCC failed to reach a consensus. The issue was turned over to a higher level committee, the Biotechnology Working Group of the President's Council on Competitiveness, chaired by Vice President Quayle. The OSTP's proposed principles for the scope of oversight for the planned introduction of organisms were published in July 1990.

In late 1990, BSCC was replaced by the Biotechnology Research Subcommittee (BRS) of the Committee on Health and Life Sciences, a standing interagency committee of the Federal Coordinating Council on Science, Engineering, and Technology (FCCSET). The FCCSET, like OSTP, is headed by the President's science advisor. The BRS's charge is said to be similarto that of BSCC. Its membership is broader and includes representatives from the Department of Energy (DOE), NIH, FDA, the State Department and its Agency for International Development (AID), EPA, USDA, NSF, the National Aeronautics and Space Administration (NASA), the Department of Commerce (DOC), the Department of Defense (DoD), the Department of the Interior, OMB, and OSTP.

(Continued on next page)

market, because it presented the risk of contamination by infectious agents. Today, human growth hormone is uncontaminated and more plentiful, because it is isolated from bacteria engineered to carry the human growth hormone gene and make the growth hormone protein.

Biotechnology can also be used to produce new products, for use as drugs or as industrial or food processing enzymes. Some proteins, like tissue plasminogen activator (tPA) and erythropoietin (EPO), occur naturally but are too expensive to synthesize chemically and too difficult to isolate from tissue. Biotechnology makes their production feasible. Biotechnology can also be used to produce modified forms of proteins with altered biological properties or more resistance to degradation than naturally occurring proteins.

Basing the regulation of biochemical produced through biotechnology on existing legislation is widely accepted. Many regulations govern the manufacture and uses of chemicals, regardless of the method of production. Most proteins produced using biotechnology, thus far, however, are intended for use as drugs, diagnostic products, or food additives. Therefore, before they may be sold, they must meet FDA requirements under the Federal Food, Drug, and Cosmetic Act (FDCA) (21 U.S.C. §301-392). All drugs must undergo years of testing in animals and in clinical trials, followed by FDA review of test results. The kind, size, and length of

The Council on Competitiveness made further recommendations in their 1991 ***Report on National Biotechnology Policy,*** which contains "Four Principles of Regulatory Review." Vice President Quayle announced President Bush's approval of these principles in July 1990.

. Federal Government regulatory oversight should focus on the characteristics and risks of the biotechnology product-not the process-by which it is created.
- For *biotechnology* products that require review, regulatory review should be designed to minimize regulatory burden while assuring protection of public health and welfare.
. Regulatory programs should be designed to accommodate the rapid advances in biotechnology. Performance-based standards are, therefore, generally preferred over design standards.
- In order to create opportunities for the application of innovative new biotechnology products, all regulation in environmental and health areas-whether or not they address biotechnology-should use performance standards rather than specifying rigid controls or specific designs for compliance.

The first of these principles restates long-standing Federal policy, while the second, on the importance of minimizing undue regulatory burdens, is obvious. The third and fourth principles, promoting the use of performance-based standards, are new to the discussion of biotechnology regulations. While this has been an important consideration in the development of other environmental regulations in the United States, rigid controls and specific designs have not been mandated for compliance with biotechnology regulations.

Another advisory committee was established by NIH at the behest of Congress. The National Biotechnology Policy Board is to make recommendations to the President and to Congress on policies to enhance basic and applied research; to enhance the competitiveness of the United States in development of commercial biotechnology-related industries and products; to assure the training of sufficient scientists, engineers, and laboratory personnel for both research and commercial development; and to enhance the transfer of technology from university and Federal research laboratories to commercial laboratories. The board is also expected to make recommendations on Federal participation in cooperative research initiatives and on regulatory policies. The board, which met for the first time in October 1990, consists of representatives from Federal agencies, industry, universities, State biotechnology centers, and foundations.

SOURCES: 50 F.R. 47174; S.A. Shapiro, "Biotechnology and the Design of Regulation" *Ecology Law Quarterly, vol. 17,1990,* pp. 1-70; The President's Council on Competitiveness, *Report on National Biotechnology Policy* February 1991; U.S. Senate, Report to Accompany H.R. 4783, Departments of Labor, Health and Human Services, and Education and Related Agencies Appropriations Bill, 1989; Department of Health and Human Services, Public Health Service, National Institutes of Health, "National Biotechnology Policy Board," unpublished, December 1990; *Biotechnology Newswatch*, Oct. 15, 1990, p. 9.

tests depend on the nature of the drug, but approval may take as long as 10 years. So far, 15 drugs and biologics based on biotechnology have been approved for human use, and more than 100 are in clinical trials awaiting approval. Diagnostic products that are not taken internally require less stringent testing, because they do not pose similar risks. Over 200 diagnostic tests based on biotechnology have been approved by FDA. Food additives are approved based on manufacturer tests demonstrating their safety under the conditions of use. In 1990, FDA approved its first food additive produced using an engineered micro-organism: it is chymosin, an enzyme used in cheesemaking (29). It also appears that FDA may consider food ingredients that are generally recognized as safe (GRAS) when produced by conventional means to also be considered GRAS when produced using biotechnology (37,38).

Altered Micro-organisms

Contained Uses

The organisms most commonly used in production facilities are neither pathogenic nor toxic and present little or no risk to workers or surrounding communities. In fact, many strains of micro-organisms fare poorly outside specialized growth facilities. Nevertheless, oversight may exist in the form of restrictions on laboratory or other contained uses of micro-organisms. Through relatively simple procedures that include the use of seals, inters, sterilization equipment, and protective clothing, containment measures can be used to limit the survival of the organisms outside the growth facility and minimize human contact with these organisms.

The Occupational Safety and Health Administration (OSHA) of the U.S. Department of Labor announced in its guidelines in the Coordinated Framework that no new regulations appeared to be necessary to protect the safety of laboratory workers (51 Fed. Reg. 23347). In the United States, the Government regulates large-scale industrial production using recombinant micro-organisms depending on how the final product is regulated. Thus, FDA has standards for facilities that use micro-organisms to produce proteins, and EPA can regulate commercial production under the Toxic Substances Control Act (TSCA) (15 U.S.C. §2601 ***et seq.).***

Planned Introductions

Micro-organisms are used commercially in waste treatment and agriculture. The first such genetically engineered micro-organism to reach the market was a microbial pesticide engineered in Australia, and introduced in 1989 (75). A derivative of an organism that had a long history of safe use, its only modification was a deletion that impaired its ability to transfer the pesticide trait (71). Biotechnology promises improved versions of such micro-organisms and further applications to the degradation of toxic substances.

A consensus seems to exist that the vast majority of altered organisms pose minimal or no risk; nevertheless, certain environmental introductions could warrant concern. This judgment is based on prior experiences with somewhat analogous situations: the introduction of other species, including exotics; the spread of novel traits in existing populations; and the agricultural use of plants genetically altered through traditional techniques, such as selective breeding (15,18,49,50,53, 57,68). Potential problems include the creation or enhancement of pests; unintended harm to nontarget species, either directly or through competition for resources; and changes in the basic biochemical processes that support the ecosystem, such as nutrient cycling (18,53).

In evaluating environmental risk, the type or amount of genetic alteration is less important than how that change affects the characteristics (phenotype) of the organism and the interaction of the organism with the environment. Several studies list risk criteria and attempt to weigh or prioritize them (18,50). These criteria include:

- familiarity with the parent organism and its modified derivatives,
- likelihood of the organism's persisting in the environment or spreading to new environments,
- likelihood of the organism competing successfully against other important organisms,
- ease with which the organism can transfer its genetic material to other organisms,
- direct involvement of the organism in basic ecosystem processes, (e.g., nutrient cycling and respiration),
- response of the organism to selective pressures in the new environment, and
- size and frequency of the releases, because greater size or frequency can increase the probability of long-term survival (18,68).

Because characteristics of the organism and the environment must both be considered, a case-by-case review process is generally viewed as necessary (18,50,68). Scaling the level of review to the level of risk is appropriate, however, such as the approach taken by NIH in overseeing laboratory research. A faster, less-detailed review may be sufficient for low-risk introductions. For example, micro-organisms judged similar to past introductions and returned to their native environment might eventually be assigned to a low-risk category or exempted from review (18,50,53,68). Another proposal suggests considering how a genetic modification alters an organism's safety, compared with that of a parental strain (48).

In the United States, most planned introductions of genetically engineered micro-organisms are subject to EPA regulations. Some introductions, however (e.g., vaccines and plant pest derivatives) are regulated by FDA and USDA.

Vaccines—The FDA regulates vaccines for human use. Many vaccines are viruses, but because they are weakened strains and have been used safely under FDA regulation for many years, regulation of human vaccines has aroused relatively little controversy.

Animal vaccines and other animal biologics are regulated by USDA under the Virus-Serum-Toxin Act (21 U.S.C. §151-158). Some local officials have voiced concern about the safety of proposed tests of new vaccines. In 1989, a proposed test of an orally administered recombinant rabies vaccine, intended to immunize wild animals, was abandoned after

State public health officials raised objections in South Carolina, but a similar test took place in Virginia in mid-1990. Other outdoor tests of recombinant animal rabies vaccines have taken place in Belgium, Canada, and France (25,27). The USDA granted 42 licenses for veterinary biologic products through the end of 1990.

