Part III

Environmental Quality

Chapter 7

Environmental Issues: Institutions and Their Regulatory Roles

Photo credit Jamie Notter, OTA Staff

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INTRODUCTION

Preface

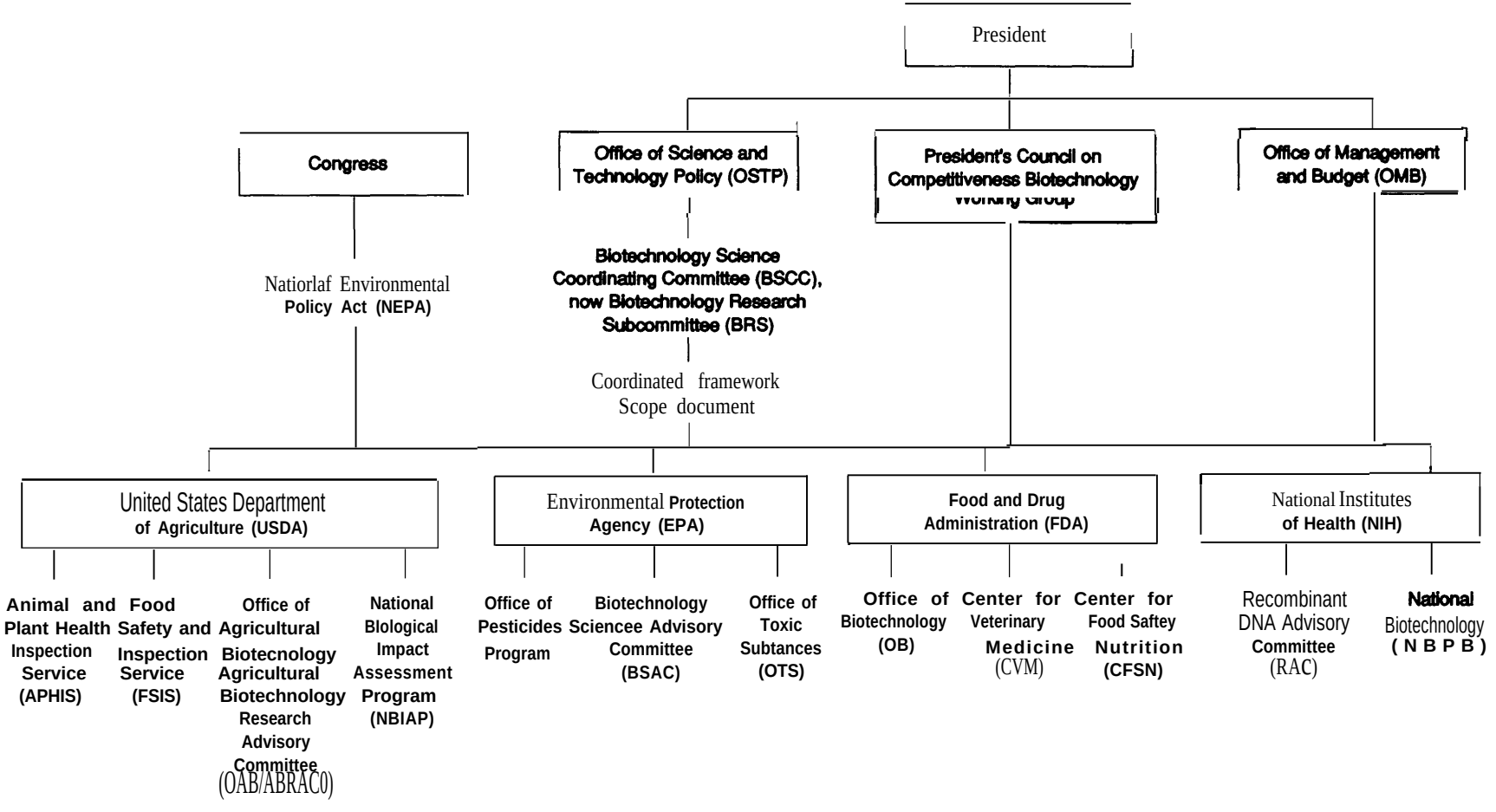
Many biotechnology products, especially agricultural products, are intended for use in the environment. Examples are transgenic cows in feed lots, insect resistant crop plants in fields, microbial pesticides applied to cropland, and transgenic fish reared in outdoor aquiculture ponds. **Virtually anything introduced into the environment will have an impact,** whether it be concrete slabs used to construct a highway or a chemical pesticide used to control insects on cotton. The task of environmental protection legislation is to determine what types of products to be used or activities to be carried out in the environment would have adverse effects significant enough to warrant regulation. Ideally, Federal environmental protection laws and regulations would be based on complete information on all the environmental risks associated with products and activities as well as their benefits, so that decisionmakers could weigh one against the other objectively. In reality, complete information is rarely available, particularly for new products: thus, the balancing of risks and benefits is difficult and open to bias.

Biotechnology has appeared on the scene during a time of intense environmental and political scrutiny of new technologies. Oversight of biotechnology thus is significantly different from that of emerging technologies in the past and may foreshadow the reception of new technologies in the future. For example, planned introductions of recombinant DNA-modified organisms will occur in a regulatory climate vastly different from that which existed as dramatically new crop varieties were introduced in the past. Key policy documents to be discussed later (e. g., 1986 Coordinated Framework statement of Federal agencies' philosophy on biotechnology, and the Council on Competitiveness' report on Administrative philosophy) stress the need to regulate biotechnology only on the basis of the risk of its products. not simply because it entails the new process of recombinant DNA technology. Tension exists, however, between this philosophy and operational development of oversight treatment. This tension often seems to be triggered by the technology itself, and has led to controversy over regulation of field tests. Special regulatory attention to a new agricultural technology could have implications for environmental safety and for the successful adoption of that technology and thus for U.S. economic competitiveness.

Most agricultural biotechnology products intended for use in the environment are or will be regulated according to legislation enacted prior to the advent of modern biotechnology, including laws intended to protect agriculture and the environment from chemical contamination, plant pests, pathogens, and so on. Despite the unusual level of scrutiny focused on biotechnology, its oversight is meant to arise naturally from the responsibilities traditionally held by different offices or services within the Environmental Protection Agency (EPA) and the U.S. Department of Agriculture (USDA). Given the panoply of laws applicable to biotechnology. this chapter provides a road map through the confusing territory of oversight responsibilities.

Figure 7-1 is the reference point used throughout the chapter. It gives a capsule overview of roles and relationships of policymaking bodies, key documents relating to designation of authority over environmental uses of biotechnology products, agencies with regulatory authority, the specific services or offices involved in regulation of biotechnology, and statutes that pertain to the use of biotechnology products in the environment. Following an introductory description of why and how regulation and oversight for biotechnology products has evolved, this chapter describes USDA's and EPA's role in these activities. The complementary roles of the Food and Drug Administration (FDA), National Institutes of Health (NIH), and State and local governments, as well as the international regulatory climate also are covered. Finally, policy issues are discussed here, among them issues of jurisdiction and coordination among agencies, scope of coverage, potential impacts of regulation on research and on agribusiness, and public participation. (See also OTA, 1988 New *Developments in Biotechnologg 3, Field Testing Engineered Organisms." Genetic and Ecologic Issues (102)* and 1991 *Biotechnology in a Global Econony) (103).* This chapter lays the foundation for ensuing discussion (ch. 8) of risk assessment and risk management issues related to impending large scale, commercial uses of agricultural biotechnology and biocontrol products.

Figure 7-l—Jurisdiction and Coordination of Environmental Policy for Biotechnology-Derived Agricultural Products[a]



USDA statutes
- Plant Pest Act
- Plant Quarantine Act
- Noxious Weed Act
- Vims-Semm-Toxin Act
- Federal Meat Inspection Act
- Poultry products Inspection Act

EPA statutes
- Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)
- Toxic Substances Control Act (TSCA)

FDA statute
- Food, Drug, and Cosmetic Act (FDCA)

[a]OSTP, Council on Competitiveness, and OMB do not have direct oversight of the Federal agencies; the connections shown are those of influence through directives, key policy documents, or review.

SOURCE: Office of Technology Assessment, 1992.

Agriculture, Field Trials, and Deliberate Release of Genetically Engineered Organisms

Progress in agriculture traditionally has depended on selection of the best of new varieties based on field testing of cultivars. The seed industry views cultivar field testing as an essential part of cultivar development programs. The main purpose of field testing is

> . . . to determine the regional environmental adaptability and market fit of the new cultivars or hybrids to know whether the items to be tested have the required disease resistance for the areas, whether they meet the needs of the industry as far as type or quality is concerned. and whether they will perform well under the environment of the region (98).

Field tests also can provide evidence that the application of currently available scientific principles and information can ensure safe commercialization of new products.

Genetically modified organisms, like any other organisms, must be field tested in the environment in which they would be cultivated. For example, whether the engineered trait is expressed effectively must be evaluated in condition-s representative of those the cultivated crop will encounter. Characteristics intended to confer drought tolerance to a plant. for instance, must appear and function effectively within the plant as it copes with representative drought-stressed environments. Greenhouse experiments, conducted in facilities designed to meet containment specifications, can provide only an initial screening; the field trial is an essential evaluative step.

Brief Overview of Concerns

As necessary and rational as field testing is, concerns have arisen over any release of genetically engineered organisms. Living creatures reproduce themselves; they may increase in numbers; and they may even exchange genes with other wild organisms. Many are worried in particular about the uncertain possible impacts that an organism with a new trait might have on other species in the local habitat.

Evolution of Regulation and Oversight

These concerns and uncertainties have stimulated efforts to articulate regulatory oversight; the spelling out of jurisdiction in the Coordinated Framework for the Regulation of Biotechnology [51 Federal Register (FR 2302-23393] (77) was a significant step in the organization of regulatory oversight. This fundamental document outlining the roles, responsibilities, and policies of the Federal agencies involved in biotechnology first actually appeared in the Federal Register in 1984, when the Domestic Policy Council of the White House announced the ''Coordinated Framework for the Regulation of Biotechnology" (49 FR 50856-50907). The framework set forth certain premises, which have guided subsequent policy:

- previously existing knowledge was regarded as pertinent,
- existing laws were for the most part regarded as adequate for biotechnology oversight, and
- different biotechnology products were regarded as falling under the mandate of different agencies (table 7-1).

Other key points of the framework include the following:

- the products of biotechnology, not the process itself, would be regulated; and
- biotechnologically altered organisms are not fundamentally different from nonmodified organisms (although the introduction to the framework recognized that certain microbial products would require the establishment of additional regulatory requirements).

The framework included a compilation of existing laws, regulations, and guidelines that are potentially applicable to biotechnology, policy statements from the regulatory agencies on how they intend to apply their existing regulatory authority to biotechnology, and proposed criteria for determining what should be subject to oversight.

In a basic sense, agencies draw their authority to evaluate ramifications of the new technology based on their own mandates, and from the National Environmental Policy Act (NEPA). (See box 7-A.) Since the framework **was** introduced, agencies have accumulated experience with deliberate releases; based on this experience, they are continuing to refine their regulatory roles. As of September 1991, USDA-APHIS (Animal and Plant Health Inspection Service), which oversees most plant-related work and animal biologics, has issued some 181 permits for field testing of genetically engineered plants or microorganisms (not including veterinary biologic). At least half of these have been issued since the beginning of 1990. (See table 7-2.)

USDA permits issued for transgenic plants with pesticidal properties have been informally reviewed by the

Table 7-l—Jurisdiction for Review of Planned Introductions in Research

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

[a]Rewiew and approval of research protocols conducted by NIH, S&E, or NSF.
[b]EPA jurisdiction for research on a plot greater than 10 acres.
[c]APHIS issues permits for the importation and domestic shipment of certain plants and animals, plant pests and animal pathogens, and for the shipment or release in the environment of regulated articles.
'EPA reviews federally funded environmental research only when it is for commercial purposes,
'Designates lead agency where jurisdictions may overlap.

KEY:NIH - National institutes of Health; S&E = U.S. Department of Agriculture Science and Education; APHIS = Animal and Plant Health Inspection Service; EPA = Environmental Protection Agency; NSF = National **Science Foundation**

SOURCE: 51 Fed. Reg. 23305 (Office of Technology Assessment, 1988).

EPA Office of Pesticide Programs under an interagency agreement. EPA has reviewed a total of 94 notices for field tests of microorganisms since the framework was published in 1986, 74 of which were for microbial pesticides. Under an interagency agreement, EPA has in addition provided comments on approximately 100 permits submitted to USDA-APHIS for transgenic plants with pesticidal properties. (See table 7-3.)

These field tests provide the foundation of information and regulatory experience for decisions regarding full-scale agricultural use of transgenic organisms. This report comes at a critical point in the evolution of agricultural biotechnology, as it moves from the laboratory toward large-scale commercialization and use.

USDA

Authority for Plants

Statutory Authority

The Animal and Plant Health Inspection Service, APHIS, was established in 1972 as a regulatory agency within USDA with responsibilities for protection of the environment. APHIS unites the programs within USDA designed to protect American agriculture from destructive pests and diseases. APHIS' activities include the development of exclusion procedures to keep pests and diseases out of the United States; and monitoring, de-

Box 117-A–The National Evironmental Policy Act (NEPA)

The National Environmental Policy Act (NEPA) is the sole Federal law that is broadly applicable to all agencies and departments involved in the research or regulation of biotechnology products intended for use in the environment. Enacted in 1970, NEPA is a reflection of increasing concern about environmental quality and calls for a "balance between population and resource use which will permit high standards of living and a wide sharing of life's amenities" [section 101(b)(5)]. NEPA requires that any agency decision on a major Federal action significantly affecting the quality of the human environment include consideration of the environmental impact of the proposed action and alternatives to the proposed action. NEPA does not, strictly speaking, restrict or prohibit any activity that may adversely impact the environment but rather outlines procedural requirements by which Federal agencies must become aware of and consider the environmental consequences before making a decision on a proposal.

The Council on Environmental Quality (CEQ) is responsible for the implementation of NEPA (CEQ Final Regulations for Implementing NEPA, 43 Fed Reg 59978, 1978), but the specific method used for compliance by individual agencies is broadly discretionary. Because EPA's mission is to consider and protect the environment through its regulatory activities, most EPA actions are considered the functional equivalent of NEPA compliance. [Warren County v. North Carolina, 528 f. Supp. 276,286 (eDNC 1981)]. Most other Federal agencies have issued their own regulations to implement NEPA.

Although agencies are given broad discretion in how they evaluate and balance environmental impacts in making decisions, NEPA does open agency actions to public and judicial scrutiny. The establishment and protection of certain environmental values by NEPA gives public interest groups and private individuals standing to bring suit to ensure compliance even though they are not directly affected by an agency action. In short, NEPA has had two principal impacts on the Federal decisionmaking process: ensuring evaluation of environmental issues by Federal agencies and increasing public participation.

SOURCE: Office of Technology Assessment, 1992.

tection, eradication, and control programs to control the movement of pests and the spread of disease. APHIS operates under a myriad of legislative authorities, some dating back to 1884.

Under the Coordinated Framework, APHIS is designated the lead agency responsible for the regulation of plant and animal biotechnology products. The assumption underlying this jurisdictional determination was that

> Agriculture and forestry products developed by biotechnology will not differ fundamentally from conventional products and that the existing regulatory framework is adequate to regulate biotechnology (51 Fed. Reg. 3123, p. 23302).

The primary regulatory authorities available to USDA that are most applicable to biotechnology (and the environment) are the Federal Plant Pest Act, the Plant Quarantine Act, the Noxious Weed Act. the Virus-Serum-Toxin Act. the Organic Act, the Federal Seed Act, the Federal Meat Inspection Act. and the Poultry Products Inspection Act. Of these statutes, two are used as the basis for the regulation of the environmental release of genetically modified organisms: the Federal Plant Pest Act, and the Plant Quarantine Act (7 CFR 340). Like the Noxious Weed[2] Act, these two acts are exclusionary statutes intended to prevent the entry into or dissemination within the United States of living organisms considered dangerous to American agriculture. These three legislative authorities traditionally have been used as the basis for inspection, quarantine, and pest eradication programs of the Division of Plant Protection and Quarantine. With the exception of the Noxious Weed Act, they now also are used by the Division of Biotechnology, Biol-

[1] A Plant Pest is defined as any living stage of: any insects, mites, nematodes, slugs, snails, protozoa, or other invertebrate animals, bacteria, fungi. other parasitic plants or reproductive parts thereof, viruses or any organisms similar to or allied with any of the foregoing, or any infectious substances. which can directly or indirectly injure or cause disease or damage in any plants or parts thereof, or any processed, manufactured, or other products of plants.

[2] "Noxious weed" is defined as any living stage (including but not limited to, seeds and reproductive parts) of any parasitic or other plant of a kind, or subdivision of a kind. which is of foreign origin, is new to or not widely prevalent in the United States, and can directly or indirectly injure crops, other useful plants. 1 ivestock, or poultry or other interests of agriculture, including irrigation. or navigation or the fish or wildlife resources of the United States or the public health.

Table 7-2—Federally Approved Biotechnology Agricultural Research Field Test Applications, USDA (through September 24, 1991)

	Private	Public
1987	9	0
1988	17	1
1989	31	7
1990	42	15
1991	47	12
Total	146'	35[b]

[a]41 tomato; 23 cotton; 17 tobacco; 14 corn; 13 potato; 13 soybean; 10 cantaloupe/squash; 6 alfalfa; 4 clavibacter/corn; 1 clavibacter/rice; 1 TMV/tobacco; 1 rapeseed; 1 sunflower; 1 chrysanthemum.
b 11 potato; *9 tobacco; 3 cucumber; 3* rice: 2 pseudomonas; 2 walnuts; 2 xanthomonas; 1 tomato; 1 poplar; 1 alfalfa.

