Chapter 9

Issues and Policy Options

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INTRODUCTION

In many ways, this is an inopportune time for a new technology to appear on the scene. Negative experiences with the nuclear and chemical industries have made the American public wary of new technologies; confidence in institutions has eroded. For both reasons, relative to technologies of the past, biotechnology has been subjected to extensive and apprehensive scrutiny and regulatory oversight. Probably, many institutions will choose to "go the extra mile" to ensure public confidence as some policy issues are resolved. In making policy decisions, it remains important, nonetheless, to distinguish between the technical basis for assessment and regulation of risk resulting from planned introductions of recombinant-DNA modified organisms and what might or might not be done additionally to maintain public confidence. Particular clarity in this regard is called for when assessing possible costs as well as benefits of new biotechnologies. Balancing safety and institutional credibility against economic competitiveness will be a fine art in much demand throughout the decade.

Adequacy of Knowledge Base for Conduct of Risk Assessment

After several years of experience with planned introductions, there seems to be a growing consensus among scientists that the risks of planned introductions of recombinant-DNA modified organisms into the environment can for the most part be assessed with available analytical capabilities.

The fields of community ecology, population biology, population genetics, evolutionary theory, and agricultural science as well as others have contributed to our current understanding of the ecology of planned introductions. Several decades of research in life history dynamics, competition, characteristics of colonizing species or disturbed habitats, disease resistance, and gene flow have provided a basis for risk assessment analysis today.

Of course, further research will add to current knowledge. Many ecologists and evolutionary biologists already are addressing the research questions generated by planned introductions; scientific presentations and publications on this topic are increasing. With increased research funding, more experiments could be undertaken to focus specifically on planned introductions. This may be especially important now as more large-scale introductions are planned. Research is needed in the fields of community ecology, population ecology, population genetics. evolutionary biology, systematic and mathematical modeling, as well as risk assessment methodologies. Interdisciplinary communication among scientists in these fields will be particularly important for future risk assessment of planned introductions.

The relatively young field of risk assessment, which is concerned with the capacity to identify and weigh risks and benefits in a structured and analytical way, has matured rapidly. Experience with other technologically oriented issues, such as pollution control and food safety, has generated principles and methodologies that can be adapted for planned introductions of recombinant-DNA modified organisms in the environment.

The often heard opinion that it is impossible to assess possible risks of any specific planned introduction sets a tone of apprehension over agricultural biotechnology that is belied by this knowledge base. Ecological understanding combined with risk assessment methodologies make it possible to analyze the potential risk of each introduction before it is allowed to take place. However, if American agriculture is to benefit from biotechnology, need exists for public education concerning the extensive capabilities on which scientists draw to ensure the safety of planned introductions of recombinant-DNA modified organisms in the environment.

Adequacy of Knowledge Base for Science- and Risk-Based Regulations

Reports of the National Research Council, the Ecological Society of America, and the scope document of the Office of Science and Technology Policy (OSTP) and Council on Competitiveness all advocate science- and risk-based regulations of biotechnology's applications. The implementation of such regulations draws on the ability of regulators to conduct adequate risk assessments.

Regulations are implemented through oversight by personnel in Federal regulatory agencies, with varying degrees of involvement by State regulatory personnel. The U.S. Department of Agriculture's Animal and Plant Health Inspection Service (USDA-APHIS) has taken the lead in designing a smoothly functioning process for the evaluation of possible risks and benefits when a specific planned introduction is proposed. Technical information to be provided by an applicant is clearly defined, so that

a thorough, science-based risk assessment can be performed. Technical personnel in fields such as genetics and ecology have joined the staff of USDA-APHIS Biotechnology, Biologics, and Environmental Protection Division, to ensure vigorous assessments. State regulatory personnel are drawn into the process so they can provide additional technical information specific to local habitats and add an additional perspective.

The Environmental Protection Agency's (EPA's) Office of Pesticide Programs has extended its review processes under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) to planned introductions of microbial pesticides; it also cooperates with USDA-APHIS in reviewing proposals for introduction of pest-resistant plants. EPA's Office of Toxic Substances recently has published draft regulations to cover planned introductions of genetically modified microorganisms; significant controversy exists as to whether these regulations are indeed science- and risk-based, or whether they simply single biotechnology out for attention because it is biotechnology. The final status of these regulations, and their implementation processes, are not yet known. State agencies have yet to be pulled into EPA regulatory processes to the extent that they are involved in USDA's.

Managing Risks of Large-Scale Introductions

As agricultural biotechnology moves toward commercialization and large-scale planned introductions, the combination of several approaches can maximize benefits and minimize risk. Technically sound implementation processes for science-based regulations are critical to risk management. Technically competent regulatory personnel must work within a framework of adequate technical information to assess actual risks and base regulations on these risks.

Beyond this, specific scientific and agronomic methods are needed to manage risks of particular planned introductions. These might include mechanisms to isolate modified plants spatially, physically, or temporally; to minimize gene flow from modified organisms into natural populations; or to lower the survivability of modified organisms or nontarget organisms that might incorporate a novel gene. The same knowledge base that has led to the generation of recombinant-DNA modified organisms is now being extended toward managing risks presented by them at an extremely fine and precise level of control.