Plant Pest Derivatives--Release of genetically engineered micro-organisms derived from plant pests is regulated by the Animal and Plant Health Inspection Service (APHIS) of USDA, under the authority of the Federal Plant Pest Act (PPA) and the Plant Quarantine Act (PQA) (see box 11-C).

Pesticides-Genetically engineered micro-organisms intended for use as pesticides are regulated by EPA under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) (7 U.S.C. §136 ***et seq.).*** Under this law, all pesticides, whether chemical or microbial, genetically engineered or not, must be registered by EPA before being sold and may only be distributed and used under the conditions approved in the registration. The EPA also grants an Experimental Use Permit (EUP) to allow limited use of unregistered pesticides for premarket testing. EUPs are usually presumed not to be required for testing new chemical pesticides on less than 10 acres, but EPA has concluded that evaluation of small-scale testing of certain genetically engineered micro-organisms is needed. To determine if an EUP will be required, EPA is amending the existing EUP rule to require that it (the EPA) be notified of plans for small-scale testing of certain categories of micro-organisms. Until a new rule is promulgated, EPA has requested voluntary compliance. In the case of micro-organisms that are pesticides and are also derived from plant pests, EPA has been designated the lead agency under the Coordinated Framework, but USDA's Animal and Plant Health Inspection Service (APHIS) also takes part in the review. As of March 1991, EPA had approved 10 applications for small-scale testing of genetically engineered microbial pesticides under FIFRA. In addition, two applications had been withdrawn, and another review had been suspended.

Other Micro-organisms—Other releases of micro-organisms into the environment may be regulated by EPA under TSCA, which is a gap-filling law enabling EPA to quickly screen chemicals that will not be reviewed under other statutes for health hazards. The act gives EPA authority to collect information on chemical substances and mixtures of chemical substances, so it can identify potential hazards and exposures. The TSCA gives EPA jurisdiction over manufacturing, processing, distribution, use, and disposal of all chemicals in commerce or intended for entry into commerce that are not specifically covered by other regulatory authorities. In practice, firms are required to provide EPA with information on the characteristics of any new chemical 90 days before commercial manufacture of the chemical begins. These requirements do not apply to small amounts of chemicals produced for research or analysis, as long as workers are informed of health risks. Noncommercial work, such as academic research, is not regulated under TSCA.

The EPA has announced, in its policy statement in the Coordinated Framework (51 Fed. Reg. 23301), that it considers certain types of micro-organisms to be chemical substances subject to regulation under TSCA if they are not regulated under other statutes. The EPA has requested voluntary compliance with its policy until formal rules are in place. Premanufacture notification is requested for intergeneric micro-organisms, that is, those containing DNA, derived from organisms of different genera, unless the transferred DNA consists of a well-characterized, noncoding regulatory region. The EPA has announced that it will amend its regulations so that the research and development (R&D) exemption would not apply to field releases of micro-organisms. It has also stated its intention to develop a significant new-use rule for pathogenic micro-organisms, and it has requested voluntary notification in the interim. Further rulemaking is needed to implement the policy, so EPA's current policy may change. As of March 1991, nine applications for field tests of genetically engineered micro-organisms had been approved by EPA under TSCA, mainly for nitrogen-fixing bacteria.

Some environmentalists charge that TSCA is inadequate for regulating environmental releases of genetically engineered organisms (39,46). The EPA's authority to regulate organisms as chemicals under TSCA has not been legally tested. Another difficulty some environmentalists find with TSCA is that it is not applicable to academic research. In addition, TSCA is a notification statute, not a licensing statute. Under TSCA, firms inform EPA of their intention to manufacture a chemical; EPA, in turn, has 90 days to review the submission. As TSCA has been applied to the manufacture of

Box 11-C-Regulation Under the Federal Plant Pest Act and the Plant Quarantine Act

Under the authority of the Federal Plant Pest Act (PPA)(7 USC. §150aa-jj) and the Plant Quarantine Act (PQA) (7 U.S.C. §151-164a, $166-167), the Animal and Plant Health Inspection Service (APHIS) of USDA is responsible for regulating plants, plant products, and plant pests that may threaten U.S. agriculture. Under these laws, APHIS also has the authority to regulate the import, interstate movement, and release of genetically engineered organisms derived from plant pests into the environment. The definition of plant pests is broad, encompassing any organism that directly or indirectly causes disease or damage to plants (e.g., bacteria, viruses, protozoa, fungi, and other parasitic plants, insects, mites, snails, nematodes, and slugs).

APHIS uses a permit system to restrict entry, dissemination, and establishment of plant pests into the United States. A permit is required for any organism if it has been genetically altered using rDNA techniques; if it is being imported, moved interstate, or released to the environment; and if the donor, vector, or recipient is a plant pest or is unclassified. APHIS may also regulate genetically engineered organisms or products altered or produced using genetic engineering that the deputy administrator determines are plant pests or has reason to believe are plant pests.

To receive a permit for a small-scale, planned introduction into the environment, an applicant must submit detailed information on the identity of the organism and how it was produced; a description of the changes in the organism resulting from introduction of new genetic material; a statement on the purpose of the introduction and details of the experimental protocol, including the size and schedule of releases; and a description of the methods used to prevent dissemination beyond the test site.

Before a permit for an introduction maybe issued, APHIS prepares an environmental assessment based on the submitted information and must notify and coordinate its review with the appropriate agency in the State where the release is planned. This process takes up to 120 days. Through mid-1991, USDA had issued more than 150 permits for the release of genetically engineered plants into the environment.

To receive a permit to import a regulated organism or to transfer a regulated organism across State lines, an applicant must submit an application containing information on the identity of the organisms and where and how they were produced, a description of how they will be transported and how they will be maintained and used at their final destination, a description of the safeguards that will be used to prevent their dissemination, and a description of the final disposition of the organisms. For interstate movement alone, an application for a single permit, good for 1 year, can cover multiple interstate transfers of multiple organisms. The USDA has issued more than 650 permits for movement.

To sell a genetically engineered plant or micro-organism that is a regulated article under PPA and PPQ, a firm must petition APHIS for an exemption from these regulations. The firm must submit data establishing that the organism is not a plant pest and is not otherwise deleterious to the environment+ No petitions have been received yet, and it is not yet clear precisely what data must be submitted to receive approval.

Individuals may also submit petitions to amend the list of organisms regulated as plant pests by adding or deleting any genus, species, or subspecies. The petition must include copies of papers from scientific literature or unpublished data that support the petitioner's contention that an organism is a plant pest and should be added to the list or that the organism is not a plant pest and should be deleted from the list. After publication in the Federal Register and an opportunity for public comment, the Deputy Administrator will approve or deny the petition completely or in part.

SOURCES: 51 F.R. 23352; 52 F.R. 22892; 7 CFR 340; H.G. Purchase and D.R. MacKenzie (eds.), *Agricultural Biotechnology: Introduction to Field Testing* (Washington, DC: Office of Agricultural Biotechnology, USDA, March 1990); J.W. Glasser, testimony before the House Committee on Agriculture, Subcommittee on Department Operations, Research, and Foreign Agriculture, Oct. 2, 1990.

chemicals, the burden of proof is on the agency, not on the manufacturer. Critics would prefer to see a statute that requires a manufacturer to demonstrate safety of a new product before a permit is issued (39,46,62).

The Scope Issue—Rules under FIFRA and TSCA have been under development since the Coordinated Framework was published. The most controversial aspect of the new rules has been the precise definition of the organisms whose release into the environment would be subject to review. A definition needs to meet several standards. It must be very clear to the regulated community which organisms are subject to the regulations and which are not. For example, in setting some types of regulations, agencies often rely on precise lists of items that are subject to regulation. In addition, a good definition

would make regulation easy for the agency to administer. It should also focus the agency's resources on those organisms most likely to be hazardous, while exempting or focussing less attention on organisms presenting minimal risk.

Developing a product- or risk-based rule, however, is more difficult than it appears. It has always been hard to define the risks posed by modified organisms. Defining risky organisms in an administratively simple way, that will be clear to the regulated community is extremely difficult. In 1988, this issue became the focus of acrimonious interagency debate (see box 11-B) (61). As a result, BSCC and the agencies' scientific advisory committees considered several alternative definitions. Some proposals were criticized for being process based, that is, that the organisms to be reviewed were identified by the process by which they were made.

Such process-based definitions maybe construed to mean that certain types of genetically engineered organisms carry inherently greater risk than their nonengineered counterparts, a view that critics charge is unscientific. On the other hand, unlike classical techniques, biotechnology can be used to produce organisms carrying traits derived from organisms of different species, potentially raising more regulatory questions (18,50). In addition, there are particular difficulties in using a risk-based definition to describe organisms subject to review under TSCA. The TSCA applies to all commercial chemicals, not only hazardous ones. It can be argued that the fact that a chemical is subject to EPA notification under section 5 of TSCA implies nothing about its risk, since TSCA is used as a method of screening all new chemicals.