SOURCE: APHIS BBEP Biotechnology Permits Unit, *Issued Permitss List,* Sept. **24, 1991.**

Table 7-3—Federally Approved Biotechnology Agricultural Research Field Test[a] Applications, EPA (through April, 1991)

	Total	Repeats
Office of Toxic Substances	20[b]	7
office of Pesticide Programs , ...	74"	34

'Field tests of microorganisms reviewed by EPA since the publcation of the 1986 Coordinated Framework.
b 10 Rhizobium, 8 *Bradyrhizobium, 2 Pseudomonas.*
[c] Includes a variety of bacteria, fungi and viruses, both nonindigenous and genetically modified

SOURCE: David Giamporcaro, Environmental Protection Agency, **personal communicatlon,** Oct. 18, 1991.

ogics. and Environmental Protection [established in October, 1988] to regulate the movement and environmental release of genetically engineered organisms.

The Noxious Weed Act has not been used to regulate genetically modified organisms. The applicability of the Noxious Weed Act to genetically modified organism is limited by the requirement that the plant be of "foreign origin' and the requirement that an organism be placed on the noxious weed list before it can be regulated.

The Federal Plant Pest Act. the Plant Quarantine Act, and the regulations issued to implement them are not intended to present unreasonable barriers to commerce. For example, inspection at ports of entry should be expedient so as not to retard shipment of agricultural products, particularly fresh produce whose value could be diminished or destroyed if the product to be inspected is held at the inspection station too long.

Agency Interpretation/Regulatory Policy

USDA's overall philosophy regarding biotechnology products is articulated in the National Academy of Sciences 1987 publication, *Introduction of Recombinant DNA-Engineered Organisms into the Environment: Key Issues (72);* and in the National Research Council 1989 publication, *Field Testing Genetically Modified Organisms." Frumework for Decisionmaking (73).* Consistent with U.S. Federal policy, USDA-APHIS bases its regulatory policy on certain key premises:

1. the products of biotechnology do not differ fundamentally from either unmodified organisms or conventional products,
2. the product should be regulated rather than the process by which it came to be,
3. end-use of the products and review conducted on a case-by-case basis should form the basis for regulation, and
4. sufficient authority for regulating the products of biotechnology is provided by existing laws.

Along with these premises is a commitment to the safe development of the new technology, and to a balanced, scientifically based and risk-based regulatory framework that protects agriculture as well as facilitates technology transfer (55).

The USDA regulations (7 CFR 340), that pertain to genetically engineered organisms are applicable to a broad range of organisms, including

> Any organism which has been altered or produced through genetic engineering. if the donor organism. recipient organism. or vector or vector agent belongs to **any genra** or taxa designated ...and meets the definition of plant pest. or is unclassified. . or any other organism or product altered or produced through genetic engineering which the Deputy Administrator deterrmines is a plant pest or has reason to believe is a plant pest.

Excluded are microorganisms that are not plant pests and produced by the addition of well characterized or noncoding regulatory regions.

Any person may petition to amend the list of organisms subject to regulation under 7 CFR 340. Such a petition must include the factutal grounds as to why the organism is not a plant pest and include scientific literature in support of this conclusion. Petitions should not include Confidential Business Information (CBI). The petition also should include any information known to the petitioner that would be unfavorable to the petition. APHIS then publishes a notice in the Federal Register for comment. A must respond to the petitioner within 180 days either by approving or denying the petition in whole or in part. Once an organism or class of organisms is delisted, it may move unhindered in commmerce with no

reporting requirements or monitoring required by the Federal Government. If, however, new information becomes available that leads the Secretary of Agriculture to conclude that a delisted organism does, in fact, pose a plant pest risk, an interim rule can be issued, effectively bringing that organism back under regulatory authority of the Federal Plant Pest Act.

It is unclear whether industry will try to petition to exempt broad classes of organisms or single. well-defined organisms. Initially some industry executives thought that they might like to delist broad classes; but some have since reevaluated this approach since the organism-by-organism delisting procedure is a market barrier to competitor-s. Broad class delisting might make it easier for some competitors to enter commerce. Furthermore, APHIS approvals provide a ''stamp of approval useful in acceptance by the public and by State governments. In addition, environmentalist groups might pose a legal challenge to stop a broad class delisting under the Federal Plant Pest Act.

Implementation

Under the APHIS regulations. anyone wishing to move or introduce an organism fitting the definition of a regulated article must receive a permit. The four kinds of permits for which applications are made are as follows:

1. a permit for release into the environment (application submitted 120 days in advance).
2. a single 1 -year permit for interstate movement of multiple regulated articles between contained facilities,
3. a single 1 -year permit for importation into the country of multiple regulated articles into contained facilities, and
4. a courtesy permit to expedite movement of organisms not subject to regulation under 7 CFR 340 (application submitted 60 days in advance) (55)

Permit applications require submission of information on the biology of the donor and recipient organisms. the molecular biology of the introduced gene(s), and plans for containment during the trial and post-trial clean-up. Information is used by APHIS to prepare an Environmental Assessment (EA) and to determine whether and under what conditions to allow the release.

The application process for Environmental Release permits is clearly delineated by USDA-APHIS, with process and pemmitting requirements contained in *Plant Pests,. Introduction of Genetically Engineered Organisms of Products, Final Rule (52* FR 22892 (1987). In addition, Biotechnology, Biologics and Environmental Protection (BBEP). USDA-APHIS. has developed a User's *Guide for Introducing Genetically Engineered Plants and Microorganisms to* provide assistance to those submitting applications for a permit under 7 CFR 340. The folloowing steps must take place:

1. completing an application for permit under 7 CFR 340, Genetically Engineered Organisms or Products. APHIS Form 2000:
2. assigning an accession number;
3. preliminary pest and environmental assessment;
4. state review/input;
5. site inspection;
6. issuance or denial:
7. appeal. if permit request has been denied: and
8. inspection of site at initiation of experinment.

From day one, scientific review proceeds. The State authorities are forwarded material by day 30 and respond by day 60. At or before day 120. the biotechnology permit is issued or denied (104).

Scientific review is based on the dutti provided in response to the APHIS permit application data requirements. Fourteen such requirements (box 7-B) include a detailed description of' the organism. the location of' the field test, and containment protocols.

Provision is made for companies to protect Confidential Business information: they can submit both a full proposal and one for public abvailability that has CBI deleted. The APHIS Policy Statement on the Protection of Privileged or Confidential Business Information (50 FR 30561 -63) delineates data or information, such as trade secrets and confidential commercial or financial information, that can be protected from disclosure under section (b)(4) of the Freedom of Information Act (5 U.S.C.552 (b)(4). This can include production data, formulas and processes, and quality control tests and data, along with research methodology and data generated in the development of the production process. To qualify as CBI, this information must be: 1) commercially valuable, 2) used in one's business. and 3) maintained in secrecy. Furthermore, APHIS must be persuaded on review of information on competition that significant commercial harm would result from disclosure. BBEP explains this option to applicants, while encouraging them to be selective as to what truly calls for CBI designation (63). APHIS requires claims of Confidentiality to be substantiated at the time of submission.

An Environmental Assessment (EA) is prepared by APHIS in accordance with the provisions of the National

Box 7-8—The 14 Types of Information Requested by APHIS in a Permit Application for Genetically Engineered Plants. 7 CFR 340

1. Information on responsible person and type of permit requested, such as movement or release.
2. All names (scientific, common, and trade) and designations necessary to identify the donor, recipient, vector, or vector agent constituents of the transgenic plant.
3. Information on the persons who developed the transgenic plant.
4. Movement of the plant.
5. The anticipated or actual expression of the altered genetic material in the plant and how the expression differs from the nonmodified plant in respect to characteristics such as morphology, physiology, number of copies of the gene, products, etc.
6. The molecular biology of the system used to produce the transgenic plant—donor, recipient, vector, or vector agent.
7. Country and locality where the donor, recipient, vector, or vector agent were collected, developed, and produced.
8. The purpose of the experiment and the experimental design.
9. The quantity, schedule, and number of introductions.
10. The processes, procedures, and safeguards used to prevent contamination, release, and dissemination in the production of the transgenic plant.
11. The intermediate and intended destinations of the product; the field trial site.
12. Safeguards to prevent dissemination at each site.
13. Biological material accompanying the plant, such as inoculum or soil.
14. Method of disposal of plant material after termination of the experiment, such as autoclaving or discing.

SOURCE: S. McCammon and T. Medley, "Certification for the Planned Introduction of Transgenic Plants in the Environment," The Molecular and Cellular Biologics **of the Potato, Michael Vayda and William Park (eds.), Wallingford, U.K. (CAB. International), 1990.**

Environmental Policy Act (NEPA) of 1969 (42 U.S.C. *4332 (1970)).* Among the components of the EA are procedural and physical precautions against risk, environmental consequences, and background biology. The development of the EA is a process intended to assure public safety.

A permit to move or introduce an organism is issued if there has been a Finding of No Significant Impact (FONSI) from **such** action, and a full-scale environmental impact statement is not required. Notice of the action and the availability of the EA and FONSI is published in the Federal Register. Special additional conditions may be added to the permit that require monitoring and data collection to ensure containment. Such test data can also contribute to the information base from which future assessments can draw. The issuance of the permit constitutes certification by APHIS that no significant risk exists to the environment or to agricultural crops from the action. Recommendations for improving APHIS assessments have included making justifications for assessment conclusions more explicit, including more opportunities for gathering data on gene flow and weediness during field tests, and encouraging more timely and complete monitoring reports (110).

Application to Plants

Small-Scale **Research**

Theory— Small-scale releases in the form of field trials are experiments. Even if companies conduct them, and although field trials are the first step toward full-scale agricultural use in the environment, they are nonetheless still research rather than commercialization activity. This activity raises some concerns, but these are, to some extent, alleviated by the small scale of field trials. The first release into the environment of an organism with a novel trait can arouse concerns simply because something relatively new is happening. The regulatory policies and procedures described above represent an attempt to address such concerns. However, given the low numbers of organisms involved, the small-scale field trial is quite a carefully controlled situation. In fact, some argue that USDA requirements for most field tests exact financial, administrative, and time costs that are disproportionate, relative to any risks presented. USDA-APHIS views the small-scale field trial as playing an educational role; data compiled from these tests will provide the underpinnings for sound and rational assessment of large-scale releases in the future. As noted earlier, each permit issued for a

small-scale field trial requires the submission of subsequent data.

One of the players in the oversight of field trials is the Office of Agricultural Biotechnology (OAB), which was established in 1987 under the Deputy Secretary of Agriculture and transferred to the Assistant Secretary for Science and Education in 1989. OAB is designed to ensure coordination of biotechnology activities within USDA. Within Science and Education, it is separate in many ways from APHIS. It provides staff support for the USDA Committee on Biotechnology in Agriculture (CBA) comprised of administrators of agencies: conducts outreach programs; and provides leadership in the development of guidelines and the dissemination of information about them. For example, a handbook, *Agricultural Biotechnology: Introduction to Field Testing was* produced in large part to help the "users" of the regulatory system in applications for field trials (11).

In line with its particular responsibility to provide guidance to researchers. the OAB staffs the Agricultural Biotechnology Research Advisory Committee (ABRAC) composed primarily of academic and industry scientists. Industry field tests. of course, are handled through APHIS. ABRAC was established in 1988 to provide advice for the Secretary of Agriculture, through the Assistant Secretary for Science and Education, on biosafety issues in the use of agricultural biotechnology and it has assisted in the development of biosafety guidelines, as well as case-by-case review of the minority of USDA-funded research projects that do not fall under other agency authorities. Its review process is modeled after that of the NIH Recombinant DNA Advisory Committee (RAC), with meetings open to the public and announced in the *Federal Register.* Two working groups established early in 1991 focus on the area of biotechnology risk assessment research as set out in the Farm Bill of 1990. These groups help set priorities and are developing a classification system and confinement protocols, integrating public comments received on the proposed guidelines for risk assessment research (70). *The Proposed USDA Guidelines for Research Involving the* ***Planned Introduction*** *Into the Environment of Organisms With Deliberately Modified Hereditary Traits was* published in the February 1, 199 Iissue of the Federal Register, part 3, with public comments due on April 2; a principal intent was to assist academic scientists and their institutional biosafety committees in the design of safe field trials.

USDA's Cooperative State Research Service established a new program in response to recommendations in a 1985 report of the National Association of State Universities and Land Grant Colleges' Committee on Biotechnology. NBIAP (National Biological Impact Assessment Program) has a mandate to facilitate safe field testing of genetically modified organisms and. thus, safe development of agricultural biotechnology. A principal charge to the program is to facilitate the appropriate application of knowledge derived from conventional field testing in the past to biotechnology field tests today. The program supports three areas of activity related to this function: information networks: facilitation of the development of biological monitoring techniques: and supper-t for biosafety research.

An information network to support the needs of public- and priate-sector researchers is being developed by NBIAP in conjunction with a number of institutions. The information network is available, over telephone lines, through an "800" number: through interlinked mainframe computers (BITNET): on floppy disks: and in printed format. An electronic bulletin board gives up-to-date information on biosafety related research activity and serves as the gateway for 14 databases. Individuals can use the network to communicate with other scientists as well. Databases include, among others: bibliographic and other listings; current literature; U.S. patents on genetically engineered species: current text of all Federal laws, regulations, and guidelines pertaining to biotechnology and biosafety; Institutional Biosafety Committee listings: and all approved applications for federally approved field test permits. licenses. and scientific reviews.

A knowledge base has been designed to help researchers identify the responsible Federal agencies to which an application should be directed and to prepare applications for permits, licenses, or scientific reviews. An ''intelligent form generator" will actually help the investigator prepare first drafts of applications. By dissembling information from existing knowledge. the intelligent form generator provides users with access to previously written standard text, technical descriptions, test-site information, and other resources from databases. Combining information with use of extensive menus leads to a technically specific application. The first, current version of the intelligent form generator is expected to be expanded from coverage of 8 groups of organisms to 79. The intent of the intelligent form generator is to lift some of the regulatory burden from the researcher. "Hyrpertext" information on biosafety is also provided.

A second function of the NBIAP is to facilitate biological monitoring of genetically modified organisms de-

literately released in the environment. NBIAP is surveying field studies that have been conducted; the information gathered should help guide future regulatory decisions. NBIAP also supports biosafety research on genetically modified organisms to improve understanding of their dispersal in the real world, and their impact on human health and the environment, to improve biosafety methods and to develop **useful prediction** models (51. 52).

Experience Base—Between July 16, 1987 and February 27, 1991, 102 permits were granted by APHIS for field testing of genetically engineered plants and microorganisms, along with 843 permits for importation or interstate movement of organisms regulated under 7 CFR 340. Twenty-one companies were issued permits by this date, including: Agricetus, Agrigenetics, Amoco Technology Co., Biosource Genetics, Biotechnica, Calgene, Campbell Institute for R&D, Canners Seeds, Ciba-Geigy, Crop Genetics International, DeKalb, DNA Plant Technology, DuPont, Frito-Lay, Monsanto, Northrup King, Pioneer, Rogers NK Seed, Rohm & Haas, Sandoz Crop Protection Corp., and UpJohn. Twelve research institutions. two of them USDA institutes, had received permits; they are: Auburn University; Iowa State University; Louisiana State University: New York State Agricultural Experiment Station (Geneva); North Carolina State University; Pennsylvania State; USDA-ARS (Agricultural Research Service), Albany, California: USDA-ARS, Fresno, California; University of California at Davis; University of Kentucky; University of Wisconsin; and Washington State University. Field trials were approved, with the agreement of the host State, for 33 States and Puerto Rico; the 102 permits granted as of February 27, 1991, gave rise to some 140 field test sites. By April 1991, 115 permits had been granted (78). By September 1991, 181 permits for field tests had been granted.

Figure 7-2 lists the new crop plants entering field trials between 1987 and early 1991, along with the novel characteristics, or genes expressed.

About half of the first generation of field tests, especially the 2 I in 1988, were for herbicide tolerance in tomato and tobacco. while the rest were almost entirely for disease and insect resistance in these two crops. Many more crops showed up in the 1989 applications, including potato, soybean. alfalfa, cotton, poplar, and cucumber: new sorts of characteristics included slowed fruit ripening and improved nutritional qualities. Modified pathogenic bacteria entered the applications in 1990, along with an increased range of cultivars and modifications, particularly in two of the country's most economically important crops, rice and corn (60).

Figure 7-2—Field Trials of New Crop Plants, 1987-91

1987-88	1989	1990	1991
Tobacco	Alfalfa	cantaloupe	Rapeseed
Tomato	Cotton	Corn	Sunflower
	Cucumber	Rice	
	Poplar	Squash	
	Potato	Walnut	
	soybean		

Genes expressed
- Herbicide tolerance
- Insect tolerance
- Virus tolerance
- Fungal tolerance
- Slowed fruit ripening
- Heavy metal sequestration
- Increased lysine production
- Antibiotic resistance

SOURCE: S. McCammon, U.S. Department of Agriculture, internal memo, 1991.

Biotechnica Agriculture. Inc., then a subsidiary of Biotechnica International, Inc., received in May of 1990 the first USDA approval to field test genetically engineered corn plants. The tests, to be conducted at the company's corn breeding station in Iowa. will analyze growth under field conditions and collect environmental data for future use. Biotechnica has coordinated other field tests, including one on tobacco with a gene coding for high levels of lysine expression (9). The company has applied for permission to conduct multiple field tests of corn engineered for improved nutritional quality; the gene transferred is one of several intended to improve corn for feed (4).

Northrup King has begun a 3-year field test of alfalfa plants genetically engineered to be compatible with a new herbicide claimed to be highly biodegradable and environmentally safe. With Monsanto. Northrup King has planted genetically engineered cotton in Hawaii to assess its resistance to various caterpillars (71).

An even longer term project was initiated by USDA-ARS researchers at the University of California-Davis. They inserted two marker genes into walnut tree embryos and will need to wait 5 years for the trees to reach maturity to assess expression brought about by the genes (76).

The first field trial of genetically engineered rice was approved at Louisiana State University. The test, taking place since June 1990 in a 110 *x* 63 foot plot in Baton Rouge, involves a marker gene and a transposon gene (that regulates gene movement) from corn (5).

USDA-ARS scientists are field testing potatoes with marker genes in Idaho, to see if the genetically engineered potatoes match the quality of conventionally bred products, under a permit issued in 1989. Some 1,000 potatoes, originally produced in a greenhouse from genetically engineered microtubers, are planted on a half-acre plot at the University of Idaho's research and extension center in Aberdeen (29).

Calgene successfully harvested field plots of its FLAVR SAVR tomato in the fall of 1990. Its permit for tomato plants engineered with an antisense gene for the pectalytic enzyme, or cytokinin pathway, was issued in May of 1990 (76). A complete listing of permits issued, applicants, organisms, and genes engineered along with date of issuance and location (State) is available in "Environmental Release Permits," printed by BBEP, APHIS, September 24, 1991.

Large-Scale Release

Theory-The USDA plans to use data from small-scale field trials to ensure the safety of large-scale releases. A variety of analyses and conferences are addressing the issue of large or commercial-scale release. For example, APHIS has organized the following three workshops to identify issues related to the large-scale use of genetically engineered crops in the environment:

1. Workshop On Safeguards for Planned Introductions of Transgenic Oilseed Crucifers, October 1990. Ithaca. New York;
2. Workshop On Safeguards for Planned Introductions of Transgenic Crops: Maize and Wheat. December 1990, Keystone, Colorado; and
3. Workshop on Biosafety Issues of Field Tests with Transgenic Potatoes, August 1991. St. Andrew's, Scotland.

A fourth workshop is planned for 1992 on biosafety issues for transgenic rice plants.

Experience ***Base—No*** commercial releases have yet occurred, nor have applications been made, although preliminary discussions have been held between company representatives and APHIS officials.

Authority for Veterinary Biologics

Statutory Authority

Under the authority of the Virus-Serum-Toxin Act (VSTA). as amended, USDA-APHIS regulates three cat. egories of veterinay bioiogical products derived through biotechnology. The establishment of these three categories was announced by APHIS in theJune 1986Coordinated Framework policy statement (51 FR 23339, June 26, [986). Based on that framework's premises that recombinant DNA derived products are not significantly different from more conventionally derived products and can be handled by a network of existing statutes, the three new categories were subsumed under VSTA's treatment of other biologics. APHIS supervises all experimental uses of veterinary biological products outside of containment conditions, under the provisions of the VSTA as amended by the Food Security Act of 1985. The implementing regulations (9 CFR 103.3) require approval from the Director of BBEP for shipment and describe required information for evaluating unlicensed biological products prior to granting such approval. APHIS also licenses biological products for unrestricted shipment in or from the United States under the VSTA, as amended.

Agency Interpretation and Regulatory Policy

The agency's policy is to balance control with flexibility in its review and approval procedures, and to adapt as necessary to new information. Products and organisms are categorized to provide practicable. reasonable procedures for review and approval: review takes place on a case-by-case basis.

Category 1 is comprised of inactivated (nonviable or killed) products prepared from recombinant DNA-derived vaccines. viruses. bacterins, bacterin-toxoids. viral subunits. or bacterial subunits. Monoclinal antibodies used prophylatically, therapeuticall y, or as diagnostics are also included. These products are viewed as presenting no risks to the environment or to safety.

Category 11 consists of products containing live microorganisms that have had one or more genes added (for expression of unique marker antigens or production of biochemical by-products) or deleted (i.e.. genes for virulence, oncogenicity, enzyme activity, or other biochemical functions). Such changes in genetic information must not lead to increased virulence, pathogenicity, survival advantages, or undesirable new or increased abilities to invade or survive in the animal host; and they must not compromise the safety characteristics of the organisms.

Under category III fall products that uselive vectors to carry recombinant-derivecl foreign genes coding for immunizing antigens or other immune stimulants. Live vectors may carry multiple such genes and successfully can infect and immunize the host. These organisms must be completely characterized and compared with the parent virus, and environmental and human or animal safety

concerns must be addressed in an Environmental Assessment or Environmental Impact Statement.

Implementation

As **with all other** veterinary biologics, recombinant DNA products must be shown to be pure, safe, potent, and efficacious, and not worthless, contaminated, dangerous, or harmful, with assurance of lack of negative effects on the environment and human and animal health prior to licensing. Additional information (e.g., demonstration of nonpathogenicity and nonreversion to virulence, or ability of the organism to maintain itself in a livestock population) may be requested. For recombinant-derived products the manufacturer also must report the cloned nucleotide sequence coding for the product.

For category 11 and 111 organisms, authorization procedures for shipping and guidelines for review of applications for field trials are done on a case-by-case basis. The categories of physical containment involved in movement of experimental products to the field are the following:

1. stringent containment conditions (level 4, isolation),
2. controlled environment (level 3).
3. Quarantined field conditions (level 2), and
4. Restricted field tests (level 1).

Unrestricted geographical distribution may occur only after issuance of a license.

In considering approval of these movements. APHIS requires four kinds of scientific information: human safety, ecological concerns, characterization of the vaccine virus, and animal safety. In addition, appropriate data would include: survival and reproduction of the engineered microorganism; interactions with other organisms; effects on the ecosystem if applicable; and scale, scope, and frequency of plasmid introduction. In short, an ecological risk assessment would include the biology of the phenotypic trait and of the parent organism, as well as characterization of the environment into which the introduction will be made; the product organism's host range and potential effect on other species might also be included.

The review cycle includes review and approval by an Institutional BioSafety Committee (IBC). State animal health regulatory officials and, if appropriate, public health officials. For trials with a small number of animals in quarantined conditions, APHIS must prepare a Safety Factor Evaluation assessing all parameters of the trial (*19).*

Application to Veterinary Biologics

Small-Scale Research

Theory—The theory underlying the approach to release of veterinary biologics is consistent with the National Research Council report (73) and the Scope Principles (i.e., that products of biotechnology are not inherently more dangerous than products of other techniques; and that existing regulations can cover them).

Experience Base—Some 46 licenses that have already been granted for small-scale release of veterinary biologics went through the full testing and now qualify for ''large-scale' release. Other projects are still in the research stage (95).

One of the best known small-scale field test cases is that of the genetically engineered rabies vaccine developed by the Wistar Institute, with its corporate partner Rhone-Merieux. This is a Vaccinia virus expression system, with a gene for a protein of the rabies virus, that is intended to stimulate an immune response, but that cannot cause rabies. Provisional approval was given early in 1989 by USDA; the actual distribution of 3,000 ampules of rabies vaccine in an odoriferous bait took place on uninhabited Parmmore Island, Virginia, in the fall of 1990. South Carolina had declined to have an offshore island field test take place within its boundaries.

The owner of the Virginia island, the Nature Conservancy. negotiated long and hard regarding the release. The Wistar Institute had to agree to provide full insurance coverage and indemnification against any lawsuits to the Nature Conservancy. The Conservancy demanded a strong voice in field trial and animal monitoring protocols. Although Wistar researchers assert that any risk from the release is very remote, the apparent ''lack of control (putting bait in the wild and waiting for animals to eat it) certainly helped to arouse concerns. A similar vaccine is being tested widely in Europe, and the Wistar Institute has had discussions regarding additional sites in the mid-Atlantic States (25).

On the basis of satisfactory results from the Virginia field trial and additional data confirming safety in other species, APHIS authorized a second field trial in Sullivan County, Pennsylvania, on June 7, 1991, with little or no adverse public comment, and New Jersey is considering a field trial as well. In contrast. early in APHIS' review of animal biologics, a suit by Jeremy Rifkin's organization, the Foundation for Economic Trends, resulted in a voluntary 2-week suspension of the license issued for the first recombinant-DNA derived category 11 pseudo-

rabies vaccine while APHIS prepared documentation of the assessment conducted during the licensing process.

Large-Scale Release for Veterinary Biologics

Theory-The USDA uses information from early small-scale trials in its subsequent assessment procedure. Biological products progress from physical containment to large-scale use in the field as follows:

1. Movement from stringent containment conditions (level 4) to quarantined field conditions (level 3).
2. Restricted field tests (level 2).
3. Unrestricted geographical distribution on issuance of a license (level 1).

Experience Base—As of October 1, 1991, APHIS had approved field testing and subsequently granted licenses for 39 Category One veterinary biological products. Twenty-six of these were for diagnostic kits; five were for bacterins, and three were for monoclinal antibodies for prophylactic or therapeutic use. The first, a bacterin, was licensed in October 1983; all have been used successfully on a large scale. Seven licenses were granted for category 11 products, all of which were designed to treat pseudorabies in swine. No licenses have yet been granted in category III, but APHIS has received, evaluated, and approved an application to field test a recombinant-DNA derived live rabies vaccine (95).

The following category I and 11 licenses have been issued:

- Salsbury Labs and Norden Labs were the first licensees for bacterins in category for genetically engineered *Escherichia coli* against swine disease.
- Molecular Genetics Inc., received licenses for category 1, therapeutic or prophylactic use, for monoclonal antibodies.
- Among the category 1 diagnostic test kits licensed were kits for equine infectious anemia, avian reovirus antibody, and feline leukemia and feline T-lymphotropic lentivirus.
- At least four companies received category 11 licenses for a modified live virus used as a pseudorabies vaccine.

Authority for Animals

Statutory Authority and Regulatory Policy

The Federal Meat Inspection Act (FMIA) (21 U.S.C. 601 et seq.) and the Poultry Products Inspection Act (PPIA) (21 U.S. C. 451 et. seq.) give responsibility to USDA's Food Safety and Inspection Service (FSIS) for the safety, wholesomeness, and proper labeling of food products made from domestic poultry and livestock. FSIS inspects the organisms and cleaned products intended for use as human food.

Under the slaughter of research animal provision of the FMIA and the PPIA, FSIS has developed regulations stating that no livestock or poultry used in a research investigation is to be slaughtered at an official establishment until sufficient data demonstrate to FSIS that the edible products derived from the research animals are safe for human consumption (9 CFR 309.17 and 381.75). These regulations pertain to the slaughter of transgenic animals as well as animals treated with recombinant DNA-derived products.

Implementation

In the event of a request for slaughtering approval, FSIS would coordinate its review with the agency having jurisdiction over the experimental product (e.g., APHIS—biologics, FDA—drugs, food. and feed additives, EPA—pesticide chemicals.) Usually, data gathered by each individual agency is adequate for FSIS evaluation. Once approved for slaughter, research animals are subject to the same inspection standards as nonresearch animals. If some animals derived through new technology, such as mosaics, chimeras, and some hybrids, differ significantly from currently inspected animals, the FSIS will determine on a case-by-case basis whether the animals are covered under FMIA or PPIA or if the acts need to be amended to require inspection. FSIS also has authority over substances used in processing meat and poultry products; the use must be in compliance with applicable FDA regulations and must be functional, suitable, and kept to the lowest level necessary (I I).

The FSIS has not yet had to test its interpretation or implementation process in a case involving animals modified through biotechnology (1 I).

EPA

EPA has jurisdiction over two broad classes of products (pesticides and ''new' chemicals) under three Federal statutes—the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA): the Food, Drug, and Cosmetic Act (FD&C); and the Toxic Substances Control Act (TSCA). Under the authority of FIFRA, EPA regulates the manufacture, processing, distribution, and use of pesticides and sets tolerance levels for pesticides in food and feed as directed by the Food, Drug, and Cosmetic Act (discussed in the food safety chapter). Under TSCA,

EPA must screen any ‘*new” chemical before it is introduced into commerce to determine whether or not its use presents an unreasonable risk to health or the environment and is not otherwise regulated. This section reviews EPA’s statutory authority under FIFRA and TSCA and discusses its application to the regulation of biotechnology products.

EPA attempts to forge a coordinated and consistent approach to its biotechnology responsibilities under FIFRA and TSCA to the extent possible given the different mandates of the two statutes. Despite these different mandates, both approaches to regulation are concerned with microorganisms having:

- ‘‘new’ characteristics (intergeneric combinations of genes) that are new to the environment in which they will be released;
- potential for adverse effects on other organisms; and
- potential for widespread exposure because they are used in the environment.

Because FIFRA regulations were already applied to microbial pesticides, an interim regulatory policy announced in the Federal Register on small-scale field trials in relation to Experimental Use Permit (EUP) regulations was the only change necessary for the ‘‘new’ biotechnology. However, a set of regulations for microorganisms is needed under TSCA so that EPA can regulate living microorganisms more readily. The agency heretofore has dealt principally with new chemicals, although microorganisms have been included in the TSCA Inventory of Chemical Substances since its establishment. Regulations could be developed by applying the statutory provisions of TSCA and EPA’s current oversight program for new chemicals to microorganisms. The delay in the development of these regulations has been noted with particular concern by the biotechnology community as likely to have caused uncertainty among applicants and would-be applicants for deliberate release.

For assistance in regulating biotechnology, the EPA formed its Biotechnology Science Advisory Committee (BSAC) in 1986 to give peer review of EPA assessments of product submissions, as well as scientific advice on its biotechnology program. Among other responsibilities, the BSAC has been involved in advising on terms for regulations, on benefits and risks of the use of antibiotic-resistance genes as markers in field tests, and on peer reviews of some EPA assessments of field test submissions (67).

Authority of FIFRA

Statutory Authority

As noted above, pesticides, including those produced using biotechnology, are regulated by EPA under the aegis of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). FIFRA was enacted June 25, 1947, “to regulate the marketing of economic poisons and devices” (6 I STAT. 168; 7 USC sec 135c); it has been amended multiple times in the intervening years with major substantive amendments in 1972. 1978, and 1988 and more anticipated in the early 1990s.

The heart of FIFRA is the requirement that all pesticides be registered. EPA must certify that the use of a pesticide does not pose an ‘‘unreasonable adverse effect’ in order to register a pesticide. In deciding whether a pesticide use poses ‘‘any unreasonable risk to man or the environment, EPA must take “into account the economic, social, and environmental costs and benefits of the use of any pesticide. ” EPA must also consider the impact of any regulatory action "on production, prices of agricultural commodities, retail food prices, and otherwise on the agricultural economy. Registration requires the submission by the manufacturer of extensive data on the efficacy and human and environmental effects of the pesticide. EPA uses this data in deciding whether to register the pesticide and whether to impose conditions on its manufacture, processing, distribution, and use.

After registering a pesticide, EPA retains regulatory control via the reregistration, cancellation. and suspension provisions of FIFRA. Section 6 (a) of FIFRA establishes that registrations are canceled after 5 years unless EPA receives a request for a new registration, at which point EPA may request new data about the pesticide and may, on the basis of this new information, alter the conditions of the registration. EPA also has the power to cancel a registration at any time if the agency finds that the pesticide poses an unreasonable adverse effect; however, the cancellation procedure is complex and time-consuming. If the use of a pesticide poses an imminent hazard, EPA may immediately suspend a registration.

Agency Interpretation and Regulatory Policy

EPA’s principal experience base lies in evaluating conventional chemical pesticides where risk issues may differ significantly from those of living organisms. Nonetheless, microbes (e.g., bacteria. viruses, fungi, and protozoa) producing pesticides or pesticidal substances. as well as plants modified to produce substances to control pests, can be interpreted as falling within the statutory

definition of pesticide. EPA's office of Pesticide Programs has built a group and experience in regulation of microbial pesticides since the late 1970s. EPA will register these products it it concludes that the benefits of their use outweigh the risks. More controversy has arisen over whether pest-resistant plants are equivalent to pesticides. since all plants have some pest-resistant characteristics naturally. EPA has never, for instance, regulated plant varieties. such as virus-resistant lines, classically bred to have "pesticidal" properties.

Microorganisms- On October 17, 1984, EPA published in the Federal Register a notice that it would "require notification prior to all small-scale field tests involving certain microbial pesticides in order to determine whether experimental use permits are required. This is in contrast to small-scale field tests of conventional chemical pesticides. An EUP is not required for the latter if under 10 acres of land or 1 acre of water is involved. The difference in policy is based on the premise that the concepts of "small scale" or ''small quantity' arc not applicable to living organisms capable of movement and reproduction. Notifications are required for field tests involving non indigenous microorganisms. microorganisms genetically altered by ''traditional means, such as mutagenesis, and recombinant microorganisms. In the case of most of these notifications. no problem is perceived by EPA and no EUP is required.

In a February 15, 1989, Federal Register notice. EPA announced its intent ion to amend FIFRA regulations to require notice for small-scale releases involving I) microorganisms whose pesticidal properties have been altered by introducing intentionally manipulated genetic material; and 2) microbial pesticides formed by the combination of genetic material from organisms from different genera.

In an attempt to maintain flexibility, EPA is currently considering a mechanism for exempting small-scale field tests of microbial pesticides from the notification requirement as increasing information and experience so justify. Only organisms with higher risk and those that arouse higher levels of public concern would remain the targets of reviews. A draft amendment to the regulations is circulating within EPA that would clarify the scope of organisms requiring notification, emphasizing only those organisms that carry significant possibility of risk or raise high levels of public concern. There has been some support for exempting nonindigenous microorganisms and microorganisms genetically altered through traditional means from notification requirements, expressed in terms of the very absence of comments received on publication of such notification in the post (67, 91).