In mid-1990, a proposed Federal policy, developed by BSCC and the President's Council on Competitiveness, was issued (55 Fed. Reg. 31118). The aim of the policy was to promote consistency among the agencies. The OSTP recognized, however, that the agencies may take different approaches in promulgating specific rules and guidelines under existing legislation. The OSTP acknowledged that agencies had difficulty in developing operational definitions of BSCC's 1986 proposal, namely, that organisms whose introduction should be subject to review would be either intergeneric organisms or those derived from pathogens. The new proposal outlines the general principle that agencies should use in determining whether a planned introduction should be subject to oversight:

> To the extent permitted by law, planned introductions into the environment of organisms with deliberately modified hereditary traits should not be subject to oversight . . . unless information concerning the risk posed by the introduction indicates that oversight is necessary.

The specific definition that was proposed, however, is not risk-based. The proposed scope includes "organisms deliberately modified by the introduction of genetic material into, or manipulation of genetic material within, their genomes," excluding:

- plants and animals resulting from natural reproduction or from the use of traditional breeding techniques;
- micro-organisms modified through physical or chemical mutagenesis, physiological processes such as conjugation, or spontaneous deletion;
- vascular plants regenerated from tissue culture;
- organisms modified through the introduction of noncoding, nonexpressed sequences that cause no physiological or phenotypic changes; or
- other organisms that could have been produced using these techniques or for which there exists sufficient familiarity to determine that their environmental effects are equivalent to those of past safe introductions.

The OSTP listed examples of risk criteria that agencies may use to evaluate planned introductions; these criteria are similar to those recommended in other recent reports from scientific societies (18,50).

In defining the scope of organisms whose introductions into the environment will be subject to regulation, OSTP ultimately proposed a largely process-based definition. The proposed scope includes all genetically modified organisms, while excluding a number of defined categories of organisms. It is unclear, however, how much this policy will change by the time it is published in its final form. In a widely leaked memorandum in May 1991, OSTP officials discussed abandoning the process-based definition for one based solely on risk. While this is an intellectually sound and internally consistent approach, it would lack administrative simplicity and could result in burdensome regulations.

Food Uses

Micro-organisms have been used since prehistoric times in baking, brewing, and fermenting. The organisms can die or be removed before the food is sold, or, as in the case of yogurt, live cultures may remain when the food is consumed. Strictly speaking, using micro-organisms in food processing is an environmental release. But because of familiarity with these organisms, their long history of safe use, their use in relatively small amounts, and their specialized environmental niches, micro-organisms in food have elicited less concern than large-scale environmental releases of genetically engineered organisms.

When Congress gave FDA authority to regulate food additives in 1958, many micro-organisms and other materials in use were recognized by FDA to have a special status-GRAS, or "generally recognized as safe'—because of their long record of safe use in food. Those entering the market since have either achieved GRAS status or received FDA clearances as food additives, based on submission of extensive information on their physical and chemical properties, intended use, and safety (21 CFR part 173 subpart B).

The FDA has decided that "the use of a new micro-organism found in a food could be considered a food additive" (51 Fed. Reg. 23310). Furthermore, a micro-organism can lose its GRAS status if it is produced or modified by new biotechnology that alters it, so that it is no longer generally recognized as safe by qualified experts. Such micro-organisms would then be considered food additives and thus, subject to premarket FDA review and clearance(51 Fed. Reg. 23313). One genetically modified micro-organism, a variety of baker's yeast, has been approved for food use in the United Kingdom (2).

Transgenic Plants

For generations, plants have been genetically altered using traditional methods of selective breeding, bringing enormous benefits to farmers and consumers. Biotechnology promises to extend these benefits by providing a means of endowing plants with new traits that are difficult or impossible to transfer using classical techniques. These new traits could result in plants more resistant to disease and insect pests or more amenable to food processing technology. Current research is also aimed at producing foods that are more nutritious and that have a longer shelf life.

Photo credit: Calgene

Genetically engineered tomatoes from a Yolo (CA) County field trial conducted in 1990.

Much less concern has been voiced about the agricultural use of transgenic plants than planned introductions of micro-organisms. Larger organisms are much easier to track, and more techniques are available to ensure their confinement. In addition, a broader, deeper range of experience exists for agricultural uses of altered plants. In the United States, over 150 field tests have been approved by USDA and have been carried out without incident. In The Netherlands and Germany, however, pressure groups protested against field tests of transgenic plants in 1989 and 1990 (44,77).

Planned Introductions

New strains of plants are usually tested in a stepwise fashion, beginning with small-scale field

tests, followed by increasingly larger tests, and finally commercial sale. Potential problems can often be recognized while the plant is being tested on a small scale. Similar procedures can be effectively used to test genetically engineered plants.

A major concern associated with the use of transgenic plants is enhanced weediness. Although domesticated crops are unlikely to become weeds, it is possible they can transfer advantageous traits to wild, weedy relatives by cross-pollination (18,19). This is not a major problem in the United States, however, where few crop plants are native species, and many crop plants have no wild or weedy relatives (50,53). Of the 15 major U.S. field crops, only sorghum, sunflower, clover, and tobacco have wild, weedy relatives in the United States (9). Some minor crop plants also have wild relatives in the United States, such as those in the crucifer family, which includes broccoli, cauliflower, kale, and rapeseed, as well as weedy yellow mustards (69).

Field trials of genetically engineered plants that carry pesticidal traits will be subject to EPA review under FIFRA. Other recombinant plants are currently reviewed USDA under the authority of PPA and PQA (See box 11-C).

Thus far, these laws have only been applied to transgenic plants containing rDNA derived from plant pests. The earliest method of transferring DNA to plants resulted in the transfer of some DNA derived from a plant pest, ***Agrobacterium tumefaciens.*** Therefore, virtually all transgenic plants to date have been subject to USDA regulation. More recently, however, new techniques for transferring DNA to plants have been developed that do not necessarily result in the incorporation of plant-pest DNA. Eventually, plants developed through these newer techniques will be ready for field testing, but unless the nature of the inserted trait triggers a review, they will not be subject to USDA regulation under PPA and PQA. Such transgenic plants that have been developed with Federal support would probably be subject to review under NIH Guidelines or USDA's research guidelines, but privately funded research would not be covered (54).

Food Uses

The FDA will regulate genetically modified plants used as foods in the same way it oversees the rest of the food supply. Whole foods (e.g., fruits, vegetables, and grains) are not subject to premarket review. The FDA, however, has authority to seize adulterated food and take steps to halt its distribution. This authority is generally used to remove foods from the market that have become contaminated. It could be used, although this has never happened, against new varieties of plants containing harmful substances.

In its policy statement in the Coordinated Framework, FDA states that a food produced using biotechnology could be in violation of FDCA if it contains a harmful substance not ordinarily found in the food or if it contains an abnormally high level of a substance that can be injurious to health. Beyond this, however, FDA has given little indication of its approach to ensuring safety of new food plants. Industry representatives have expressed a desire for more guidance. In December 1990, Calgene, a California plant biotechnology firm, asked FDA to approve its use of ***kanamycin,*** a marker gene that makes plants resistant to the antibiotic, (59).

An industry consortium, the International Food Biotechnology Council (34), has proposed a set of scientific principles for evaluating the safety of food and food ingredients derived from plants and micro-organisms altered through the application of biotechnology. The proposal is based on existing law and practice. A decision-tree for each category of product-food derived from micro-organisms; single chemical entities and simple, chemically defined mixtures; and whole foods and complex mixtures—encompasses a series of detailed questions about the food. The answers would lead to a decision to accept or reject the food or subject it to further study (34).

Food safety is likely to be an increasingly important topic of public concern. Appropriate FDA regulation of genetically altered products is critical if a public already suspicious of food additives and pesticide residues is to be confident about the benefits of biotechnology-derived foods.

Transgenic Animals

Genetic alteration of animals to serve human needs is also a centuries-old process. Biotechnology has the potential to accelerate this process and produce animals with increased growth performance, feed conversion efficiency, leanness, or disease resistance. Transgenic animals can also be used to produce pharmaceutical proteins, much in the way bacteria or cultured cells are used. For example, a gene can be altered so that the protein appears in the

credi R. Brinster nd R E. Hammer, School terinary Medicin Pennsylva

Th ma b g a 2 we -od mce ma g ra pe me The mo se h gh co ai a wg e
mpo d mo metal p mot eg a fused ma g wth alg Th mai wi hege
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transgenic animal's milk, from which it may be purified (47). Eventually, this process may provide a cheaper alternative to protein production in mammalian cell culture, which remains expensive. Transgenic animal models of disease, containing genes that mimic human genetic defects, are also an increasingly important research tool.

The regulation of transgenic animals is still uncertain. Activities potentially subject to regulation under existing legislation were outlined in the Coordinated Framework, but no rules have been proposed and little guidance given.

Planned Introductions

Environmental releases of a few types of animals, mainly insects or worms considered to be plant pests or animals containing genetic material from plant pests, may be regulated under PPA. Transgenic animals derived from infectious, contagious, pathogenic, or oncogenic organisms may be subject to regulation under the Animal Quarantine Statutes and the Virus-Serum-Toxin Act. Federally funded research is subject to research guidelines of the funding agency (54). Releases of genetically engineered fish are not regulated under Federal law (35).