Plants—In 1987, the EPA Office of Pesticide Programs (OPP) and USDA's Animal and Plant Health Inspection Service (APHIS) agreed to review cooperatively proposals for field tests transgenic plants that fall under the Federal Plant Pest Act. Currently, while tests are at a small scale. on an operational level APHIS takes the lead, with OPP providing comments. Under discussion is the possibility that OPP take the lead when the plants are grown on a large scale for food use. In some cases, the products of large-scale tests might be intended for food or teed USC. Modifications to 40CFR 152.40 CFR 158, and 40 CFR 172 may be needed fo new data requirements and variations on Experiment Use Permits. EPA might regulate field trials of plants with pesticidal properties, or it might set tolerance levels for residues in approved food products.

To gain input as it develops procedures t-or evaluating transgenic plants, EPA conducted a workshop in June. 1990 to discuss scientific issues and seek guidance on the information needed to conduct these evaluations (23). In November of 1990, EPA held a second information gathering conference, this one focusing exclusively on pesticidal transgenic plants. One topic addressed is how to adopt the agency's usual "maximum hazard". testing approach, in which artificially high concentrations of a chemical are used to evaluate the safety of plants that produce a pesticidal chemical in small amounts; if extra supplies of the chemical are generated (in bacteria) for the tests, will this material be identical to the plants chemical, so that the test is valid? Such complexities not withstanding, EPA under FIFRA has a much more focused task—regulating substances designed to harm some living systems—than FDA, which will have to consider the much broader arena of genetically engineered plants as food. (See ch. 10 and 11.)

Other Organisrns-Microorganisms used against other insects, such as nematodes or parasitic wasps, do not fall under the purview of FIFRA. However, the demands of particular isolated cases can elicit FIFRA staff involvement. In one case, parasitic wasps were used to control infestations in certain grain elevators in Texas. The FDA inspector checking for insect parts in the food requested a tolerance level from EPA. EPA could not comply because it had never registered the wasps as a pesticide. After much interagency communication back and forth, EPA developed a memo of exemption. This was the one case to date in which EPA staff has dealt with animal

microorganisms. EPA is not involved, for example, in a case of a pesticidal nematode carrying bacteria because it is seen as a microorganism system. If, however, the bacteria in the system were genetically engineered, OPP would want to take a look at it (91).

Implementation

Basically, EPA reviews a proposed test and decides whether to allow the test, request more information, or require an Experimental Use Permit, for which the target review time is 90 days. Companies are encouraged to hold discussions with FIFRA officials prior to the notification and EUP stages.

Review is conducted on a case-by-case basis by FIFRA staff. A list of data that must be submitted with a notification is available and includes, among other components:

- the identity of the microorganism;
- means and limits of detecting the microorganism in the environment;
- physical, chemical, and biological features influencing the growth and survival of the microorganism;
- information on likely survival in the environment(s) into which the microorganism will be introduced;
- the genetic manipulations involved. in detail;
- data on potential for gene transfer, detailed description of the test program, including monitoring; and
- any additional factual information on possible adverse effects.

Aspects considered by staff include: hazard and exposure, potential problems or issues, important questions needing answers, and likelihood of risk.

Staff positions are then shared for comment with intra-agency workgroups, other Federal agencies if appropriate, State agencies, and, if needed, the BSAC. Although a State-FIFRA Issues Research and Evaluation Group exists, EPA does not yet seem to have tapped or developed an established, extensive system of State-level biotechnology contacts comparable to that of USDA. Public comment is regarded as important; for some proposals, several opportunities have been provided. Notice of all notifications appear in the Federal Register; significant EUP's, including all biotechnology EUP', are placed in the Federal Register as well. Companies are encouraged to inform local communities of upcoming field tests.

If the analysis indicates unreasonable risks are likely, EPA can impose restrictions. Risk management can include constraints on use, disposal, and manufacture, as well as mitigation, monitoring, or other actions. As a way of checking on its evaluations, and adding to its information base for future tests, EPA has worked on the development of monitoring methods that will lead to understanding of the possible fate and dispersal of microorganisms in the environment (67).

Application of FIFRA

Small-Scale Release

Theory—EPA under FIFRA approaches small-scale field trials on a case-by-case basis.

Experience Base—From 1984 up to 1989, the Office of Pesticide Programs (OPP) reviewed 36 submissions (notifications and EUPs) under FIFRA. Of 25 notifications reviewed, 21 were approved with no EUP required, 1 was withdrawn, and an EUP was required for the remaining 3. Of 11 EUPs reviewed, 10 were approved, with a decision on 1 pending (96). Companies making submissions included: AGS, Mycogen, Monsanto, Ecogen, Rohm and Haas, Crop Genetics International, and Sandoz. Universities included the University of California, Montana State University, Cornell, and the University of Arkansas. Nearly half of the tests involved *Bacillus thuringiensis (85).* So-called ''pesticidal plants," transgenic plants that produce pesticidal chemicals, are reviewed in conjunction with USDA-APHIS, with EPA-FIFRA staff providing comments to USDA-APHIS. Tomato plants engineered with *Bacillus thuringiensis* toxin genes and tobacco plants engineered with Tobacco Mosaic Virus coat protein genes are examples. Both have been explored by more than one company. Companies whose applications for transgenic pesticidal plants received informal review by EPA are: Rohm and Haas, Monsanto, Agrigenetics, Sandoz, DuPont, and Agracetus (97).

The first review of an EUP application for a genetically engineered microbial pesticide (a test by Advanced Genetic Sciences, Inc., of the Ice-minus (INA) *Pseudomonas syringae)* took nearly 2 years from receipt of application to the field test. Two lawsuits involving Federal and State courts temporarily stopped the test; many administrative proceedings at the State and local levels caused further delays.

In contrast, a later application on an EUP submitted by Crop Genetics International in December of 1987 was granted in May of 1988, less than one-half year later. The field test was begun in June and data for the test were submitted in application for an extension and ex-

pansion of the EUP. This test involved the insertion of a *Bacillus thuringiensis* toxin gene into a plant endophytic bacteria (67).

OPP considers any microbial pesticides to be biotechnological in the broadest sense; even biochemically based pheromone products are biologically active systems designed to alter the behavior of insects. At least three-quarters of the Office's workload is comprised of nonrecombinant microbial pesticides; recombinant products represent only 1 to 5 percent of the number of notifications received. While numbers of new chemicals to be reviewed have plateaued over the last 5 to 6 years, microbiological/biotechnology products are increasing linearly such that they now comprise approximately one-third of the reviews. Plans exist to add biologically trained staff during the upcoming year (91).

The early stages of the regulatory life cycle of a new microbial pesticide is illustrated by a planned introduction of dead recombinant organisms into the environment. In 1986, Mycogen discussed its killed recombinant bacteria with FIFRA staff who, on receiving requested data proving that the bacteria were in fact dead, told the company that it did not need to submit a notification. In 1988, the company was moving its trials into sites larger than 10 acres, the stage where an EUP was obtained from EPA. In 1989-90, field tests took place on some 5,000 acres per year. In 1991. the company had several products approved for registration as a pesticide (91).

EPA has also approved field trials of live recombinant organisms by Repligen and Sandoz Research Corps. Field trials of recombinant *Bacillus thuringiensis* on soybeans infected with beet army worms were approved for the fall of 1990 at Sandoz's Mississippi station (86). Interest in microbial pesticides is growing among large companies.

Large-Scale Release

Although naturally occurring, classically derived, and killed recombinant products have moved through large-scale testing and commercial registration, no large-scale releases of *liverecombinant* organisms have as yet been approved under FIFRA. However, at least one company has had a series of discussions with EPA staff on testing design.

Authority of TSCA

Statutory Authority

The Toxic Substances Control Act (TSCA) was enacted in 1976 to regulate the manufacture, processing. and use of chemicals that may pose an unreasonable risk to human health or the environment (15 USC section 2601-54) (13, 87). Because Congress intended TSCA to be gap-filling legislation. it gives EPA broad regulatory authority over a range of substances not regulated under other Federal laws. In determining the appropriate type and level of regulation to impose. EPA must ''consider the environmental, economic, and social impact of any action [it] takes or proposes to take" {15 USC sec. 2601 (2)]. As with FIFRA. EPA must carry out a risk benefit analysis before imposing restrictions on the manufacture, processing, or use of any chemical.

TSCA primarily is a mechanism for screening new chemicals. EPA can review new chemicals for unreasonable risk through the mechanism of manufacturers being required to submit a premanufacture notification (PMN) to EPA prior to the manufacture of any new chemical, i.e. , any chemical not included on the EPA inventory of chemical substances (TSCA sec. 5, 40CFR 720.25). Under TSCA. EPA has the authority to limit or prohibit the manufacture, processing, or distribution in commerce of a new chemical substance if it determines that the chemical substance may present an unreasonable risk to health or the environment, or pending the development of sufficient data to assess whether the chemical substance presents an unreasonable risk. The burden is on EPA to establish risk rather than on the manufacturer to establish the absence of risk. If EPA ascertains that a chemical poses an unreasonable risk or that there is insufficient data to determine the effects of the chemical, EPA can require the manufacturer to test for toxic effects. TSCA subsection 8(e) requires that manufacturers and processors maintain records of "significant adverse reactions to health and the environment (40 CFR 717. 12) and requires submiss ion to EPA of any information supporting a conclusion that a chemical or microorganism presents a substantial risk to health or the environment.

Under its authority to limit or prohibit use of new chemicals posing unreasonable health or environmental risks, EPA may establish conditions for the manufacture. processing, packaging, exposure. and labeling of such chemicals or ban them outright. EPA also can issue controls over chemicals through the significant new use (SNU), reporting, and imminent hazard provisions. The SNU provision requires prior notification for a significant new use of a chemical as defined by EPA. The agency then can set conditions, limitations. or prohibitions based on a new intended use of a chemical. Finally, as with many Federal statutes, TSCA has an imminent hazard provision

that enables EPA to take action quickly if a chemical poses a serious risk (15 USC sec. 2606).

Agency Interpretation and Regulatory Policy

1986 Coordinated Framework Policy—EPA primarily uses TSCA section 5, with its requirement for a PMN prior to the manufacture of any new chemicals to deal with products of biotechnology. The Coordinated Framework (51 FR 23302-23393, June 26, 1986) (77), which designated responsibilities for various biotechnology products held by various Federal agencies, included a policy statement by EPA as to how the agency intended to use TSCA for the regulation of biotechnology; the statement described the categories and microorganisms subject to TSCA, review procedures, and types of information to be submitted for risk assessments. At the most fundamental level, living organisms are considered to be chemical substances under TSCA. Basically, EPA views certain intergeneric microorganisms (microorganisms formed by deliberate combinations of genetic material from organisms in different genera) as ''new chemicals' and therefore under its purview. TSCA pertains to microorganisms used in commercial applications *not* regulated under FIFRA, FDCA, and other statutes; these applications include chemical production, waste degradation, conversion of biomass to energy, and other environmental and industrial uses.

While intergeneric microorganisms are subject to review, naturally occurring microorganisms are not considered ''new' and therefore are not subject to the prenotification requirements of section 5(a)(1) of TSCA, although they may be subject to regulation under other sections of TSCA (i. e., the significant new use rules under section 5(a)(2)). Naturally occurring organisms are implicitly considered to be on the TSCA inventory of substances available in commerce. As for all substances subject to TSCA, manufacturers, processors, or distributors of microorganisms must notify EPA immediately if they become aware of new information suggesting risk from the microorganisms to human health or the environment (section 8(e)).

1988–89 ***Draft Proposed Regulations—in*** general, EPA's efforts to develop regulatory policy have not met with success, and 5 years after the appearance of the Coordinated Framework there still exists no firm EPA biotechnology regulations. Two principle efforts towards developing those regulations will be discussed here—the draft proposed regulations of 1988–89, which did not come to be; and, in the next section, the draft proposed regulations of 1991, which are the source of current controversy. Since the issuance of the Coordinated Framework, EPA, in consultation with its Biotechnology Science Advisory Committee, worked in 1988 and 1989 to develop draft TSCA regulations for biotechnology. Under the 1986 Framework policy, small-scale biotech R&D efforts involving field tests of intergenerics were requested to submit a PMN. The 1989 draft regulations under TSCA proposed a new regulatory mechanism, the TSCA Experimental Release Application. This mechanism involved the use of Environmental BioSafety Committees (EBC's), based on the concept of Institutional BioSafety Committees (IBC's) established earlier through the NIH-Recombinant DNA Advisory Committee (RAC).

This draft EPA rule was reviewed by the interagency Biotechnology Science Coordinating Committee (BSCC) at several meetings. Many concerns were reportedly raised, including the scientific basis for the draft regulations. EPA responded to some comments by sister agencies by making some modifications and then sent the draft proposed regulations to the Office of Management and Budget (OMB) for clearance. BSCC requested that OMB hold clearance until BSCC had time to review its interagency; friction ensued (92).

A Request for Comment on Regulatory Approach was published by EPA in the Federal Register on February 15, 1989 (54 Federal Register 7027). Questions raised for comment included: scope of the microorganisms to be subject to EPA's review; scope of EPA's review of R&D field releases of microorganisms into the environment; breadth of definition of ''commercial purposes' by which EPA would have authority under TSCA in educational and research facilities; definitions of 'release to the environment' and ''contained facility"; and to what extent review was to be performed for EPA by independent expert review groups, such as Environmental BioSafety Committees. The draft regulations did not survive. Rulemaking was delayed until EPA policy and plans for TSCA could incorporate the scope document arrived at by interagency consensus.

1991 ***Draft Proposed Regulations—The*** most recent draft TSCA regulations, integrating some eight specific rules, appeared and were extensively reviewed in 1991. Once EPA has completed the process of responding to the recommendations of the BSAC Subcommittee regarding this draft, the regulations enter the final phase of the Agency's internal review process.

Under EPA's portion of the 1986 Framework Policy, reporting by persons intending to introduce intergeneric

microorganisms into the environment for R&L) purposes is voluntary. EPA is now proposing that this is no longer voluntary. However, researchers intending to introduce intergeneric microorganisms into the environment for R&D purposes would at least have the option of filing a TSCA Experimental Release Application. or TERA, as an exemption from a full 90-day notification that would otherwise be required from commercially oriented applicants. The expedited TERA review would generally be completed in 60 days. The extent of the reporting of environmental R&D required will depend on the eventual selection of an interpretation of the statutory phrase ''commercial purposes. In addition, EPA proposes to exempt some categories of microorganisms when introduced into the environment for R&D purposes (30). The proposed approach is different from the agency's treatment of chemicals, for which review of small-scale R&D activities is not required, presumably because, unlike microorganisms, chemicals cannot reproduce, disseminate, and transfer genetic material.

In 1986, EPA had stated that it would try to derive exemptions for some organisms used in contained facilities: in the current draft, some organisms in contained facilities are exempted from review and only a short review is required for specified lists of industry's "workhorses, such as *Bacillus subtilis.* The list is expected to grow with experience.

The agency views the new document as following directly from the coordinating principles and scientific rationale of the ''scope document' published by the Office of Science and Technology in 1990 as proposed "Principles for Federal Oversight of Biotechnology: Planned Introduction in the Environment of Organisms with Modified Hereditary Traits' [55 Fed. Reg. 31, 120 (1990)] (discussed later). EPA has stated that it will subject to regulatory scrutiny only those "new" organisms that seem likely to present risks. Definitions of "new*' and "risk" are subjects of debate. Some view the 199 I draft-proposed regulations as inconsistent with the OSTP draft's risk-based philosophy. The TSCA 1991 draft proposal effectively singles out recombinant-DNA modified microorganisms for oversight. by exempting other categories such as classical transformation systems (e. g., conjugation or chemical mutagenesis). or rearrangements, deletions, or amplifications of genetic material by recombinant techniques. These exclusions are based on EPA's view that such things could—and do—occur naturally and are thus not . 'new. in contrast to recombinations formed with genes from different genera.

EPA is proposing three alternative interpretations of ''commercial purposes'" in its current draft rule: it may draw a very big net. The first involves selection of commercial indicators that would govern whether a particular field trial would be subject to oversight. The second would apply commercial indicators to R&D conducted in laboratories and greenhouses, for example, and would consider any environmental field release as commercial. and thus subject to screening. The third would permit researchers to rebut the presumption that a field trial was for commercial purposes by showing a lack of commercial intent.

Having potentially drawn so many activities into its ''commercial" net, TSCA would defer to whatever agency would most sensibly handle that activity. TSCA's own coverage might not increase to a great extent. Academic laboratories may well fall under the scope of this ''con~-mercial purpose' if, as is so often the case today. they have some form of a relationship with a company or perhaps even if their home institutions have dealings with industry—as most universities do. Another point of controversy of the proposed draft is its attempt to institutionalize good laboratory procedure and record keeping even in academic laboratories, which previously have not been considered under its jurisdiction (21).

The outcome and the acceptability of the draft are not yet known. It contains controversial points and, 5 years after the appearance of the Coordinated Framework, there exists no track record for quick finalization of EPA biotechnology regulations.

Implementation[3]

EPA currently requests industry to comply voluntarily with the PMN (remanufacture notice) requirements for commercial R&D involving field test releases with intergeneric microorganisms. (Commercial-scale releases are subject to mandatory reporting requirements.) Because the standard TSCA PMN form is not applicable to microbial products, the Program Development Branch of the Chemical Control Division prepared a document, "Points to Consider in the Preparation and Submission of TSCA Premanufacture Notices (PMNs) for Microorganisms, ' in 1990. The document is intended to give guidance for contained system (fermentation) PMNs and

[3] **Note - the preceding section, "Agency Interpretation** and **Regulatory Policy** ." discusses development of **EPA policy,** which **includes proposed implementation. This section examines** *currently practiced* **implementation.**

environmental release PMNs. It specifies points of desired information, including: description of recipient and donor microorganisms, construction of the PMN microorganisms, characteristics of the PMN microorganisms, production process, worker and consumer exposure, environmental behavior of the PMN strain, and environmental release protocols.

Manufacturers or importers of intergeneric microorganisms in and for commerce are required under TSCA section 5(a)(1) to submit a PMN at least 90 days prior to manufacture or import. Communication with a Program Manager in the Program Development Branch, Chemical Control Division, and EPA's Office of Toxic Substance is recommended prior to submission of a PMN. Submitters are encouraged to minimize information withheld as confidential; however, two versions, one with and one without CBI, can be submitted. Companies must now pay a fee of $2,500 for each PMN or consolidated PMN submitted; small businesses must remit $100 per PMN. The EPA publishes a notice on each PMN submission in the Federal Register (17).

Review of PMN's is conducted on a case-by-case basis, and can involve both EPA scientists and outside scientific experts. Following submission of the PMN, EPA has 90 days to make a determination as to if and how to regulate. During this time a scientifically based hazard assessment and an exposure assessment are conducted. (See ch. 8 and U.S. EPA (1987) Toxic **Substances Discussion of Premanufacture** Testing Policy and Technical Issues; Request for Comment. Federal Register 44, 16243-44).

Among the items of information reviewed are:

- the identity and characteristics of the source organism,
- the methods and genetic material used to manipulate the source organisms,
- the nature of any new traits or functions,
- purpose and intended effect of application or release,
- characteristics of the site of application,
- method and numbers involved in application,
- containment and mitigation methods,
- monitoring procedures, and
- data on environmental fate and effects (10).

If EPA determines during the 90-day period that a new chemical substance may present an unreasonable risk to health or the environment, EPA can prohibit or regulate the substance; if it does not do so, the submitter may proceed. An extension to a 180-day review period can occur, for good cause. Other agencies may be asked for comment, and appropriate State regulatory agencies are contacted. Visits to test sites may occur. The BSAC may review submissions and EPA evaluations. Public comment is viewed as important (67).

Application of TSCA

Small-Scale Research

Theory—EPA approaches small-scale field trials on a case-by-case basis. Unlike commercial research involving chemicals, under the 1991 draft of proposed regulations, recombinant DNA small-scale field tests will receive no automatic exemption from the PMN requirement, although an alternative application process (the TERA) may be used.

Experience Base— Since 1986, EPA's Office of Toxic Substances (OTS) has reviewed 20 premanufacture notices (PMNs) for release, with the most recent review completed in April, 1990 (18). It has been speculated that the absence of notices over the last year may reflect an economic climate unfavorable to commercial development of environmental uses of microorganisms (economic climate seems not to have affected plant submissions); uncertainty as to EPA's regulatory role; or the evolution of the science itself. It may be that biotechnology is to some extent moving away from deliberate release of microorganisms; plants may be easier to manipulate than previously thought. Some suggest that the lack of notices received under TSCA simply reflects the fact that no company is now actively developing rhizobia or other microorganisms subject to TSCA. Bioremediation, the commercial use of microorganisms to degrade toxic waste, will probably not significantly utilize genetic engineering in the near future. It has been suggested, however, that this particular delay may be related not simply to technical reasons but also to uncertainty about regulatory interpretations.

The first biotechnology application under TSCA was filed by Biotechnica in February 1987. The application was to field test, in Wisconsin, genetically engineered strains of *Rhizobium meliloti* to see if these increased alfalfa yields through nitrogen fixation.

A Subcommittee of the Biotechnology Science Advisory Committee reviewed the field test protocols and recommended that Biotechnica provide a fuller description of the experimental methods being employed at the site in terms of plot design and monitoring of the organisms after release into the field plot. After consideration

of BSAC suggestions and other public comments, Biotechnica obtained EPA approval to conduct the field test in spring of 1988.

Another early submission was a request in June of 1987 from Monsanto to field test a fluorescent microorganism genetically engineered to be more easily distinguished from other soil microorganisms under laboratory conditions. EPA completed its review in October of 1987. The field trial was held and it demonstrated the usefulness of the gene as a marker for monitoring. Monitoring of the field trials demonstrated that the organism colonized roots; that the population continued to decline; and that migration was limited (67).

With the exception of Monsanto's field trial, all other environmental use submissions under TSCA have been from Biotechnica. Biotechnica's tests have involved microorganisms genetically modified for improved detection in the environment (antibiotic resistance) and for enhanced nitrogen fixation resulting in potential yield increases (18).

Commercial-Scale Release

Commercial-scale release of genetically modified microorganisms has not yet occurred. EPA might be expected to follow the same case-by-case pattern for commercial-scale release as it has for small-scale release research. As a matter of interest, there have been commercial-scale uses of genetically modified microorganisms in contained systems. Reviews have been completed on 10 PMNs involving the commercial-scale use of intergeneric microorganisms in contained fermentation systems for the production of microbial enzymes.

OTHER AGENCIES

National Institutes of Health (NIH)

The RAC, the Recombinant DNA Advisory Committee at NIH, wrote the now-classic Guidelines for research in recombinant DNA at federally funded institutions and has reviewed cases for compliance with the guidelines. The original Guidelines, issued in 1976, counted deliberate release as one of five classes of experiments ''not to be initiated at the present time"; in the Guideline revisions of 1978, ''deliberate release into the environment of any organism containing recombinant DNA" was prohibited, but provisions were made for waivers through the RAC and NIH; in 1982 revisions, such ''prohibitions" became ''experiments that require RAC review and NIH and IBC approval before initiation' (66).

"Deliberate release" was listed as one of the triggers for RAC review (May 7, 1986, Federal Register, vol. 5 1(88), p. 16960). In fact, however, the RAC has not reviewed any cases since 1987. Since then, EPA and USDA have interpreted their authority to have purview over the vast majority of experiments involving deliberate release. RAC's acquiescence to this allocation of oversight is made clear in its ''Talbot Amendment, stating that once approvals or other clearances have been obtained from an agency other than NIH, the experiment may proceed (Aug. 24, 1987, Federal Register 52(163), p. 31, 849). In addition, the RAC at its February 4, 1991 meeting, voted to consider deleting planned environmental deliberate release as one of the triggers for its involvement in biotechnology regulation. After duly publishing notice and receiving public input, the RAC met on May 31, 1991 and voted to relinquish this overview. The decision now stands before the Director of NIH. NIH funds very few scientists involved in deliberate release; it also lacks qualified staff to conduct EA's. The RAC, however, intends to maintain its overview of work with transgenic plants and animals *inside* laboratories, animal rooms, and greenhouses. RAC's relinquishing of national overview does not preclude local Institutional Biosafety Committees (IBCs) from considering planned introductions or from bringing up problems to the RAC (108).

Food and Drug Administration (FDA)

Because FDA's authority is over the final food product in interstate commerce. it does not regulate research and therefore is not involved currently in the environmental issues concerning deliberate release research. Exceptions are its jurisdiction over live attenuated vaccines and feed additives including live microorganisms. However, if FDA gives some form of approval for the commercial use of transgenic plants for food, it may have to evaluate the potential environmental consequences of that approval, under the National Environmental Policy Act (NEPA). If a company asked FDA to affirm GRAS (Generally Recognized as Safe) status for a food or to state that a particular variety of plant is acceptable as a source for food, FDA would likely have to assess the environmental consequences of the field use of the plant as part of its evaluation of the food product. An FDA ''advisory opinion, however, might not be a major Federal action requiring an environmental assessment.

In its reviews, the agency in the past has limited its environmental assessment to the manufacture and use of the petitioned-for substance. It typically has not reviewed the environmental consequences of the original produc-

tion or development of the materials used at the manufacturing site. In the case of agricultural commodities, however. the plant itself might be viewed as analogous to the manufacturing facility.

If USDA has evaluated the environmental consequences of the field use of the plant, FDA should be able to make use of that information in its own evaluation. It is also possible, although not necessarily likely, that FDA may be able to exclude categorically from its own environmental review those plants that have been reviewed by USDA for commercial use (24).

STATE AND LOCAL GOVERNMENT

Spectrum of State Approaches to Regulation

Significant concern has been expressed regarding the involvement of State governments in the regulation of biotechnology. In addition to coordination with Federal agencies. discussed in a later section. a significant question is the degree to which States should take on independent review authority. On the one hand, State governments may be argued to be "closer to" the people that they are safeguarding and therefore regarded as particularly able or trustworthy as regulators. On the other hand, duplication of Federal regulatory requirements could prove to be an untenable burden on companies. Excessive. idiosyncratic requirements at the State level also might inhibit industrial development. Furthermore, a patchwork of varying State regulatory regimes across the Nation could lead to significant uncertainty on the part of industry, a shopping around for receptive States, or a simple unwillingness to move into product lines related to biotechnology. Compliance with different standards in different States could be a costly problem for industry.

State legislation relevant to biotechnology in 1990 included 19 bills spread among 13 States. These fall in the areas of DNA testing (9). bST (4). R&D and economic development (3), deliberate release (l), general regulations (I). and other (I). In the same year, some 48 bills in 18 States were introduced but not enacted. These referred to bST (20), DNA testing (I l), R&D) and economic development (10), deliberate release (3), general regulations (2), and other (2).

Over the past several years, the nine States of Florida. Hawaii. Illinois, Maine. Minnesota. New York. North Carolina, Oklahoma, and Wisconsin have enacted statutes pertaining directly to field testing of genetically modified organisms. with Maine and New York simply creating advisory committees to study issues. In 1991, West Virginia amended its plant pest act to pertain specifically to biotechnology. Many State statutes simply require notification of field test applications to particular State agencies that are to cooperate with the Federal process. Only North Carolina and Minnesota require additional permits. Policy stances taken by various States fall into a broad spectrum. from no or very little administrative or legislative activity (approximately half the States) to moderate activity to, in a few cases, initiation of new regulatory procedures (16). Case study illustrations of this range of activity follow.

North Carolina

In June 1988 the North Carolina Department of Agriculture and the North Carolina Biotechnology Center formed an Advisory Committee to determine whether or not any State regulation was needed and, if so, to develop a suitable regulatory framework. The 27-member Committee included university and private-sector researchers, administrators, business executives, lawyers. and farmers and representatives of government, public interest, and other groups. The committee's recommended regulation was passed by the North Carolina General Assembly in August of 1989 as the Genetically Engineered Organisms Act. Funds were appropriated for a staff biotechnologist in the North Carolina Department of Agriculture to administer the law, which requires a permit (either general or limited) for environmental release and for the sale of genetically engineered organisms, with public notice given (8, *16).*

Minnesota

In response to public suggestions in 1987 for rule changes to the Minnesota environmental review regulations, the Minnesota Environmental Quality Board formed a working group on environmental release, which recommended that the EQB should be a coordinating body for genetic engineering. A Task Force was formed, and its report was implemented by legislation in 1989. A permit is required for environmental release of genetically engineered organisms. The EQB is charged with establishing an advisory committee. reviewing proposals, and adapting rules for an environmental work sheet and for a permit for releases (8, 16). Recently, issuance of resultant proposed regulations under the EQB law have caused much controversy. A process for permitting, including an environmental assessment worksheet, would be required for each release of a genetically engineered organism (defined fairly broadly.) Legislation in 1991 created areas of specific permit authority for the Minnesota Agriculture

Department (transgenic plants; genetically engineered and experimental pesticides; and genetically engineered fertilizers. soil, or plant amendments). EQB regulations would therefore cover transgenic animals and nonagricultural engineered microorganisms. Both agencies, however, must follow the same specific procedures in proposing environmental assessments (34).

California

The well-publicized field tests of ice-minus bacteria in Monterey County in 1983-84 (see U.S. Congress, OTA. 1988 for the full case study) (102) led to a recommendation that California clarify its biotechnology regulations. Thus, an Executive Order in 1985 established the California Interagency Task Force on Biotechnology. The Task Force systematically identified, evaluated, and communicated the level of regulatory control already pertaining to various biotechnology activities in California. The first product was a handbook, ''Biotechnology-California Permits and Regulations," published in 1986, with at least 3,000 copies distributed by the summer of 1989. The chief finding was that the current regulations were quite complete in their coverage of biotechnology. Four permit procedures were enhanced to provide for increased input from the public (8, 16).

New Jersey

Stimulated by the repeated introduction (without enactment) of a State legislative bill that would have regulated environmental release, and by the enactment of several local ordinances for such regulation, the New Jersey Department of Environmental Protection developed a white paper on recommendations for the development of State policy on biotechnology. Following informal discussions among agency representatives, an Interagency Committee on Biotechnology was appointed by Departmental Commissioners in the fall of 1989. with university advisors. The committee is evaluating:

- the effectiveness of State laws to regulate biotechnology,
- coordination with Federal agencies,
- the needs of industry in complying with regulations,
- other States' policies,
- the need for biotechnology education, and
- appropriate roles of the State and its agencies.

The first priority is evaluation of New Jersey statutes and coordination with Federal agencies, with the objective of compiling a California-like handbook (8).

Inter-State Gatherings and Consensuses of State Regulators

In recognition of the importance of State regulatory agency officials as part of the full system of regulation. the USDA hosted conferences in 1989. 1990. and 199 I on "Federal and State Regulation of Biotechnology ." Emphasis was placed on clear communication from Federal agency representatives to State agency representatives about the details of the implementation of Federal biotechnology regulations. The 1990 meeting attracted some 130 people. the great majority from State agencies. University, private-sector. and environmentalist representatives attended as well. The third meeting, in 1991. concentrated on the issues of large-scale commercial release.

In recognition of the varying degrees of unease felt by State regulators having to come to grips with biotechnology, a special workshop for State agencies, "State Oversight of Biotechnology, " was held in conjunction with the second Federal conference, sponsored by the University of California Systemwide Biotechnology. Research and Education Program and the New Jersey Department of Environmental Protection. Case histories of the development of various State policies were shared. Brainstorming seminars led to a consensus set of recommendations for State regulatory officials. The resulting document, "Guidance for State Governments on Oversight of Biotechnology, " included the following "Points to Consider" for States considering how to handle biotechnology oversight:

1. evaluation of the existing (Federal and State) oversight framework for biotechnology;
2. organization of a task force to include representatives from multiple agencies, industry, academic and public interest groups; and
3. activities of the task force, which should include identifying and reviewing existing State statutes and Federal agency roles; recommending needed actions. if any; delineating clear pathways for applicants to follow; working with local governments; and communicating with and involving the public (39, 59).

In 1991, a follow-up workshop emphasized specific points at which coordination between State and Federal agencies could be fine-tuned.

Spectrum of Local Approaches to Regulation

The first local response to biotechnology occurred in Cambridge. Massachusetts. in the ordinances passed in

1977. Concerns over genetic engineering research in university laboratories led to sometimes heated hearings and local regulations. Some years later, an equilibrium seems to have been reached between town and gown. Some companies find the existence of known local regulations to be positive, although others find them problematic and subject to change with newly elected local politicians.

Such an open clash has been fairly unusual, although in one 1989 case the city of Burlington, Vermont and the University of Vermont clashed over the construction of a building to house much of the university's molecular biotechnology research. The city demanded input into, if not the approval of, experiments to be conducted in a new building. The University refused, and the press attacked the University's stance (6). In March of 1991, a Memorandum of Understanding between the city and the University called for the establishment of a task force to discuss plans together. Like Cambridge, Burlington was not particularly concerned with deliberate release.

In New Jersey, on the other hand, initial local concerns focused on perceived risks associated with deliberate release of genetically engineered organisms. When State-level legislation was not enacted, concerned politicians provided to municipal governments model ordinances to restrict the environmental release of genetically engineered microorganisms. By early 1990, six municipalities had adopted such ordinances. Other municipalities debated such ordinances, but decided against enactment, in part because pertinent expertise was recognized as lacking at the local level (41).

To forestall negative public reactions, the AgBiotech Center of Rutgers University in New Jersey began working with the local community from the earliest moment. They formed a Citizens' Advisory Committee to provide input and air public concerns over its planned field-trial facility for genetically engineered plants. Local planning boards, a homeowner's association, farmers, and agricultural organizations appointed members to the committee. The committee reviews plans for the facility and applications for field trials therein. The committee also is charged with communicating information to the public (88).

INTERNATIONAL REGULATORY CLIMATE

Biotechnology, as a scientific endeavor and an industrial activity, is international in scope. Those concerned with U.S. economic competitiveness or with the global environment have reason to be interested in the degree to which deliberate release regulations are internationally consistent and coordinated. A brief sketch of regulatory approaches in several countries follows.

Europe

Status of Regulations, EC 1992

European Community (EC) directives were passed in April of 1990 concerning contained use and deliberate release of genetically modified organisms. Member States were supposed to draft national laws by October, 1991, in alignment with these ''minimum standard' directives. Each State can, and some may well, add more restrictive measures; different member States will achieve different balances regarding restrictiveness of regulations. Pressure groups such as the Greens in Germany, for example, will attempt to counteract the voices of industry concerned with economic competitiveness. Despite the potential for some country-to-country variation in regulatory rigor, the directives are meant to provide more of a ' 'bottom line" consistency among States in terms of protecting the environment than was present in the past.