Food Uses

The Food Safety and Inspection Service (FSIS) of USDA is responsible for ensuring the safety, wholesomeness, and proper labeling of food products prepared from livestock and poultry, under the authority of the Federal Meat Inspection Act (21 U.S.C. §601 *et seq.)* and the Poultry Products Inspection Act (21 U.S.C. §451 *et seq.). The* FSIS inspects cattle, sheep, swine, goats, horses and other equines; poultry; and food products prepared from these animals, but it has no oversight over fish or other aquatic animals. According to USDA's policy

United States Department of Agriculture

Animal and Plant Health Inspection Service

Technical Bulletin No. 1783

User's Guide for Introducing Genetically Engineered Plants and Microorganisms

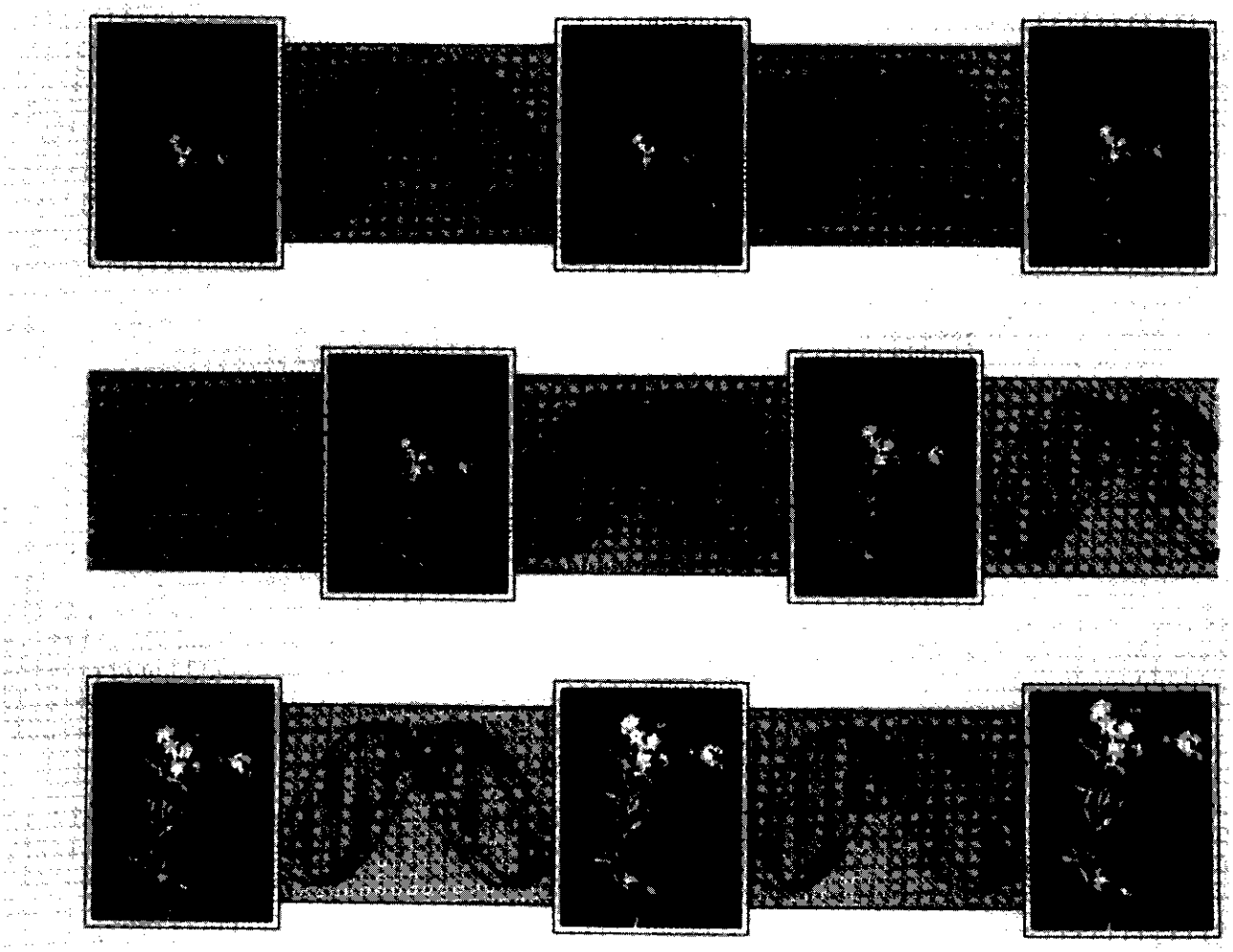

Photo credit: The U.S. Department of Agriculture

The U.S. Department of Agriculture (USDA) has developed a user's guide for introducing genetically engineered plants and organisms. As of July 1991, USDA had approved 165 permits for field test in 34 states and Puerto Rico.

statement, published in the Coordinated Framework, genetically engineered food animals would be treated like new breeds-subject to the same inspection procedures as traditionally inspected animals. The FSIS could also amend its regulations to ensure that genetically engineered organisms intended for use as food are not adulterated(51 Fed. Reg. 23343). The safety of transgenic animals could be evaluated by considering the primary and secondary effects of the gene product, much as drug or pesticide residues in food are evaluated (8).

Implementation and Coordination of Regulations

The Coordinated Framework has settled a number of issues concerning agency jurisdiction. For many products it is clear which agency has primary responsibility. The FDA has adapted existing procedures for the regulation of drugs, biologics, and medical devices to the regulation of products developed using biotechnology; EPA and USDA have established procedures for reviewing small-scale field tests of genetically engineered micro-organisms and plants. The review process is functioning more smoothly as the agencies have gained experience (30,58,64,67).

Nevertheless, the system is not without its problems. From the outset, the regulatory system has been criticized as too confusing for the regulated community, particularly for scientists working in universities or small firms who have little experience with regulation. This situation is made worse by the lack of published guidelines and rules. The USDA did not issue its research guidelines until early 1991 (56 Fed. Reg. 4134). The EPA's proposed rules for small-scale field testing under FIFRA and TSCA have faced long delays. Although field tests are being conducted, the policy is subject to change, making long-range planning difficult for industry. In addition, the organisms now being tested in small scale will soon be ready for large-scale testing and, eventually, product approval. But regulatory requirements for gaining approval to market certain types of products, particularly foods, are unclear (14). The FDA has given industry little indication of the regulatory barriers it will face in bringing new foods to market.

One reason agencies can be slow to confront new regulatory issues is an inability to anticipate new problems and novel areas of research. In addition, regulatory procedures are cumbersome and do not readily lend themselves to new and rapidly changing technologies. Another problem, long recognized by students of the regulatory process, is the strong incentives bureaucracies have to move slowly or not at all. Indeed, agencies face criticism if in acting quickly they make mistakes (55).

Academic researchers, especially agricultural researchers, also find agency requirements, which officials of large firms accept as a part of the cost of doing business, to be burdensome (20,24). This situation tends to discourage academic biotechnology research that would lead to an encounter with a regulatory agency, thus discouraging work on subjects with little potential for commercial reward—including products aimed at small markets, environmental research, and research addressing agricultural problems of the Third World (24,66,71). The cost of meeting regulatory requirements has a similar effect on industry, discouraging research on products whose commercial potential is relatively small (26). Some critics maintain that the major problem with regulation is even more fundamental; that is, the resources that must be devoted to meeting regulatory requirements are disproportionate to risks as currently perceived (23,26,42,65).

NATIONAL REGULATORY POLICIES

Several industrial nations and the EC are developing and implementing biotechnology regulations, based in part on international scientific criteria. Strong incentives favor international harmonization of such regulations. Export-oriented countries, especially small countries without large home markets, need regulations compatible with those of potential importers of their products.

Regulations, however, are also influenced by public opinion and cultural attitudes toward risk, health, and the environment (17). Substantial country-to-country differences in public opinion on environmental concerns are common. This can be seen, for example, in the different public responses to the use of nuclear power in France and Germany (51). In Germany, the Green Party platform calls for a total ban on biotechnology research, development, and production; the organization has been particularly influential in this regard (see box 1 l-D).

Box 11-D-Green Parties

The Green parties, although still a small minority, have been increasingly successful in local and parliamentary elections throughout Europe. In the June 1989 elections to the European Parliament, the number of seats held by members of Green parties more than doubled, compared with the previous election, reaching 39 out of 518. Until recently, the former West Germany's ***Die Gr nen was the*** most successful Green party in Europe in terms of membership, electoral votes, and financial strength. They received 5.6 percent of the vote in the March 1983 Federal parliamentary election and increased its share to 8.3 percent in January 1987. In December 1990, however, in the first election after German reunification, the western German Greens suffered a resounding setback The party, which had taken no formal position on reunification, received only 3.9 percent of the vote. Because they failed to capture the required 5 percent of the vote, all 46 Green members of the Bundestag lost their seats. An eastern German coalition of Greens and civic movements, however, won 8 seats. Racked by internal dissention, the Green Party's future in Germany is uncertain.