According to the EC Directive on the Deliberate Release of Genetically Modified Microorganisms, No. 90/220/EEC, releases are permitted only in countries with relevant national approval procedures. The EC hopes for an EC-wide approval procedure for releases of commercial products. This would allow free distribution of products throughout the EC. Deliberate releases will be evaluated and approved or disapproved on a case-by-case basis; hence, there may be room for flexibility in and evolution of regulations. Environmental impact assessments and consent by competent authorities are prerequisites of release.

Different stages in establishing a basis for national decision making have been reached by different EC countries. Approximately one-half of the member States passed implementing legislation by the October 1991 deadline. In the United Kingdom (UK), a biotechnology regulatory framework is part of an introduced Environmental Protection Bill that is intended to form the basis of future detailed regulations. In Germany, the Gene Law was enacted in July 1990. Under pressure from some of its largest industries, Denmark retracted its extremely stringent 1986 law; deliberations as to implementation of EC directives are ongoing. In France, procedures are straightforward and nonburdensome; over 50 field trials have taken place. In the Netherlands, permits for field trials are granted by the Ministry of the Environment

(105). In France, some 67 "uncontained experiments" took place between 1987 and 1990 (12).

Some analyze EC directives with a positive spirit and view the goal of developing a coordinated science-based approach to regulation as helpful to biotechnology in the long run. Science-based regulation, even if it varies among member countries, may well be preferable to idiosyncratic applications of disparate laws already on the books in different countries (47).

In any event, it is not yet clear what balances will be achieved by diverse countries weighing such factors as environmentalist pressures, industry lobbying, scientific findings, and competitiveness concerns. The foundation is laid for commonality, but the likelihood is that different countries will find their own paths. True homogenization is not likely to be achieved by "Europe 1992. The loathing that industry feels for regulatory uncertainty might give the United States at least a transient competitive advantage over at least some countries if regulatory uncertainty here is minimized.

The Fourth Hurdle

The "fourth hurdle" causing real worry among biotechnology advocates refers to a fourth criterion for European regulations of biotechnology. This fourth criterion would be the inclusion of socioeconomic values in the approval process. The **usual three technically based hurdles** for regulations generally are safety, quality, and efficacy (15). The fourth hurdle is controversial, and of great concern even to U.S. industry. Perhaps discussion of this hurdle has peaked already, and it may be declining in importance. However, observers believe that interest could intensify again at any moment. An attempt based on socioeconomic values to ban veterinary growth hormones was voted down late in 1990, suggesting that institutionalization of such values may be unlikely (47).

Harmonization

Despite differences among member states and among EC directorates, European countries and the United States are making good-faith efforts to harmonize regulations. Enlightened self-interest regarding economic competitiveness doubtless plays a role.

Several forces for harmonization include: The Organization for Economic Cooperation and Development (OECD). the Office of International Epizootics (OIE), United Nations Agencies (UN), The World Bank, and bilateral discussions with the European Commission (EC). The OECD, which includes 25 industrialized countries, many but not all of which are European, has several projects related to regulation of biotechnology, including:

- Good Development Practices;
- Guidance for the Design of Small-Scale Field Research With Genetically Modified Plants and Micro-Organisms;
- Good Industrial Large-Scale Practices:
- Monitoring of Genetically Modified Organisms Introduced into the Environment: Findings and Suggestions;
- Performance Evaluations for Plant Cultivar Development; and
- Food Safety.

OIE discussions focus on development of internationally equivalent. appropriate standards for evaluation of veterinary biological products derived through biotechnology. Within the EC, bilateral discussions have occurred through the U.S./EC Bilateral Discussions on the Environment, the High-Tech Group, and the Task Force on Biotechnology Research (57).

Perhaps the most compelling example of harmonization is the development of a common document on biotechnology safety by the 23 member countries (including many European countries, as well as the United States. Canada. and Japan) of the OECD. First published in-house as "Good Developmental Practices (GDP) for Small-Scale Field Research, " it was reworked and released f-or public comment in 1990. GDP outlines scientific principles and conditions for proposal review and also gives guidance to researchers designing small-scale field tests of plants and microorganisms. The document may be augmented by another paper(s) as more data are compiled: the basic approach is aligned with the principles advocated in the 1989 National Academy of Sciences report on safety in field testing (73). Acceptance of this document by 23 countries has been a significant step toward international harmonization of biotechnology field-trial regulations. The fact that the United States was the lead country in developing the document ensures good harmonization with U.S. regulations: this. in turn, should facilitate international trade (55).

Currently, the United States is the designated lead for OECD in drafting an OECD discussion paper on scientific issues associated with performance trials of plant cultivars. A principal objective of this endeavor is to enable policy bodies to make recommendations and decisions based on sound science when they consider large-scale plantings of new agricultural crops. including those developed with new biotechnology techniques (24). This represents a stage beyond the small-scale research cov-

ered by GDP as performance trials involve more plants and there may be no means of ensuring that plants remain confined to experimental sites. Performance trials, however, still qualify as R&D; issues associated with commercialization of plant crops are not directly addressed in this OECD paper.

Canada

Status of Regulations

Following the lead of a Federal Government task force in 1980, Canada implemented a national biotechnology strategy in 1983 and established the Interdepartmental Committee on Biotechnology in 1985. The committee began with the premises that the product rather than the process would be regulated, building on current legislation. Additional concerns could be addressed with guidelines. Canadian regulations would harmonize with those of other countries wherever possible and practicable. A biotechnology users' guide to Federal regulations has been updated recently, assisting applicants with identification of appropriate agencies, contact people, and procedure. In 1987, an ad-hoc committee was formed on environmental release. Agriculture Canada, dealing with organisms used in agriculture, and Environment Canada, along with Health and Welfare Canada, dealing with microorganisms used for nonagricultural uses, are the chief players in the regulatory arena (14).

Currently, regulatory bodies and others in Canada are considering a draft of Proposed Notification Regulations for Biotechnology Products under the Canadian Environmental Protection Act. Developed by Environment Canada and Health and Welfare Canada. notification requirements will eventually become regulations under the new substances provisions of the Canadian Environmental Protection Act (CEPA) and will apply to new biotechnology products manufactured in or imported to Canada. Notification and assessment periods as well as information required are defined based on whether the biotechnology product will be used in contained manufacturing or released into the environment. All biotechnology products will be considered new substances under these regulations.

Environment Canada is currently in the process of developing a Domestic Substances List for those biotechnology products in commercial use in Canada between 1984 and 1986. Once a microorganism is added to this list, no further notification is required by a user if the product is used for the purpose specified in the list.

Guidelines are being prepared to assist those needing to submit notifications for this list. For release into the environment, notification would be required prior to importation. commercial manufacture, small-scale field trials, or large-scale field trials. Currently, information required for a field trial would include: objectives, site details, experimental design, site supervision, introduction protocols, containment procedures, monitoring procedures, termination procedures, and mitigation procedures. In the interim, while the proposed regulations are being developed, notification to Environment Canada is recommended for those with intent to manufacture or import into Canada biotechnology products (80).

Harmonization

Probably the closest working international relationship in the area of biotechnology regulation exists between the United States and Canada, which may not be surprising given their geographical proximity and free trade agreement. EPA officials have met with representatives of Environment Canada and have had informal contact with other relevant Canadian agencies. USDA officials have met with Agriculture Canada officials yearly for 4 years and communicated between meetings on rationale, procedure, and so on. U.S. companies can do field tests in Canada; requests that U.S. officials accept Canadian field test data are expected in the near future. Review systems similar to the U.S. biotechnology permitting system have been established by Canada, taking into account the basic principles on the safety of field testing shared by all OECD countries (60).

Japan

In general terms, Japan's regulation of biotechnology is in line with international standards. Research guidelines are based on the early NIH guidelines, and industry guidelines are consistent with OECD. The Ministry of Agriculture, Forestry, and Fisheries (MAFF) issued the first regulations on environmental release of plants in the summer of 1989 (103). Government guidelines emphasize a step-by-step approach to field tests and a case-by-case basis for approval (94). USDA has worked with MAFF on how to conduct reviews and in a consultative group on monitoring. Japan's environmental directorate is looking at microbiological field releases. One field test has been approved to date in Japan; Japanese companies are requesting field trials in Mexico (58).

Recognition of the importance of facilitating field trials is growing in Japan. In the second half of 1990, for example, Japan's MAFF announced its intention of or-

ganizing an incorporated association of over 100 Japanese biotechnology-related companies. In addition to promoting biotechnology in relevant industries. the Society for Techno-innovation of Agriculture, Forestry, and Fisheries (STAFF) is expected to be involved in promoting and authorizing field trials of genetically modified organisms (45). In addition, Japan's first isolated. open-air field site for transgenic plants has been constructed in Tsukuba, Ibaraki Prefecture, by the National Institute of Agro-Environmental Science (NIAES). NIAES scientists plan to test environmental effects of tomatoes engineered to resist the tobacco mosaic virus.

Developing Countries

In general. developing countries have neither biotechnology regulations nor focused biotechnology staff in their regulatory agencies. One relatively unusual example of activity is the recent formtaion of the Genetic Engineering Approval Committee in India. The group regulates the production and release of genetically engineered organisms and potentially harmful microorganisms (76). A variety of efforts from the developed countries, some based on differing premises, are being made to include developing countries in current regulatory approaches.

The early stages of harmonization may take place quite naturally in developing countries that have some serious interest in biotechnology. Such countries tend to send representatives to the United States to learn about approaches taken here. APHIS-BEEP for instance. has exchanged information with China, India, Mexico. Costa Rica. Brazil, Argentina, Chile, Nigeria. Kenya, Zimbabwe, Thailand. and the Philippines on regulatory philosophy, mechanisrms by which that philosophy is implemented, and ways to handle risk assessment and risk management. USDA has held a variety of conferences on related topics, which are well attended by international representatives.

Various U. N. agencies are exploring different avenues through which to assist technology transfer of biotechnology to developing countries while safeguarding environmental and human health. The U. N. Industrial Development Organization (UNIDO) has developed a voluntary code of conduct to provide guidance for introducing biotechnology products into developing countries. The World Bank has hired a biotechnology advisor to consider biotechnology issues with the Consultative Group on International Agricultural Research (CGIAR). although most of the 18 CGIAR centers are not yet close to field trials. The National Research Council has published a panel report on "Plant Biotechnology Research for Developing Countries. * Some developing world observers question the appropriateness of automatic wholesale adoption of stringent regulations by developing countries (42).

POLICY ISSUES

Jurisdiction and Coordination

Mechanisms of Coordination at the Federal Level

The 1986 Coordinated Framework, described earlier, was a crucial step in establishing and clarifying jurisdictional authorities for a new technology with diverse applications. To further clarity jurisdiction as biotechnology matured toward products, and to help Federal agencies formulate regulations and guidelines based on existing statutory authority, the Biotechnology Science Coordinating Committee (BSCC) was established by the Office of Science and Technology Policy (OSTP). (50FR 47174-47195, November 14. 1985). BSCC was charged "to monitor the changing scene of biotechnology and serve as a means of identifying potential gaps in regulation in a timely fashion, making appropriate recommendations for either administrative or legislative actions.

Until recently, the BSCC provided a forum for senior policy officials from USDA, EPA, FDA. NIH. and NSF as they attempted to coordinate policy. promote consistency in review procedures, and identify key issues. One outcome of this forum was the interagency funding of the 1989 National Academy of Science (NAS) report, ''Field Testing of Genetically Modified organisms: A Framework for Decision-Making." The BSCC also has helped to resolve jurisdictional conundrums, such as whether EPA or USDA is the lead agency in cases of dual jurisdiction. Despite such positive contributions, however, the BSCC had difficulties achieving consensus on important issues such as risk assessment and management, levels of oversight appropriate for certain organisms. definition o! deliberate release, and coherent standards for oversight (11). These difficulties arose in part because different agencies have different statutory mandates and built-in approaches to regultaion. BSCC also was criticized for its ''closed-door' deliberations and for ''rneddiling" in regulatory agency affairs. Nonetheless. the committee helped initiate formulation of broad principles for regulation (27).

In the absence of agreement within the BSCC, Dr. Allen Bromley. director of the Office Of Science and

Technology Policy, decided that the identification of organisms subject to Federal oversight ''had policy implications beyond the jurisdiction of the BSCC" [55 Fed Reg. 31,120 (1990)] and the issues should be addressed by the appropriate policy body—the President's Council on Competitiveness. Moved under the aegis of the Working Group on Biotechnologyof the Council on July 31, 1990, a "scope document" pertaining to initial releases of biotechnology-derived organisms into the environment was published for public review and comment [55 FR 147, 31118 (1990)] by the Office of Science and Technology Policy. The document, ''Principles for Federal Oversight of Biotechnology: Planned Introduction into the Environment of Organisms with Modified Hereditary Traits, ' proposed principles for ensuring the safety of planned introductions, while still not unnecessarily inhibiting the process. Certainly, interagency disagreement has existed. It has been said, however, that the extent of collaboration on biotechnology issues among Federal agencies that took place in the drafting of the Principles is unprecedented (61).

The scope document expands on the Coordinated Framework; its criteria for regulatory oversight are risk-based, with the objective of differentiating between organisms that do and do not require oversight at various levels of jurisdiction. Federal agencies may implement the criteria in their own ways as they categorize organisms according to the risks associated with environmental release and thus can be excluded or exempted from oversight. Some introductions may be considered similar to preceding, safe introductions; for others, risk information or current regulations make additional Federal oversight unnecessary. On the other hand, unfamiliar organisms or organisms that might present a risk not yet assessed would be subject to an assessment (62).

The scope document considered all organisms with deliberately modified hereditary traits as potentially subject to oversight, regardless of the techniques used to produce them. However, exclusions from such oversight should be granted to introductions posing no risk. Examples include: plants and animals produced through natural reproduction or breeding and microorganisms modified by chemical or physical mutagenesis or the transfer of nucleic acids through physiological processes. Such exclusions are based on previous safe experience with products produced with these traditional processes. In addition, organisms produced by other processes, including recombinant DNA techniques, should be exempt from oversight if they pose no greater risk to the target environment than parental strains that are considered safe.

An extremely broad class of organisms potentially is subject to oversight. In this sense, the products of new biotechnology are not singled out as inherently more risky than those resulting from nonmolecular techniques such as plant breeding (55 Fed. Reg. 147,13 1118 (1990). Nonetheless, exclusion from oversight, based as it is on criteria of familiarity, is possible for virtually all methods of modification except those using molecular or rDNA techniques. Just as operationally, regulatory examination to date has been triggered by the process of recombinant DNA, in the near future, at least, other novel techniques are equally likely to draw the attention of regulators, if only because they point to the presence of a novel product. The apparent contradiction between this reality and the scope documents attempt to focus on products, not processes, mirrors the conflicting views of those scientists and industry representatives who maintain that the products of biotechnology pose no unique risks; and those who believe that the novel characteristics of biotechnology products and scientific uncertainty about risks warrants extra caution. The ''product versus process' debate continually resurfaces. An exceedingly fine line divides regulation of a biotechnology *product* and regulation of a process. USDA's approach to the balancing act between process as trigger and product as legitimate focus is to review any implications for the safety of the end-product that might arise from the technique applied. For example, clean characterization of the gene transferred is particularly important if the genetic material is taken from a plant pest, so it is clear that no unwanted genetic information is transferred.

This pragmatic approach should be readily applicable to novel techniques in addition to recombinant DNA itself. Using the safety of the product as the focus for review allows regulators to take into consideration any and indeed all pertinent aspects of any techniques or processes leading to novel products, thereby avoiding gaps in coverage. Algorithms for using risk as the trigger for oversight have been and are being developed (69). Some companies. well advanced in their product development, desire regulations that effectively will end the product v. process debate so that progress can be made in bringing products to market.

On February 27, 1992 the Office of Science and Technology Policy published in the Federal Register (vol. 57, No. 39) its revised scope document, describing policy on "Exercise of Federal Oversight Within Scope of Statutory Authority: Planned Introductions of Biotechnology Products Into the Environment. " A principal change from the draft published earlier is the elimination of a previously controversial exclusion category—exclusion for

conventional technologies. By eliminating this exclusion from oversight, some policy makers believe the new scope document is more consistent with its own premise, i.e., that no special risk is attached to the recombinant DNA modification process. Oversight of conventional and new technologies is, however, left to the regulatory agencies.

Agencies are continuing to craft regulations and guidelines in response to the scope document's policy directives that existing statutes provide sufficient authority for adequate regulation and that regulation should be risk-based. EPA, for example, is crafting its regulations for biotechnology; regulations under TSCA still have not been finalized. USDA's ABRAC guidelines for research have been put out for comment. As biotechnology moves to the commercialization stage, where releases could occur on a large scale, amendments may or may not be needed.

Coordination among agencies is critical, as regulatory policy evolves to avoid redundancy and delays in policymaking. Several interagency bodies will play a coordinating role, including the Office of Management and Budget (OMB), BRS (the research-oriented successor to BSCC), the National Biotechnology Policy Board. and the President's Council on Competitiveness (COC).

The Biotechnology Research Subcommittee (BRS), of the Committee on Life Sciences and Health, is part of the Federal Coordinating Council on Science, Engineering, and Technology (FCCSET). Formed in 1990, the BRS succeeded the BSCC and focuses on issues such as research priorities, needs, and training rather than on policy issues. As an interagency body, the BRS includes the acting heads of the NIH and the FDA, with additional representatives from the State Department and its Agency for International Development. the EPA, USDA. NSF, NASA, Department of Commerce, Department of Defense, Department of Interior, Department of Energy, Office of Management and Budget, and OSTP.

The Administration's final policymaking body for biotechnology, the Council on Competitiveness (COC), includes the Vice President; the President's Science Advisor: White House Council; the Secretaries of HHS, Commerce, Defense, Treasury, Energy, and Agriculture,; the EPA Administrator; the NSF Director; the U.S. Attorney General; and the Chairman of the Council of Economic Advisors. Biotechnology issues will be considered first by the Council's Working Group on Biotechnology.