An outgrowth of local environmental groups of the early 1970s, the Greens have become an umbrella group for organizations whose concerns are often unaddressed by the major parties. They draw support from peace and disarmament activists, antinuclear-power protesters, and supporters of equal rights for gay people, women, and members of minority groups. Some of their success may be due to the Greens' position as an alternative to established parties and thus, the obvious choice for the disillusioned voter. Green supporters tend to be, for the most part, moderate-to-radical left politically, well-educated, and employed in the white-collar service sector of the economy, in particular, universities. Although some of their supporters are radical leftists, one Green party slogan proclaims: "We are neither left nor right, but out in front."

The Greens are less an organization than a movement. The beliefs of their members vary, and policies supported by Green parties in different countries vary as well. Tensions within Green parties are similar to those among U.S. environmentalists-between the most radical environmentalists (deep ecologists) and those who put the needs of people first. Some generalizations are possible, however. Policies supported by the Greens include: presentation of the natural environment; unilateral disarmament; a nonaligned, nuclear-free Europe; and aid to the Third World targeting the development of self-sufficient economies. Central to the Greens' philosophy is dissatisfaction with traditional political organizations and representative democracy. The Greens maintain that government policy often reflects the interests of the military and industry, rather than the will of the people. Therefore, they favor decentralization of decisionmaking power, including the use of plebiscites to decide major issues. The organization of Green parties reflects this support for "direct democracy." Local party branches are autonomous, and their leadership is either collective or rotates among members. Meetings are open to the public, and grassroots participation is encouraged. Since their recent losses in Germany, however, some Greens who disagree with this lack of organization have become more vocal in their support for a more-established leadership.

The Greens part company with traditional leftists in their emphasis on alternative lifestyles, based less on material well-being and modern technology and more on individualism, community solidarity, and self-determination. Because many Greens are skeptical about the benefits of new technology and increases in economic growth and industrial productivity, they often reject attempts to weigh risks to the environment against the needs of industry. One spokesman, a specialist on the chemicals industry for the British Green Party, stated that "economic growth should be limited and that the health and safety of the planet should become the chief criteria by which to judge the worth of any activity."

The Greens strongly favor increased controls on the chemical and energy industries and a phase-out of nuclear power. Now that the expansion of the nuclear power industry has come to a virtual standstill in many countries, their attention has turned to biotechnology. Like their positions on other environmental issues, the position of the most extreme Greens concerning biotechnology is not based on estimates of risk to public health or ecological balance. Rather, they oppose biotechnology because it is unnatural and "speeds up evolution." To the Greens, the protection and preservation of the natural environment is sacrosanct.

SOURCES: A. Coghlan, "Chemicals Industry: Guilty until Proven Innocent," *New Scientist*, vol. 123, No. 1678, Aug. 19, 1989, p. 23; K.J. Kelley "A Green Fringe," *The Progressive*, vol. 54, No. 4, 1990, pp. 30-33; F. M ller-Rommel, "The German Greens in the 1980's: Short-Term Cyclical Protest or Indicator of Transformation?" *Political Studies*, vol. 37, 1989, pp. 114-122; M.G. Renner, "Europe'sGreenTide," *World-Watch*, vol. 3, No. 1,1990, pp. 23-27; S. Schmemann, "GermanGreens, Still Fighting One Another, Survey Election Debacle," *The New York Times*, Dec. 7, 1990; J.H. Vaughan, "The Greens' Vision of Germany," *Orbis*, vol. 32, 1988, pp. 83-9S; H.J. Veen, "Prom Student Movement to Ecopax: The Greens," *The Washington Quarterly*, vol. 10, 1987, pp. 29-39.

Box 11-E--State Regulations

Several States have considered new legislation or have developed regulations based on existing legislation regulating field tests of genetically modified organisms or the use of certain products developed using biotechnology. This is due to a perception of gaps in Federal legislation and oversight, to the fact that Federal agencies do not require notification of local officials or citizens in the area of test sites, and to a belief that Federal agencies are not attuned to local needs.

Hawaii, Illinois, and Wisconsin require notification before the release of genetically engineered organisms into the environment. Two other States, Minnesota and North Carolina, have more formal permit systems for field tests. Minnesota has empowered its Environmental Quality Board to coordinate State and Federal regulations pertaining to field tests and to issue permits for field tests not regulated elsewhere by the State government. A recent North Carolina law mandates an in-State review of proposed fieldtests. A 10-member Genetic Engineering Review Board will write detailed regulations to be used by North Carolina's State Department of Agriculture when evaluating field trials for both research and commercial purposes. Under these regulations, researchers would submit essentially the same information that they now supply to Federal agencies.

The North Carolina law has received mixed reviews. Some fear that other States will follow North Carolina's lead, resulting in a confusing patchwork of laws that will impede research and slow the course of commercialization. Others see benefits. Although the new law adds an extra layer of review, it imposes no new data requirements on researchers. The law may also help ensure public confidence in the regulatory system while prohibiting additional regulation on the part of local communities, It has also been argued that by submitting to State laws, companies may protect themselves from legal challenges.

Two States, Wisconsin and Minnesota, have enacted legislation imposing a temporary ban on the use of bovine somatotropin, a product derived from a genetically engineered micro-organism (see box 1 l-F).

SOURCES: Industrial Biotechnology Association, *Survey of State Government Legislation on Biotechnology, May 15,* 1990 and fall 1990; G. Blumenstyk, "States Are Seeking Mom Regulation of Biotechnology," *The Chronicle of HigherEducation,* Aug. 8,1990, p. A13; M. Crawford, "Should States Regulate Biotechnology?" *Science, vol. 245, 1989,* p. 466; J.L. Fox, "Wide Acclaim for North Carolina Regulations," *Biotechnology, vol. 7, 1989,* p. 1002.

Prior incidents, related or unrelated, have raised public awareness and political sensitivities. For example, initial concerns about the hazards of rDNA research arose in the mid- 1970s, roughly coinciding with an accidental release of smallpox virus from a London laboratory in 1973. The incident, unrelated to rDNA research, also coincided with the election of a Labour Government and an increase in parliamentary interest in workplace safety. Consequently, in the United Kingdom the first controls on biotechnology were based on general workplace legislation (6).

In the United States, sporadic concern about particular aspects of biotechnology regulatory policy has arisen. Local protests against releases of genetically engineered micro-organisms occurred in 1986 and 1987 in California and Missouri, respectively (68). Although general opposition has since dissipated, several States have introduced and in some cases enacted legislation regulating planned introductions (see box 1 l-E). More recently, farm, consumer, and environmental groups have raised concerns about the use of bovine somatotropin (BST), a hormone that increases milk production (see box 11-F). Some scientists attribute public concern about biotechnology to scientific illiteracy in the general population. In addition, according to cross-national studies of health, safety, and environmental regulations, increasing public concern about such hazards tends to coincide with public distrust of those responsible for ensuring public safety: scientific experts, the civil service, and the business community (73).

Worldwide, there have been three basic approaches to the regulation of biotechnology; they generally parallel approaches to controlling environmental pollution and nuclear power.

. **No regulations.** A number of countries with active investment in biotechnology have no regulations specific to biotechnology. In most growth-oriented countries (NICs) of the Pacific Rim (e.g., Taiwan, South Korea, and Singapore), biotechnology has been targeted as a strategic industry. Some industrialized European Nations, including Italy and Spain, which have no regulations specifically dealing with biotechnology, expect to develop them to

harmonize with EC directives on biotechnology.

- Stringent biotechnology-Specific regulations. Some northern European countries have responded to public pressure to impose stringent regulations specific to biotechnology by enacting new legislation. Under a 1986 law, Denmark prohibits the deliberate release of genetically engineered organisms without the express permission of the Minister of the Environment. Germany enacted new legislation imposing tight restrictions in 1990. The EC's 1990 directives on contained use and deliberate release of modified organisms, while not as restrictive as the Danish or German laws, follow a similar approach, i.e., directives specifically regulate the use of biotechnology.
- Limited restrictions. Australia, Brazil, France, Japan, The Netherlands, the United Kingdom, and the United States allow the use of biotechnology with some restrictions and oversight (see boxes 11-G; 11-H; and 11-1). In these countries, regulations based on existing or amended legislation governing drugs, worker health and safety, agriculture, and environmental protection are being applied to the use of biotechnology. Stringency varies, as do the enforcement mechanisms.

No Regulations

The newly industrializing countries of the Pacific Rim (e.g., South Korea, Singapore, and Taiwan) are consciously imitating Japan's postwar route to economic success. These governments place heavy emphasis on economic growth and development, with particular interest in the production of high-technology exports. Years of neglecting the environment in Pacific Rim countries, however, have resulted in severe industrial pollution, and, in recent years, public awareness of environmental problems has risen. There is increasing evidence of public interest in regulations designed to protect health and safety and the environment. Some observers expect the Pacific Rim countries will eventually follow Japan's lead in the development of biotechnology regulations as well (28,32).

Stringent Biotechnology-Specific Regulations

Denmark

In contrast to the approach of most Pacific Rim Nations, Denmark and Germany have enacted new legislation specifically regulating biotechnology products and techniques. In Denmark, the Environment and Gene Technology Act (EGTA), passed by the parliament in 1986, gives the Minister of the Environment broad power to regulate the use of genetically modified organisms. The law restricts biotechnology research with these organisms to registered laboratories. The production, marketing, use, or import of substances or products containing genetically manipulated organisms or cells is not permitted, except with the approval of the Minister. Pharmaceuticals and feedstuffs, however, are exempt from this provision.