A significant action in biotechnology by the COC was the publication of its "Report on National Biotechnology Policy' in February, 1991. ***(See*** box 7-C.) The thrust of the report is that biotechnology products essentially are equivalent to products developed through other procedures and that, therefore, the domestic biotechnology industry should not be burdened by ''excessive restrictions. The report also suggested that the COC and its Biotechnology Working Group take the lead in coordinating regulation of products introduced subsequent to the 1986 Coordinated Framework. The Working Group was also charged with coordinating communication among industries; streamlining review procedures; reevaluating regulations as necessary; and dealing with inconsistencies of international. State. and local policies, regulations, and laws (28).

Responses to the COC Report are predictably diverse, ranging from those of environmentalist groups, who still call for special regulatory attention to biotechnology, to industry representatives, who hope that the report will push toward clearly defined regulatory criteria. thus enabling company executives to estimate accurately the time and costs involved in winning approval for testing and marketing biotechnology products (2).

The new National Biotechnology Policy Board, established by the Administration according to the instructions from the Senate Appropriations Committee in its report on the 1989 HHS budget. will play a purely advisory role. Its public members as well as voting governmental members report to the HHS Secretary (100). The Board will review research. nonconfidential privately funded biotechnology activities. and the development of industries and products and make recommendations to the President and Congress (84).

Comparison of USDA and EPA Approaches to Biotechnology Oversight

Each of the two major agencies involved in biotechnology oversight must, under its own specific mandates, attempt to provide technically sound judgments on risk, while expediting regulatory procedures and developing a foundation of experience on which to base future judgments. Types of information used by EPA and USDA to make regulatory judgments include 1) that required for the evaluation of deliberate release applications or notifications, 2) experience base, and 3) application and notification processes. By far, the largest experience base with regard to field trials is that of USDA-APHIS in working with transgenic plants. In terms of products licensed for real-world use, USDA's largest experience base is with category I (animal biologics). While EPA's Office of Pesticide Program deals

Box 7-C—Council on Competitiveness
Report: Four Principles of Regulatory Review

1. Federal Government regulatory oversight should focus on the characteristics and risks of the biotechnology product-not the process by which it is created.
2. For biotechnology products that require review, regulatory review should be designed to minimize regulatory burden while assuring protection of public health and welfare.
3. Regulatory programs should be designed to accommodate the rapid advances in biotechnology. Performance-based standards are, therefore, generally preferred over design standards.
4. 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-shouid use performance standards rather than specifying rigid controls or specific designs for compliance.

SOURCE: The President's Council on Competitiveness, Report on National *Biotechnology Policy*, 1991.

with **increasing numbers** of microbial pesticides, the Office of Toxic Substances has had few recent applications for planned introductions of recombinant DNA modified microorganisms and the subject matter of its applications has been limited narrowly to nitrogen fixation. The time required for, and general types of steps involved in application and notification processes are roughly comparable for the two agencies. From 3 to 6 months seem to be required for these processes. APHIS, with its large body of experience, probably has the most regularized review processes today.

Coordination With States

A few State governments independently have promulgated deliberate release regulations (see State and Local Government). Most feel that effective coordination with the Federal agencies will suffice.

The COC's Biotechnology Working Group is charged with coordinating Federal laws, regulations, and poilcies with those at the State level. As a practical matter. the task of coordination lies with the individual agencies themselves. USDA and EPA use State input in different ways. Based on its traditional network of connections with State-level agricultural departments, USDA has explicitly incorporated State review applications for field tests into its overall review process. USDA also has brought together Federal and State regulators of biotechnology in annual national meetings. EPA, on the other hand. does not have a tradition of elaborate, direct connections to State environmental departments. Recently. EPA has attempted to identity biotechnology "point people" in State environmental departments (68). However. many State regulators may not feel "bin the loop" in terms of knowing what EPA is doing in biotechnology regulations and how their State should play a part (64, 93). EPA pubilcty acknowledges the importance of receiving State input. **but procedures** for gathering this input are far less for**malized than is the case in USDA.** Still, EPA's TSCA Office did consult with State regulators for each of Biotechnica's seven field test requests (32). For the relatively few release PMNs handled, EPA-OTS has developed an informal set of steps to:

- **include telephone contact with the appropriate State regulatory** agency or agencies concerned with a particular submission;
- make available a nonconfidential version of the PMN on request;
- include State personnel in a site visit;
- make available public docket materials on request;
- provide opportunity for State personnel to comment on the Agency's draft risk assessment; and
- give State personnel a draft of the TSCA section 5(e) order. with conditions for the field test (30).

Coverage

Scope

Possible Gaps—Some concern has been voiced that under the current allocation of regulatory responsibility for biotechnology, some releases might slip through the cracks. An often cited potential gap in jurisdictional authority pertains to genetically engineered plants that are neither pesticidal nor themselves plant pests. In such a case, where neither EPA-FIFRA nor USDA-APHIS has clear responsibility, the question has been raised, who would have oversight over field trials'! (35)

In the past, regulatory oversight for field trials largely has been allocated with "traditional" recombinant DNA in mind. Even newer techniques have arisen. however. such as biolistic or gene gun approach to injecting genes into organisms. How will the new techniques being de-

veloped fit into the oversight structure'? Should they be? Can the experience base derived from "traditional' recombiant DNA be applied to new techniques?

As the science of biotechnology advances. it is likely that genes of more than one trait will be inserted into a plant variety being developed. This mixing of genes could lead to an overlap of authority. For example. a *Bacillus thuringiensis gene* for pest resistance could trigger EPA review under FIFRA in a food crop; a gene for a nutritional component could trigger FDA responsibility: while the use of a plant pest vector could trigger USDA oversight. Even though USDA-APHIS and EPA-FIFRA have a history of cooperation, some difficulties could arise in treating such situations. A company might have to submit three packages for review due to the different roles of each agency. This could comprise a regulatory burden.

It also has been asserted that. apart from federally funded research, Federal oversight of genetically engineered animals is limited to selected invertebrates and animals with genetic material from plant pests. While most livestock animals would probably generate little risk to the environment if genetically engineered, aquacultural species have been cited as potentially more problematic. The possibility of escape of genetically engineered fish from outdoor aquacultural ponds to watersheds. where interbreeding with natural populations could occur. gives rise to ecological concerns *(35). (See* box 7-D.)

Thus, while some observers are concerned about possible limits to and gaps in Federal oversight of transgenie plants and animails. some assert that by far most cases of release of transgenic *animals wuld* **be covered** by USDA Science and Education (for research), USDA-APHIS (for plant pest invertebrates and animals carrying animal diseases). FSIS or FDA (for use of animals as food). FDA and APHIS (for animal drugs and biologics). and the Public Health Service (for interstate movement of etiologic agents that carry human disease.) Only research not receiving Federal funding, in which the animal is not a plant pest. not an agent for animal or human disease, not given a drug or biologic. and not to be sold as food (92) could constitute gaps in oversight of transgenic animals. Thus, while some observers are concerned about possible limits or gaps in Federal oversight of transgenic plants and animals, others expect the natural evolution of oversight to occur. It remains to be seen whether the regulatory framework is flexible enough to catch such cases, and how, for example, the system handles genetically engineered plants that are neither engineered for pest resistance nor themselves plant pests.

Current and Projected Treatment of Such Organisms and Products—For its part, USDA-APHIS seems to be willing to extend its range of oversight regarding genetically modified plants. Plants' abilities to act as pests can be viewed in a broad context. Potential disruption of the environment by novel plants could in the broadest sense qualify a plant as a potential pest. Some environmentalists feel that USDA already is stretching its statutory scope to deal with biotechnology, and may not have the authority to extend its scope still further.

Box 7-D—Fish Regulations: Something To Carp About?

The gene that regulates growth in the rainbow trout was transferred into carp by a team of scientists from the University of Maryland, Auburn University, and Johns Hopkins University. In experiments to date, the carp have grown 20 to 40 percent larger than their unmodified relatives. Among some participants in the fish farming and research industry, enthusiasm runs high over the prospect of impacting the Nation's $900 million fish farming industry and, eventually, helping to feed the hungry of the world. Others emphasize caution. The American Fisheries Society, composed of fisheries scientists, has recommended close monitoring by the Federal Government, tight control over the environmental release of a modified fish, and sterilization of the fish (75).

The transgenic fish project was started in 1986; in February 1990, USDA approved the project but protests from four public groups persuaded the North Auburn Fisheries Research Unit, at Auburn University, the site of the **project, to redesign the pond.** The new place was approved by USDA in November 1990, pending inspections early in 1991.

Current design places the fish in 10 outdoor earthen ponds, set on concrete stabilizers, surrounded by chain-link fences covered with bird netting, double and triple screened drains and ditches. Beyond these is a 17-acre lake filled with predatory fish, and then a pond with chemical and mechanical barriers before the local creek (1).

SOURCE: Office of Technology Assessment, 1992.

Exemptions—Exemptions, as opposed to accidental gaps in coverage, are cases or classes of planned introductions deliberately excluded from regulation. Many questions underscore the dynamic, evolving nature of the regulatory situation. For example, will—or should—the trend toward examining new products of biotechnology carry over to the products of ''traditional field trials. which now are exempted implicitly from review'? Or, as novel techniques become more familiar, will they be less likely to serve as triggers for product review? In other words, will we learn enough to exempt certain products resulting from certain biotechnology techniques'?

The NIH RAC has relaxed its recombinant DNA Guidelines as an increasing experience base has indicated the appropriateness and safety of so doing. The 1989 National Research Council's report on biotechnology endorsed such an experiential approach to environmental releases:

> As field tests are performed, information will continue to accumulate about the organisms. their phenotypic expression, and their interactions with the environment. Eventually, as our knowledge increases, entire classes of organisms may become familiar enough to require minimal oversight . . . (73).

The 1990 draft Scope principles reinforced the idea that information-based familiarity can lead, when appropriate, to exclusion from oversight. Both EPA and USDA endorse the concept that biotech oversight can evolve on the basis of information gathered. Already, these agencies are beginning to exempt from review or expedite review of certain classes of organisms or products if certain conditions are met (65).

EPA Definition of a Microorganism as a Chemical Compound

The application of TSCA to biotechnology has raised some controversial and as yet unresolved issues. Paramount among these concerns is the inclusion of biotechnology products under the definition of a chemical substance, whence EPA draws its authority to regulate genetically engineered microorganisms. Although it is clear that DNA molecules can fall under the definition of chemical substances, it is less clear whether the host organism can be so defined. On the one hand, Witt writes: "Calling microorganisms chemicals is tantamount to calling chemists chemicals—or regulators chemicals. On the other hand, some in industry feel strongly that microorganisms have uses that are directly connected to their chemical nature and that EPA jurisdiction is very reasonable (107). EPA's interpretation has on occasion been called "ripe for litigation" (53).

In any case, it is unclear "whether the scheme of regulation envisioned and currently employed for conventional chemicals is suitable for oversight of biotechnology' (48). Regulatory approaches for chemicals may be difficult to apply to living organisms. Indeed, the fact that TSCA regulations for biotechnology products have not yet been finalized, despite having gone through various iterations, may result in part from the difficulties inherent in manipulating rules conceptualized for chemicals into rules appropriate for living organisms, although EPA has reviewed microbial PMNs under TSCA since 1986. Other problems may include technical difficulties in defining ''new organisms, interagency disagreements, interpretation of 'commercial purposes, and the small-quantities exemption. Nonetheless, the intent of Congress that TSCA serve as gap-tilling legislation seems to invite its use for some biotechnology products that would otherwise have no obvious regulatory home. From the coordinated framework, the role of TSCA in biotechnology seems to have been accepted. on at least an operational level, even it' the broad definition of a chemical compound has not been universally popular.

The trigger under TSCA for PMN is manufacture of a chemical, not the issue of safety. Therefore, when this traditional trigger for TSCA is applied to biotechnology, it is not consistent with the emphasis based on technical risk in the Scope Principles. It is often argued, however, that since all new chemicals must be reviewed. no implications of risk are ascribed automatically to biotechnology products falling into this net.

Commercial v. Research Authority

EPA—Because TSCA is a commercial statute, it arguably does not apply to the deliberate release of genetically engineered microorganisms in nonindustrial settings. EPA currently requests industry to comply voluntarily with the PMN requirements for commercial R&D involving field test releases with intergeneric microorganisms. Academic researchers performing comparable releases may be seen as left out of the loop, in a regulatory limbo. Congress expressly exempted small-scale research and development from TSCA authority. Much depends on the breadth of EPA's interpretation of "commercial purposes. For example, academic research may be colored by commercial intent because it maybe funded by an industry source: because patent rights are assigned to a company for commercial development; or even because a researcher's home institution receives private-

sector funding. One possibility is that all field test releases will count as commercial in intent. However, problems may arise with a broad net approach. Other agencies, as well as universities, may question the validity of this approach. EPA's possible move into the R&D laboratory under a similar approach is likely to arouse fears of excessive layers of bureaucracy among laboratory researchers.

USDA—The possibility of EPA penetrating further and further into the realm of research, despite its commercial mandate, has a counterpoint: USDA appears to be exploring ways to step back a pace from its review of field trials conducted as academic research. The agency's "Proposed USDA Guidelines for Research Involving the Planned Introduction in the Environment of Organism With Deliberately Modified Hereditary Traits." (FR56 (22):4134–4151) seems to place much of the weight of the research review process at the institutional level, with the goal of minimizing the weight of bureaucracy on researchers while still ensuring safety. The agency's Agricultural Biotechnology Research Advisory Committee (ABRAC) played a substantial role in developing these guidelines. It is important to note that, in any event. these guidelines are just for USDA-funded research; APHIS still supplies the principal regulatory coverage.

Criticism of the current situation regarding research includes alleged confusion over agency jurisdictions. For example, when Biotechnica International field tested genetically engineered nitrogen-fixing bacteria. it did so under a 1989 consent order from EPA. However, when a researcher at Louisiana State University sought to do followup studies at the site, State officials, various Federal officials, and ABRAC became involved as EPA oversight and jurisdiction became less evident. EPA clarified its position with State officials, and USDA agreed that EPA would maintain jurisdiction until it chose to relinquish that jurisdiction. While the main question appears to have been over the research value of continuing to monitor the site. rather than any safety question. it demonstrates some degree of uncertainty over jurisdiction (26).

Potential Impacts of Regulation

Negative Impacts

Questions have been raised regarding the short-and long-term impacts of' the regulatory climate on research. It is frequently postulated that academic researchers do not possess the organizational whet-withal to proceed through a regulatory maze, and may find the bureaucratic and financial weight of regulatory approval procedures so burdensome that they will choose not to carry experiments through the field trial stages (74). This perception could block research at a key step, since the field trial is the stage at which * 'the rubber meets the road, at which the predictions of the lab are tested in the real world. The impacts on research of the rulemaking process in Federal regulation of biotechnology were explored in a national survey conducted in 1989 (52, 83). Of 355 responses to the question. ''Have you ever been discouraged from conducting field tests with genetically modified organisrns?," 16 percent said yes. Among private-sector responders, 23 percent felt they had been constrained. Some 12 percent of responders replied that they had chosen not to proceed with a field trial even though they had a genetically modified organism ready. Legalities, uncertainties about regulation, time needed, and paperwork required were cited as reasons for the decision not to proceed (52. 83). Criticism has been leveled as to the methodologies employed in the survey. Whether or not the percentages point to a dramatic ''regulatory burden on research seems open to interpret at ion.

Some feel that the survey captured a real reluctance among some researchers to go through the field trial. In any case, it is not clear that regulation rather than tough resource allocation decisions drives the decision to delay (or forego) field trials (83).

A 1990 survey based on personal interviews of 35 researchers and regulatory affairs specialists revealed overwhelming agreement that the coordinated framework is working and that APHIS is helpful and timely in its response to permit requests, while EPA seems to be improving. Most responders, however, asserted that biosafety and biological monitoring protocols were overly cautious, with potential implications for allocation of personnel time (16).

A third study surveyed 430 recombinant DNA scientists regarding their perceptions of the influence of activist pressures on recombinant DNA research. Some 63 percent view current safety mechanisms as adequate and 26 percent view them as overstringent; many perceive public controversy and litigation as having led to unwarranted obstacles in the regulatory arena (81).

A premise of USDA's Proposed ABRAC Guidelines is that the local Institutional BioSafety Committees (IBC's) can provide helpful advice to academics, streamlining the regulatory procedure. According to the level of safety

concern, IBC oversight ranges from simple notice to IBC review and either approval or disapproval by the IBC and the USDA. Since IBC's previously have dealt principally with laboratory-contained experiments, they may require training to play a helpful role at the field trial stage; more agriculturally and ecologically trained members will need to be added. The University of California system-wide biotechnology program has sponsored an educational meeting for institutional biosafety officers who can work with the IBC's on matters of deliberate release (43).

Possible Positive Impact on Research

Although regulations of genetically engineered organisms may possibly inhibit one line of research (field trials). it may stimulate another—ecological research. As risk assessment methodologies are being devised for evaluating releases of recombinant DNA modified organisms into the environment, ecologists and population biologists are turning their attention toward related questions. The Ecological Society of America report on deliberate release describes a pressing need for interdisciplinary research (99). The concept of deliberate release has provided a compelling focus for questions of ecological community dynamics, migration of genes into populations, evolutionary change, and other fundamental problems. Furthermore, many researchers are stimulated by the opportunity to channel their research toward a useful analysis. Such lines of work do not fall neatly into most categories of research funding; thus funding sources may need to adjust their emphases since this work has an important role to play in the evolution of agricultural biotechnology. The 1990 Farm Bill addressed this need by setting aside funds for risk assessment research, equaling 1 percent of whatever the department spends in biotechnology research. Questions pertinent to risk assessment research, as well as the relationship between ecological research and risk assessment are described at greater length in chapter 8.