In addition, the deliberate release of genetically modified organisms is specifically prohibited in Denmark, although the Minister of the Environment may make exceptions. The Minister of the Environment has agreed not to grant approval for releases without the consent of the parliament committee for the environment (3). Approval for field testing two strains of genetically engineered sugar beets was granted in July 1989 (41,60).

A 1987 order covers small- and large-scale research and production facilities using engineered micro-organisms and is largely aimed at protecting worker health and safety. Administered by the National Labor Inspectorate, it specifies containment conditions for R&D.

The EGTA was amended in 1989, easing some restrictions that industry found most onerous. For example, pilot plants are now treated as research laboratories, rather than as production facilities, and, as such, are subject to fewer regulations. A second change allows a company to continue working after a complaint has been lodged against it with the Environmental Appeals Board. Previously, such work had to cease until the complaint was dismissed.

Nevertheless, industry representatives charge that the approval process is still too time-consuming and burdensome (52). However, the 1989 amendments and field-test approvals suggest that, in practice, the regulations may come to be no more severe than those in other European countries.

Germany

New legislation enacted in Germany in 1990 was welcomed by the regulated community, because it ended a period of regulatory uncertainty (56). In 1989, the Administrative Supreme Court for the State of Hesse ruled that because there was no law

Box 11-F--Bovine Somatotropin

Bovine somatotropin (bST), also known as bovine growth hormone, is a naturally occurring peptide hormone produced by cattle. Among other functions, it regulates the production of cows' milk. The hormone can be manufactured using genetically engineered organisms in a standard fermentation process, resulting in a nearly identical copy of the natural substance. When supplemental injections of small doses of bST are administered to dairy cows, milk production increases by as much as 10 to 25 percent. The cows may eat more feed, but there is an increase in milk production per unit of feed. The increased production results in a significant decrease in the production cost of a unit of milk.

Like all animal drugs, whether or not genetically engineered, the use of bST is subject to FDA regulation. To receive approval to market any animal drug, the manufacturer must demonstrate that the drug is safe and effective when used in accordance with the label directions. It must also be shown that the drug and its metabolizes do not appear as unsafe residues in the edible tissues of the animal at the time of slaughter or in other animal products, e.g., milk or eggs. Although FDA has not yet approved bST for marketing, the agency found, in 1985, that the meat and milk from experimental herds are safe for human consumption. A NIH panel reached the same conclusion in 1990. The FDA must evaluate the hormone's effects on the health of cows before it can grant final approval.

In addition to concerns about the effects of bST on human health and animal welfare, concerns also exist about consumer acceptance. A 1990 survey of Wisconsin consumers found that 77 percent would prefer to drink milk from untreated cows, and 67 percent would pay as much as 22 cents additionally per half-gallon for non-bST milk.

The strongest resistance to bST in the United States probably comes from farm activists who believe that bST will increase economic pressures on small farmers already pressured by increased farm productivity by larger farms. Since the 1950s, dairy farming has changed considerably, as a result of technologies that save time and labor such as, bulk milk handling, silo unloaders, and improved milking equipment+ Higher quality feeds, artificial insemination, and better disease control have also contributed to productivity increases. In 1955, the average cow in the United States produced less than 6,000 pounds of milk per year. By 1985, average milk production was close to 13,000 pounds yearly. This increase in productivity has resulted in a dramatic decrease in the number of dairy farms and a corresponding increase in their size. With or without the use of bST, this trend is expected to continue.

Industry officials, however, emphasize bST's "size neutrality." Unlike other new technologies, use of bST does not require a large investment or impose along delay before benefits are realized. Therefore, bST can be used profitably by operators of both large and small farms. Farmers who are poor managers, however, and whose cows are badly nourished or unhealthy are unlikely to realize benefits from bST use. A 1987 USDA study found:

(Continued on next page)

to "expressly permit the application of genetic engineering, such facilities may not be built and operated" (4). The ruling prevented the use of a Frankfurt production facility, operated by Hoechst AG, from manufacturing genetically engineered human insulin. Although this decision was binding only in the State of Hesse, new investment in production facilities in Germany ceased afterward. The 1990 law will allow biotechnology production to proceed.

The new law is based on the findings of a parliamentary commission, which spent 2 years compiling a thorough report on all uses of biotechnology. Although the commission reached consensus on a wide variety of issues, the Green Party representative took exception to many conclusions. The commission strongly supported the use of biotechnology in developing pharmaceuticals, diagnostic products, chemicals, and foodstuffs—including transgenic plants and animals. But, the commission, also concerned about contained uses of micro-organisms, favored extending the current controls on government-funded, contained uses to apply also to industrial production facilities. The commission was emphatically opposed to the environmental release of genetically engineered micro-organisms and viruses, except for vaccines (15).

The comprehensive Genetic Technology Law, largely based on the report of the parliamentary commission, is broad in scope, covering recombinant micro-organisms, viruses, cells, plants, and animals, in addition to plasmid vectors. The law specifies conditions for building and operating production facilities, releasing engineered organisms into the environment, and transporting organisms. Specific requirements are outlined for both research and commercial production.

Adoption of bST, when viewed at the national level, simply reinforces the 30-year trend toward increased milk production per cow and declining dairy farm numbers. When viewed at the farm level, bST use could prove profitable for almost all commercial dairy farms. But inefficient producers who lack management skills and who do not adjust feeding and health procedures to reflect increased milk production from bST-treated cows are not likely to capture all of bST's potential benefits. Hence, bST will not significantly affect the national trend towards large dairy farms in all regions.

Nonetheless, temporary bans on the sale and use of bST were in effect in Wisconsin and Minnesota until mid-199l.

Similar issues are being addressed in Europe. The U.K.'s Veterinary Products Committee sees no risk to human health or to the environment stemming from bST use, but it has recommended that bST not be licensed for sale because of questions about the manufacturing process and bST's effects on animal welfare. The European Community (EC) is also hesitating to approve bST use. In 1989, the EC placed a 15-month moratorium on the use of bST and later extended the moratorium until the end of 1991, so that the EC Commission could complete its studies. In March 1991, the EC's Committee for Veterinary Medicinal Products found that milk and meat nom treated cows are safe. Some members of the committee, however, recommended further studies on the effects of bST on the health of cows. But EC! member nations are now free to authorize the use of bST.

The ultimate impact of the use of bST on international trade is unclear. If bST is used in the United States but not in other countries, opportunities for commercial export might grow, as domestic U.S. prices may fall below international prices. It is not known, however, whether potential importers would accept milk from bST-treated cows.

SOURCES: Office of Technology Assessment, U.S. *Dairy Industry at a Crossroad: Biotechnology and Policy Choices, 1991.* J. Juskevich and C.G. Guyer, "Bovine Growth Hormone: Human Food Safety Evaluation" *Science,* vol. 249, 1990, pp. 875-884; R, Fallert et al., *bST and the Dairy Industry: A National, Regional and Farm-level Analysis,* Economic Research Service, U.S.Department of Agriculture, Agricultural Economic Report No. 579, October 1987; D.P. Blayney and R.F. Fallert, *Biotechnology and Agriculture: Emergence of Bovine Somatotropin, Commodity* Economics Division, Economic Research Service, U.S. Department of Agriculture, Staff Report AGES 9037, June 1990; "Thumbs Down for Milk Hormone," New *Scientist,* vol. 127, No. 1728, Aug. 4,1990, p. 25; The Economist "Bad Moos," vol. 316, No. 7667, Aug. 11, 1990, pp. 66-70; G. Gugliotta, "A Wonder Drug or a Threat?" *The Washington Post,* June 24, 1990; B.W. Marion and RL. Wills, "A Prospective Assessment of the Impacts of Bovine Somatotropin: A Case Study of Wisconsin," *American Journal of Agricultural Economics,* vol. 72, 1990, pp. 326-336; R. Jennings, personal communication, December 1990; Technology Assessment Conference, "NTH Technology Assessment Conference Statement on Bovine Somatotropin," *Journal of the American Medical Association,* vol. 265, 1991, pp. 1423-1425.

The law divides work with rDNA into four safety levels, depending on the source of the DNA, the host organism, and the vector. The most widely used organisms are included in the lowest safety level. At this level, authorities must be notified of plans to open facilities for research. Research considered to be riskier, requires formal approval before work can be undertaken. All industrial or commercial work is also subject to formal approval, but disclosure and public hearings are required only for work at Safety Levels 2 through 4. The law also holds operators of facilities liable for damages, and it requires operators of facilities approved for work at Safety Levels 2 through 4 to arrange for liability coverage.

The Lender, or State governments, are responsible for implementing and enforcing the regulations, an approach which is typical of German regulatory policy. The Advisory Board for Biological Safety (ZKBS), a part of the Federal Ministry of Health, plays an advisory role. Some fear that this places the burden of enforcement on local agencies lacking necessary expertise (16,45). In the last half of 1990, however, five firms received permission to operate production facilities (76).

The law also grants authority to the health ministry for regulating deliberate releases of genetically engineered organisms and for approving products containing genetically modified organisms. It lists information that manufacturers must provide and requires that public hearings precede releases of genetically engineered organisms whose spread cannot be limited. Germany's first release of genetically engineered organisms, a field test of altered petunias at the Max Planck Institute in Cologne, took place in summer 1990, after a year's delay due to public opposition (63).