As guidelines are finalized and disseminated, and risk-assessment research proceeds, regulatory uncertainty should be reduced for researchers. With reduced ambiguity, as well as steady increases in information and experience, researchers may well venture more boldly in greater numbers into the field trial stage. Institutional BioSafety Committees may become better versed at giving advice and assistance to researchers, as may other university offices and field trial supervisory staff. Thus, the potential negative impacts on research **could** prove to be short-lived. In the future, technology transfer of genetic engineering advances may be mediated through industry-sponsored, university-based field trials. Although many companies would prefer to keep work 'bin-house. ' others may place greater value on the objectivity y of university research and the capacity of university facilities. While possible contlicts of interest would have to be resolved, both parties could thus continue to contribute to field trial research. (See box 7-E.)

The positive stimulus of the regulatory climate to ecological research may be at or nearing its peak at this time: in the short- and mid-term, assessment methodology will be developed and refined. Data gathered will be synthesized. Eventually, in the long run, assessments of the results of releases may well become yet one more subfield of ecological research, one more way to approach interesting problems that exist in a real-world context.

Impacts of Regulation on Agribusiness

Only half of the agricultural biotechnology companies surveyed by Burrill and Lee (7) consider Federal agency jurisdiction over the testing and selling or distribution of biotechnology products clear-cut. Nonetheless. only a minority believed that they had experienced Federal regulatory delays. Some 16 percent found delays in relation to product testing; some 16 percent found delays in relation to selling and distribution (7).

For the most part, at least the large agricultural companies find that the APHIS system is predictable and works well, without inhibiting industrial activity (38, 40). Moreover, even those concerned with the competitiveness of industry also acknowledge the role of regulations in ''shielding" industry from unfortunate occurrences that could. by thus capturing public attention. slow commercial product development (79).

At least one small start-up agricultural biotechnology company, Calgene. has fared well under the current regulatory structure; between November of 1987 and October of 1990, Calgene received approvals from USDA for some dozen field trials for three genetically engineered crops in five States; the average approval time of 113 days is viewed as extremely reasonable. Representatives of Biotechnica, Pioneer, and Northrup King have also testified as to the effective workings of the APHIS system for genetically engineered plants (89).

It has long been alleged that the strategic business plans of some smaller companies may have been, and may continue to be, influenced by the regulatory climate, as well as by public concern over biotechnology. The company Mycogen, for instance, deliberately used killed rather than living recombinant bacteria as pesticides; Ecogen

Box 7-E—EPA Research and USDA Research

EPA has established a research program focused on the use of microorganisms in biotechnology and intended to meet the technical needs of the regulatory program. The six areas of research are as follows:

1. development of methods for detecting, enumerating, and analyzing microorganisms in complex samples from a variety of real-world habitats;
2. development of data and predictive models related to transport or spread between the point at which release occurs and other locations;
3. determination of potential for survival, growth, or colonization of released microorganisms under various conditions and environments;
4. assessment of factors affecting stability of genetic material and likelihood of gene exchange;
5. detection of any negative environmental response; and
6. criteria and methodologies for controlling risk.

Inhouse EPA scientific staff are developing a complementary extramural research program. Regular independent peer review is intended to keep the orientation of the research toward the risk assessment needs of the regulatory staff while still encouraging scientific quality and contributing basic information on microorganisms in the environment (67). The Research Office is thought to have worked very closely with the FIFRA staff, directing research towards assistance in developing evaluation procedures. The biotechnology assessment budget, however, was cut in 1991.

The 1990 Farm Bill (S. 2830) contained provisions governing USDA research. In addition to promoting Federal funding for "high-priority research" in areas including biotechnology, the bill created a Biotechnology Risk Assessment Research Program. A competitive research grant program is authorized for environmental assessment research "to the extent necessary to help address general concerns about the environmental effects of biotechnology"; research is authorized that will assist regulators as they develop policies on planned release. Eligible areas of research include: biological and physical containment methods, methods of monitoring dispersal of genetically engineered organisms, and gene transfer between genetically engineered organisms and related cultivated or wild species. The Secretary of Agriculture is required to consult with APHIS, ABRAC and OAB on specific areas of research (44).

SOURCE: Office of Technology Assessment, 1992.

has developed products with naturally occurring or nonrecombinant organisms (33). DNA Plant Technology (DNAP). which has to consider agricultural and food regulations, has deliberately adopted a "bifocal' business development approach, developing products through innovative uses of nonrecombinant technologies, such as tissue culture, as well as exploring the potential of recombinant plants. This reduces their vulnerability should regulations for the commercialization of biotechnology prove untenable to them. While DNAP currently has one regulatory staff member, it foresees the likelihood of adding more (20). With training in use of the "Intelligent Form Generator, " a software program designed by the National Biotechnology Impact Assessment Program to walk scientists through the production of an application, the NBIAP program director predicts th\aut a field trial application can be generated in less than 2 hours. Without this computer aid, he estimates. completing an application could take 1 to 2 months, with a staff, and up to 6 months without a staff (3). Resolution of regulatory processes and ambiguities will be critical as companies ready themselves to move to large-scale use of recombinant plants.

One point raised by the private sector is the need for clarification of EPA role under FIFRA regarding transgenic plants with pest-resistant properties. Clarification of scope of review, preparation of a guidance document on data requirements, and harmonization with APHIS are regarded as necessary to reduce regulatory uncertainty for industry (37, 109).

The vast magnitude of trials necessary for the development of any new crop variety makes it particularly important to clarify regulatory roles and requirements with respect to recombinant technology. The seed company ICI Garst, for example. has compiled figures on the development of corn varieties (82). In 1990, some 350,000 plots were used for nonrecombinant plants. The following numbers demonstrate the sheer number of lincs involved in generating new varieties in 1990 and expected in 1994 (table 7--l).

Table 7-4—Genetic Lines Needed for New Corn Varieties

Stage of developement	Number of Lines 1990	1994
New inbreds	79,000	92,000
Preliminary hybrids	34,000	39,000
Advanced hybrids	5,600	8,000
Experimental hybrids	1,600	2,400
E - hybrids	125	150
R - hybrids	30	30
N - hybrids	10	12
New commercials	9	9

NOTE: E-Hybrids are hybrids exchanged among breeders with the company; R-Hybrids are regional uniform strip tests; N-Hybrids are national uniform strip tests.

SOURCE: ICI Garst Seed Co., 1991,

Obviously, were genetically engineered plants involved in such trials, and if these had to pass a complex set of regulatory requirements, agricultural companies would be forced to weigh their options very carefully. The costs of meeting regulatory requirements might prohibit them from bringing promising recombinant plants to full commercialization as new varieties. On top of the sheer numbers involved, another key point is that multitrait selection is the normal approach to plant breeding and development of improved varieties; the approach is to improve a number of traits concurrently; multiple recombinants might be combined in different trials. **Furthermore,** seed from the later stages of testing is sold. Agricultural practices do not separate variety from variety; all seed corn is stored in grain elevators in bulk. Clearly this is not a set-up readily amenable to special treatment for biotechnology. The restrictions governing small-scale field trials would be logistically infeasible. Developing even a conventional hybrid can cost approximately one million dollars. Although biotechnology can improve efficiency in the early research stage, by making new genes available quickly and precisely, industry emphasizes that the rigors—and the orders of magnitude-of the hybrid testing scheme will not change.

Thus, the regulatory climate will have a significant impact on whether or not biotechnology is widely used as a tool in the seed industry. Assessments of the impact of regulations on industry will need to take this into account. A responsible but reasonable and clear regulatory path towards commercialization will be crucial to the successful implementation of biotechnology in agriculture.

Public Participation

The U.S. public today questions the use of new technologies . Based in part on general environmental awareness, skepticism about science, and negative experiences with the chemical industry and the nuclear power industry, this questioning attitude is now a potent force. Today, many analysts of biotechnology sound the clarion call of public participation; if the public is to accept biotechnology, people must have access to information, and be able to play a role in debating controversies, and achieve a sense of trust in policy makers (54, 90). Federal regulatory agencies sometimes do not receive the full trust of the public. State agencies tend to be somewhat better trusted. When Federal agencies share information and involve the public, they are likely to build confidence in their procedures. FDA attempted this by publishing scientific information relevant to its decision on bST in *Science.* The meetings for media and other segments of the public held by USDA represent another example of public confidence-building through involvement. A positive public perception of biotechnology is obviously critical to its growth; beyond this, participation by the public **can contribute to the beneficial development of biotechnology; questions** raised can indeed be pertinent. Although the public has channels through which it can participate in regulations. it may not be aware of them.

For example, public input into the review process for field trials is officially ensured through notifications in the Federal Register. Environmental assessments and pending approvals are so published. Clearly, however, the ‘‘general public’ does not as a rule pore through the Federal Register. Various environmentalist and public interest groups do, however, and can bring matters to a wider audience. In some cases, such groups challenge approvals. For example. ice field tests (102) of ice-minus bacteria used to protect crop leaves from frost in 1987 were significantly delayed due to such challenges. A very narrow nongovernment subset of the public is brought into the picture when scientists external to the agencies perform scientific reviews to augment staff review in problematic cases.

Public input also can arise when States receive field trial applications from the Federal agencies. Depending on an individual state's review process, representatives of the public may well participate. The 1990 Special Workshop for State Agencies, “State Oversight of Biotechnology, came to consensus on the importance of a public participation component for any State biotechnology task force (39).

At the institutional level, public membership is mandated for Institutional Biosafety Committees (IBC’s), which seem likely to be called on more and more frequently to

examine plans for field trials at an early stage within institutions.

One somewhat sensitive area in terms of public participation is that of confidential business information. As discussed earlier. Federal agencies have the legal right to protect confidential information deemed critical to a company's competitiveness. In fact, companies submitting applications for field trials can submit two forms of an application. one for in-house review. under confidentiality terms. and one with confidential information deleted. for open distribution. Only the few States with legal protection for confidential business information can be sent the complete form. Of course, the more blanks that appear in an application, the more likely that proposal will be regarded with public distrust or unease. To minimize public unease, Federal officials encourage companies to keep their designated CBI to a minimum. Complaints have been voiced when information unnecessarily designated as CBI has been unavailable to the public (35).

Public input into the process leading toward field trials has changed since the early and mid 80s, when court injunctions and vandalism were commonplace. Relative acceptance of the role of field trials and their safety has grown. Indeed, evidence exists that, together with an increased experience base, positive public involvement in biotechnology regulation can expedite the field trial process. (See box 7-F.)

The quieting of local public opposition to biotechnology field trials seems to be evidenced quite widely. The great majority of field trials approved at the Federal and State level have met with little if any opposition by the public (106).

Opposition activity now seems to be directed primarily at special cases. A current example is that of crop plants genetically engineered to withstand particular herbicides, which can then be sprayed readily over the field, as they will cause a problem only for the noncrop plants. Environmentalist spokespeople specializing in biotechnology are far from happy about this as a goal for agricultural biotechnology. In brief, despite industry protestations that this approach allows the strategic use of particularly benign herbicides, environmemtalists see this as a mechanism to excuse, if not encourage, application of environmentally hazardous chermicals. (See Goldburg et al., 1990 (36) for a thorough discussion of antiherbicide tolerance views; also Goldburg, 1989 (35).) Early in 1991, the National Wildlife Federation (NWF) petitioned the USDA regarding Calgene Inc.'s application to field test genetically engineered cotton in 12 States. Calgene's October 1990 application to USDA proposed a 25-site test of cotton engineered to break down the herbicide bromoxynil. Whereas Calgene maintains that use of this cotton would significantly decrease herbicide use. NWF has petitioned the USDA to halt this broadscale testing until a thorough risk assessment has been conducted as to the impact on aquatic ecology and human health (22). In this case, the value question relating to herbicide tolerance begins to be tied to questions of progressively larger scale release. moving toward commercial release.

The responses of public interest groups to large-scale releases may well intensify: it remains to be seen whether other components of the public will take a similar view. such that the current atmosphere of acceptance turns to opposition as commercilazation is approached. Significant factors will include: technical experience base derived f-rem small-scale tests to date, activism on the part of environmentalist groups, media attention. public confidence in the regulatory agencies. and public perception of-—-and education about—biotechnology and risk-benefit assessments.

If decisionmaking is to be informed. education of the public about biotechnology risks and benefits must take place. Many advise that the evolution of biotechnology regulations benefit from the hard lessons of other industries. such as the nuclear industry, and emphasize education of and participation by the public. Thomas Jefferson has been quoted appropriately in this regard: " If we think the people not enlightence enough to exercise their control with a wholesome discretion, the remedy is not to take it from them. but to inform their discretion'" (46).

Public perception of biotechnology has been analyzed by OTA (101), and others (50). Apprehension over the novelty and power of biotechnology is mixed with a desire for the products of biotechnology. Two biotechnology trade associations (the Industrial Biotechnology Association (IBA) and the Association of Biotechnology Companies (ABC) have prepared materials and established committees related to public education. USDA ran several meetings as early as 1987 to work with the media and others toward public eductaion. Many of the Nations State and university biotechnology centers view education about biotechnology as one of their principal roles. Increasingly, high school teachers are taking courses in, and teaching. biotechnology': the media also is becoming more

Box 7-F—Two Experiences With Public Response

In the early years of field trials, 1983-87, two sets of experiments involving ice-nucleating bacteria in California drew local public opposition as well as public interest group opposition. Suits were filed in the case of Tulelake, California, and an injunction was enforced against the University of California researchers until an environmental amendment was made; in the case of Monterey County, the County Supervisors, making use of their zoning authority, banned such experiments for 1 year, forcing Advanced Genetic Sciences (AGS) to go to the Contra Costa County's Board of Supervisors for approval. Although a legal challenge was not upheld, many of the plants were uprooted as vandalism. (AGS had aroused particularly negative response beginning in 1985, when it had tested the bacteria in trees on its headquarters' rooftop, without authorization.) Through the various vicissitudes, the University of California test was delayed from 1983 to 1987; the Advanced Genetic Science's test was delayed from late 1985 to spring of 1987 (102).

in 1988, Biotechnica International received Federal and State approval for a small-scale field test in Wisconsin of *Rhizobium* genetically engineered to increase alfalfa yield for which the PMN's had been filed the year before.

In 1987, Biotechnica had conducted an extensive community relationship program in the county and the state where the field trial was to take place. This program involved: presubmission briefings to opinion leaders; press releases and brochures in layman's language, including a risk-benefit, "Question and Answer" style brochure; public meetings in the county sponsored by the company as well "as attendance by company representatives at State government and legislature committee meetings; and media relations. For the first 6 months, interest was high in the community and a small group of activists opposed the trial. After the last public meeting in the summer of 1987, no further opposition emerged and, despite intense media interest, no demonstrations or protests occurred at the time of the test itself in April of 1988. For subsequent tests, the company has followed a scaled-down program of community relations, with substantially less community interest. The local comfort level with this biotechnology venture seems to have increased significantly (31).

SOURCE: Office of Technology Assessment, 1992.

sophisticated and therefore more able to convey accurately technical and issues in biotechnology.

Problematic Issues

USDA Conflict of Interest?

The criticism has been leveled that USDA faces an internal conflict of interest because it has a dual responsibility to promote research and to regulate in areas of biotechnology (49). USDA officials make the argument that the Department of Health and Human Services is in the same situation, but has the luxury of having its division of' labor more readily perceived by the public as distinct. Within the same Department of HHS. the National Institutes of Health have responsibility for research and the Food and Drug Administration has responsibility for regulation. A comparable, but less visible or publicly understood, division exists within USDA. The Assistant Secretary for Science and Education is responsible for biotechnology research activities (including those of the Agricultural Research Service and the Cooperative State Research Service), whereas the Assistant Secretary for Marketing and Inspection Services is responsible for departmental regulation of biotechnology [delegation of acthority by the Secretary of Agriculture, published July 19, 1985 (Fed. Reg. 29367 (1985).] APHIS and the Food Safety and Inspection Service (FSIS) are the USDA regulatory agencies involved (55). Coordination between the research and regulatory arms of USDA is the responsibility of the Committee on Biotechnology in Agriculture (CBA). The Office of Agricultural Biotechnology (OAB) is set up to develop policies and procedures for research in agricultural biotechnology, coordinate environmental safety review of proposed USDA-supported research with genetically y engineered organisms, provide staff support for the CBA, and provide staff support for the Agricultural Biotechnology Research Advisory Committee (ABRAC). ABRAC in turn is to review research guidelines and proposals and provide scientific advice to research and regulatory agencies in biotechnology (56).

The existence of these committees demonstrates that the research and regulatory arms of USDA do interact. In fact, the agency would be criticized if there were no attempts at coordination, although the degree of coordination actually achieved has been questioned. The co-

existence within one agency of NIH and FDA seem to set a relevant precedent. Conflict of interest may be avoideed within USDA by:outside Crotiques, such as advice from ABRAC and othcr external sources of review. as well as by the perception of. and loyalty to, distinct yet complementray missions on the part of APHIS and Science and Education.

Burden of Proof of Safety

U.S. society today desires a zero-risk society. Arising naturally from this attitude is a desire for regulatory agencies, or science, to prove safety. The agencies are attempting to build databases through small-scale field trials and, by analyzing and extrapolating from such information. to significantly reduce the probability of any risk occurring from larger scale releases. However, absolute proof of safety will never be achieved in biotechnology field releases, just as it will never be achieved in any other dimension of society.

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