The European Community

The EC has enacted two directives that deal specifically with biotechnology regulation: one directive regulates contained use of genetically modified micro-organisms and the other regulates the deliberate release into the environment of genetically modified organisms (12,13). Member

Box 11-G-Regulations in Japan

Japan's regulations on biotechnology generally follow international standards. The research guidelines, based on early versions of NIH Guidelines, were developed by the Ministry of Education, Science, and Culture and by the Science and Technology Agency to cover research in public and private institutions, respectively. Because the procedure for updating guidelines in Japan is relatively slow, the research guidelines tend to be more stringent than NIH Guidelines.

Guidelines for industrial applications are generally consistent with OECD recommendations. These guidelines were issued by the Ministry of International Trade and Industry in June 1986 and were followed by the publication by the Ministry of Health and Welfare of guidelines for producing pharmaceuticals and biologics.

The first regulations covering the **deliberate** release of recombinant plants were issued in the summer of 1989 by the Ministry of Agriculture, Forestry, and Fisheries. The Environment Agency has drafted safety guidelines for fieldtests of genetically modified micro-organisms, and rules for the release of transgenic animals are in preparation. The Ministry of Health and Welfare is developing guidelines for assessing the safety of food and food additives produced using rDNA technology. There is no body attempting to coordinate these various activities.

Reports about public perception of biotechnology in Japan are varied. Although some products advertised as biotech products have been well-received, community protests against the building of new research facilities have occurred, and surveys show that the public is wary of the technology. One survey of the readership of a Japanese science magazine, for example, found that respondents had serious misgivings about biotechnology, especially about food products and environmental introductions of modified organisms. Almost three-quarters had reservations about the marketing of genetically engineered fish, and 78 percent were very apprehensive about the prospect of planned releases of genetically engineered microbial pesticides in the United States.

SOURCES: H. Uchida, "Evolution of Recombinant DNA Guidelines in Japan," *Safety Assurance for Environmental Introductions of Genetically-Engineered Organisms,* J. Fiksel and V.T. Covello (eds.) (New York, NY: Springer-Verlag, 1988); C.C. Martin, "Japanese Bioindustry rends Turn Into Firmly Established Strategies," *Genetic Engineering News,* vol. 10, No. 2, 1990, pp. 2&21; Bulletin of the Atomic Scientists, "Biotech Lab Recalls Biowar," *Bulletin of the Atomic Scientists,* vol. 46, No. 1, 1990, p. *6;* D. McCormick, "Not As Easy As It Looked," *Bio/Technology,* vol. 7, 1989, p. 629; N.S. Shimbun, "Environment Agency Drafts Safety Guidelines," *Nikkei Sangyo Shimbun, Mar. 24,* 1990, p. 13; *Pharma Japan, "MAW to Prepare Safety Standard* for 'Bio Foods,' " *Pharma Japan, vol. 1222,* Sept. 24, 1990, p. 18.

countries must review their laws to bring them into harmony with EC directives by October 1991.

Contained Use—The directive on contained use is based in part on the Organization for Economic Cooperation and Development (OECD) recommendations, and it sets minimum standards for R&D and for industrial operations. Member countries must adopt regulations on the contained use of genetically modified micro-organisms that are at least as stringent as those in the directive.

Regulatory requirements depend on whether the modified micro-organism is associated with high or low risk and whether the work is large-scale or small-scale, noncommercial research. Records of the research must be kept for the use of low-risk organisms at the small-scale level. For small-scale work with high-risk organisms or large-scale work with low-risk organisms, researchers must notify the appropriate national authority, which then has 60 days for review. Large-scale uses of high-risk organisms are not permitted without the explicit approval of the national authority. The authorities must also be notified before a new facility using these micro-organisms may be used. EC member states must periodically provide information obtained from these notifications to the European Commission, the EC's executive branch.

Because the directive sets a minimum standard and member countries may impose more stringent standards, regulatory requirements are likely to differ among countries. These differences may provide incentives for firms to establish production facilities in countries with the least restrictive regulations, thereby defeating one of the purposes of economic integration.

Planned Introduction-Unlike the directive on contained use, the directive on deliberate release of genetically modified organisms is not a minimum standard; the ministers ruled that this directive is primarily a measure to regulate trade rather than to protect the environment. This ruling limits the ability of member states to impose stricter regulations.

Box 11-H—Regulations in France

In France, where little public concern exists about the use of biotechnology, a committee in the Ministry of Research and Higher Education must be notified of an intent to perform rDNA research. The Ministry of Agriculture reviews releases of genetically modified organisms, but notification is voluntary and the committee's recommendations are not compulsory. Government agencies are now working with trade associations to develop a set of voluntary guidelines for research, contained use, and deliberate release.

SOURCES: **Office of Technology Assessment, 1991.**

The directive on deliberate release is also based on OECD recommendations. Before a modified organism may be released, the relevant national authority must give approval, based on a case-by-case review of the researcher's detailed environmental assessment. The appropriate authorities in other member states must be kept informed and may, within 90 days, suggest improvements in the proposed experimental protocol. The authorities in other member states, however, do not have veto power.

The directive on deliberate release also describes requirements for placing genetically modified organisms on the market. The manufacturer or importer must obtain the approval of the national authorities in the country where the product will first be sold, and the national authority must inform other member nations of its approval. If there are no objections from the other states, the product may be sold throughout the EC. If many member countries raise objections, approval to market the product may be revoked. Alternatively, the dispute may be resolved through binding arbitration by a committee of national representatives and a chamber of the Council of Ministers.

In enacting directives that specifically regulate genetically modified organisms, the EC has established a regulatory procedure that is significantly different from that of the United States. In the EC, regulation is explicitly based on the method by which the organism has been produced, rather than on the intended use of the product. This implies that the products of biotechnology are inherently risky, a view that has been rejected by regulatory authorities in the United States. In addition, manufacturers are concerned that their new biotechnology-derived products may face additional regulatory barriers before they can be marketed, for the product may also be subject to further regulations based on its intended use (l).

Box n-I-Regulations in the United Kingdom

In the United Kingdom, the Health and Safety Executive has issued guidelines under the general authority of the Health and Safety at Work Act of 1978. It is mandatory to notify the Health and Safety Executive, and hence, the Advisory Committee on Genetic Manipulation (ACGM) of the intent to carry out genetic manipulation for research or planned introductions. Employers are requested to provide substantial information on the details of the experiment or production process.

Guidelines for planned releases were issued by ACGM in 1986. At first, only notification was required, and ACGM provided guidance on detailed procedure. Since November 1989, ACGM notification of proposed releases has been required by statute. Under the Environmental Protection Act of 1990, ACGM, now renamed the Advisory Committee on Genetic Modification, continues to oversee industrial R&D and basic scientific research. Its subcommittee responsible for case-by-case reviews has become an independent statutory committee, called the Advisory Committee on Release to the Environment (ACRE). It advises both the Health and Safety Executive and the Secretary of State for the Environment on human health and safety issues and, in particular, environmental issues associated with proposed releases. New regulations are to be put in place under the Health and Safety at Work Act and the new Environmental Protection Act. ACRE and ACGM share six common members and a common secretariat.

SOURCES: Environmental protection Act 1990; B. Ager, "The Oversight of Planned Release in the U.K.," *Safety Assurance for Environmental Introductions of Genetically-Engineered Organisms*, J. Fiksel and **V.T. Covello (eds.) (New York, NY: Springer-Verlag, 1988); R Jennings, British Embassy,** Washington, DC; personal **communication, December 1990.**

Industry officials also fear that one country could delay product approval for the whole EC by forcing lengthy reviews (43). In addition, they are concerned that national authorities may institute burdensome requirements. Because EC directives leave considerable discretion to national authorities, much depends on how national laws are written and implemented.

An industry group has identified another 12 regulatory initiatives, either proposed or being discussed by the European Commission, that could influence the use of biotechnology (11). One of these, a directive on the protection of workers from risks related to exposure to biological agents, was adopted by the Council of Ministers in November 1990.

Another EC legislative proposal would add a new requirement for regulatory approval for veterinary products. Although it is not specifically directed at regulating biotechnology, it could have an effect on some biotechnology products. In addition to the standard requirements of safety, quality, and efficacy, the legislation would require a firm to address the socioeconomic consequences of the use of its product. Such a requirement, known as the "fourth hurdle," could prevent the introduction of bST, because bST could increase production of milk, a product often in surplus in the EC. An amendment to the Veterinary Products Directive that would require the inclusion of socioeconomic criteria in the approval process for veterinary products was approved by a small majority of the European Parliament at its frost reading, but it was rejected at the second reading in November 1990. A similar requirement, however, is still under consideration in a draft proposal for a Community regulation concerning the use of substances and techniques stimulating the productivity of animals (21,22).

Limited Restrictions

The use of biotechnology began long after most industrial nations had developed laws and administrative procedures-including laws pertaining to drugs, agriculture, the environment, and worker safety-for regulating hazardous substances. In general, regulation of biotechnology began with an evaluation of how biotechnology could be regulated under existing law and whether new legislation was necessary at all (53). Australia, Belgium, Brazil, Canada, France, Japan, The Netherlands, Switzerland, and the United States, for example, have applied existing laws to biotechnology.

Also important has been the development of a scientific basis for regulating engineered organisms, an area in which OECD has been influential (see box 1 l-J). The OECD's recommendations comprise the basis of biotechnology regulations in many member nations.

Since OECD's 1986 report, other analyses of biotechnology safety issues, particularly planned introductions of modified organisms, have been developed by government task forces or scientific societies in OECD member nations (15,49,50,57, 68). Most country-to-country differences in biotechnology regulation among OECD members stem from legal, procedural, and administrative differences. These differences affect the design and implementation of all regulations for health and safety or environmental protection, not just biotechnology.

Several studies comparing U.S. and European regulations concerning pesticides, food additives, industrial chemicals, workplace safety, and air and water pollution have found that regulatory systems in other industrial nations are markedly different from the U.S. system (10,36,73,74). In other countries, bureaucrats are more likely to be granted discretion in implementing and enforcing regulations, and they often enjoy good working relationships with representatives of regulated industries as a result. Fines and litigation are rare. Agencies are more likely to use informal cooperative methods to obtain compliance, and these agencies see their interactions with the regulated community less as an adversarial relationship and more as an opportunity to provide advice and information. This is possible because, in other countries, agencies rarely have to justify their decisions. There is little oversight by legislatures and courts, and there are few provisions for public notification or participation.

This situation is beginning to change, however, particularly with respect to issues of great public concern, such as nuclear power and biotechnology (72). Nevertheless, biotechnology regulations probably will not be implemented or enforced using procedures similar to those used in the United States.

Biotechnology regulatory policies in France, the United Kingdom, and the United States, for example, vary widely in terms of complexity and enforcement. The French procedures not only are the simplest but are also voluntary. In the United Kingdom, the Advisory Committee on Genetic Manipulation, now called the Advisory Committee on Genetic Modification, has been overseeing the use of biotechnology on a case-by-case basis and has issued guidelines, rather than more inflexible regulations. But the committee has now, apparently, introduced a more formal system.

Box 11-J—The Organization for Economic Cooperation and Development

The OECD, an international organization founded in 1%1, is the major forum for discussion of economic policy by member States. These include most of the industrial world: Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Japan, Luxembourg, The Netherlands, New Zealand, Norway, Portugal, Spain, Sweden, Switzerland, Turkey, the United Kingdom, and the United States.

The OECD is committed to economic development and the expansion of world trade, in addition to achieving the "highest sustainable economic growth and employment" possible, while maintaining financial stability. The OECD has limited power but often works behind the scenes to promote international understanding of the economic impact of national policies.

In addition to holding regular meetings attended by each country's permanent representative, and yearly meetings at the ministerial level, OECD maintains a number of committees on specific issues, such as economic policy and development assistance, Delegates from national governments may also meet as expert bodies to discuss particular issues, such as biotechnology.

In 1983, OECD member countries setup a committee of experts to examine safety issues associated with the use of engineered organisms in large-wale industrial applications and agricultural and environmental applications. Recommendations on contained uses were issued in 1986.

The report's conceptual framework resembles the NIH Guidelines. It describes containment requirements for organisms, based on the level of estimated risk. It outlines a control standard known as Good Industrial Large-Scale Practice (GILSP), based on extending industrial experience and practice with micro-organisms to widely used, low-risk genetically engineered organisms. The containment requirements for low-risk organisms are minimal. More stringent containment strategies are recommended for organisms that present increased risk. The report lists criteria for determining whether an organism should be grown under GILSP or under more stringent standards, but it does not assign specific organisms to risk categories.

The OECD report also recommends a case-by-case review of environmental and agricultural applications of biotechnology. A stepwise progression of experiments--from the laboratory, to the greenhouse, to the small-scale field test, and then to larger field tests-is recommended, so that experience can be gained and safety evaluated. Detailed recommendations on conducting small-scale, low-risk field tests are being prepared.

SOURCE: Office of Technology Assessment, 1991.

The development of biotechnology regulations in the United States has been more difficult. Local protests have taken place at release sites, and periodic litigation has been brought by environmental groups. Infighting has also taken place among the Federal agencies responsible for developing regulations and policy statements (14,6 1), which rely more on precise definitions and detailed standards than French and British regulations (see box 1 l-B).

EFFECT OF REGULATION ON COMPETITIVENESS

At best, regulations that effectively reduce risk can result in an overall benefit to society. But measuring the benefits of biotechnology regulations are difficult. These regulations are intended to prevent problems that have never actually occurred; this means that assessing the probability of an adverse effect of biotechnology cannot be based on precedent. But some of the benefits derived from Federal biotechnology regulations can be listed.

- Some products produced using biotechnology warrant premarket review and approval to reduce risk to health or the environment.
- A Federal review process enables agencies to act as clearinghouses for safety information.
- A thorough Federal regulatory system can alleviate public concern and ensure public confidence in biotechnology.
- The absence of Federal regulations could result in a confusing array of State and local regulations that, in turn, could stifle commercial innovation and development while also increasing costs.

Whether the benefits derived from regulating biotechnology outweigh the costs of regulation is the subject of debate. Reduction of risk through more stringent regulation may increase direct and indirect costs to industry, government, and ultimately the

public. When regulations differ from the international norm, either in policy approach or in stringency, investors and researchers may move to other locations or shift to other investments. This general problem of regulation is especially acute in biotechnology, because of the wide variety of regulatory approaches around the world. The direct and indirect costs associated with biotechnology regulations include:

- the **cost** of filing applications and planning and performing field tests;
- benefits lost as a result of keeping useful products off the market;
- delays in product introduction, resulting in lost revenues, reduced market share, and delayed returns on investments;
- inappropriate health and safety regulations that pose barriers to trade; and
- another layer of uncertainty added to an already risky investment-for a potential product to be commercially viable, it must not only meet the criterion of competitiveness in the marketplace but must first meet regulatory criteria (33).

Large, diversified corporations are usually better able to shoulder the costs of regulation than start-up companies, which may find the costs prohibitive. It is quite common for small biopharmaceutical firms to license potential products to larger corporations, not only for marketing and distribution but also because the larger firms can finance environmental assessments and clinical trials more easily.

Regulations may bring on changing patterns of investment. Several major German corporations are building plants and research facilities in the United States and Japan rather than Germany partly because of the less stringent regulatory environment. For example, BASF AG is building its new genetic engineering research facility in Massachusetts, Bayer AG is expanding a biotechnology laboratory in Connecticut, and Henkel KGAA is building a new facility in California (5).

An uncertain regulatory climate also inhibits investment. Long delays in developing regulations make analysis of the potential return on an investment much more difficult. The time involved in establishing a reasonable yet comprehensive oversight mechanism in the United States, particularly a mechanism applicable to field testing, may have already contributed to depressing investment in U.S. agricultural and environmental applications of biotechnology. Ultimately, this loss of investment results in less innovation and lower technological competitiveness.

SUMMARY

Internationally, there have been three approaches to regulation: no biotechnology-specific regulations in most of the growth-oriented countries of the Pacific Rim and in some European nations, stringent regulations in countries with high levels of public concern about biotechnology (e.g., Denmark and Germany), and limited restrictions in most industrialized Nations, including Canada, France, Japan, the United Kingdom, and the United States. The EC has enacted directives that are specific to biotechnology-derived products. In Europe there has also been proposals for adding an additional criterion for regulatory approval of veterinary products. This "fourth hurdle" would require socioeconomic assessments of new products. American manufacturers fear that this criterion will be used to keep their products off the market in Europe.

In the United States, new legislation is considered unnecessary because the risks posed by the new products are thought to be similar in kind to those associated with similar products developed using other techniques. Under existing legislation, FDA has approved many new products, and USDA and EPA have established procedures for reviewing field tests of modified plants and micro-organisms. Although farm activists are concerned about the potential economic effects of BST, public concern about the contained uses of modified organisms and their testing in the field has dissipated in the United States. However, some problems remain:

- Mechanisms established to provide Federal coordination of activities related to biotechnology have, instead, become the center of interagency, ideological disputes over the scope of proposed regulations.
- The time required for clinical trials necessary for FDA approval of new drugs and biologics hurts young firms attempting to commercialize their first products.
- The EPA has yet to publish proposed rules for the regulation of micro-organisms under TSCA and FIFRA.
- The EPA considers micro-organisms to be chemical substances subject to TSCA, an interpretation that could be legally challenged.

- There is a lack of information necessary to assess the risks associated with some planned introductions, most particularly in microbial ecology.
- The FDA has given little indication of its intentions concerning the development of regulations and procedures for evaluating the food safety of genetically modified plants and animals.
- Field-testing requirements have been criticized as too burdensome, especially for the academic community, and disproportionate to the small risk associated with these organisms, particularly transgenic crops with no nearby wild, weedy relatives.

The problems associated with developing regulations add to the costs borne by fins, and are especially burdensome for small biotechnology-based firms. Despite these difficulties, there is anecdotal evidence that some European firms have decided to open research and production facilities in Japan and the United States, in part, because of the more favorable regulatory climate.

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