The effectiveness of such methods can be evaluated through monitoring. Various methods of monitoring are being refined to make possible statistically valid sampling for presence or absence of genes or recombinant-DNA modified organisms in other than the target species or the target environment. As monitoring techniques improve, we can extend our knowledge of the basic dynamics of introduced organisms and genes. This will provide a foundation for assessing and managing any risks associated with planned large-scale introductions.

ISSUES

Extent That Regulations Are Product-Based Rather Than Process-Based

The reports of the National Research Council and the Ecological Society of America stated that the techniques of biotechnology are not themselves inherently risky or unmanageable. (See ch. 8.) In line with these findings, the early Coordinated Framework and the scope principles put forth by OSTP and the Council on Competitiveness recommend that biotechnology should not be regulated as a *process. (See* ch. 7.) Rather, a central tenet for biotechnology regulation is that the various *products* of biotechnology should be regulated, just as are products of other technologies. For example, a biotechnology-derived microbial pesticide should be assessed and managed for any risks offered by that particular product in the same way that a traditionally produced microbial pesticide would be handled. Of course, different specific questions may be asked that are appropriate to the techniques and characteristics of each product, but biotechnology is not to be prejudged as especially dangerous.

The product and process distinction has generated a great deal of controversy in the past. However, as the experience base with biotechnology has grown, the premise of judging each product on its own basis rather than automatically implementing special regulations has gained wide acceptance. The extent to which this premise has been implemented is questionable.

USDA-APHIS

Through its focus on plant pests, USDA-APHIS has been able to include, along with other organisms under its purview, any vector, vector agent, donor, organism, recipient organism or any other organism or product produced through genetic engineering if it can be defined as a pest. (See ch. 7.) This approach also makes it possible for regulated articles to become exempted from

special review, as evidence indicates their safety. This provision is particularly important as large-scale commercialization arises.

Even though the oversight net has deliberately been cast broadly in these early days of genetic engineering, the process of genetic engineering itself is not the trigger for special review by USDA-APHIS. Rather, the product or organism itself—and its salient characteristics, such as the vector involved—is the trigger for review primarily in accord with the scope principles.

EPA-FIFRA

Under FIFRA, the Office of Pesticide Programs (OPP) also has applied an existing mandate to products of biotechnology, not only microbial pesticides but also plants that produce compounds aiding them in resisting pests. (See ch. 7.) By pulling these so-called "pesticidal plants" under the rubric of its oversight for pesticides, EPA-OPP seems in one sense to be focusing on the product rather than the process by which it was generated. However, a question exists as to whether or not "pesticides" is the appropriate category for these particular products, especially since naturally occurring and agriculturally bred plants all produce some antiinsect compounds. To assume authority over plants genetically modified to be resistant to pests, EPA-OPP seems to have chosen to look only at plants that had gone through a biotechnology process, leaving naturally occurring and agriculturally bred pest-resistant plants alone.

EPA-TSCA

Under TSCA, EPA's Office of Toxic Substances (OTS) has promulgated a draft rule for oversight of microorganisms that does not fall under other authority. (See ch. 7.) However, under these draft regulations, essentially all microorganisms other than those modified through biotechnology techniques are automatically exempted from review, whereas those modified through biotechnology techniques are labeled "new" and therefore subject to regulation. When the only products subjected to special review are biotechnology products, a question arises as to whether or not the regulations are contradicting the scope principles by focusing on *process.* The draft regulations under TSCA have been charged by some with automatically and unfairly assigning a special riskiness to organisms modified through biotechnology, while exempting organisms known to be potentially dangerous, but that are not produced through a biotechnology process. This discrepancy, and perhaps its final resolution, underscores a central tenet of regulation—that regulation should be based on scientifically determined risk.

Evolution of Regulations

In the early stages of establishing regulation, special attention naturally is focused on the new technology, and a framework of flexible guiding principles is adopted as different agencies begin to deal with its ramifications. Regulations based on scientific assessment of risk begin to be defined. As these regulations are discussed and tested through early implementation, additional scientific data on risk becomes available. Regulators can distinguish between early posited risks and actual risks, as well as identify any risks not predicted in the early days of the technology. As oversight for the products of the new technology becomes more technically valid and precise, based on the salient characteristics of the *product,* it increasingly becomes a matter of standard operating procedure.

As the ramifications of a new technology become more familiar the process behind it subsides in importance and its products provide the focus for risk assessment and oversight. In this way society can benefit from useful new products, while being assured that the risks of that product have been assessed and controlled. With regard to biotechnology, agencies are at various stages of this idealized evolutionary pathway for regulatory oversight. As more experience is gained and data are fed into the system, further progress should be made.

Appropriate Review Authority for Plants Modified Via Recombinant-DNA To Be Pest-Resistant

Under the Coordinated Framework, EPA's Office of Pesticide Programs took on authority for plants into which genes coding for compounds toxic to insects had been introduced. (See ch. 7.) The premise was that these were special ''pesticidal plants' that presented similar risks to the environment, food, and human health as traditional chemical pesticides applied externally in large volumes to plants.

This premise has been questioned for several reasons. EPA-OPP has in the past dealt with chemicals and, to a small but growing extent, microorganisms. For the most part, EPA-OPP has expertise in chemicals and some microorganisms but not plants. Furthermore, compounds that are part of plant tissue obviously do not cause pesticide run-off and other such environmental problems (so long as they are alive); they are distinctly localized. Most of the compounds are not complex, like many synthetic compounds, and may well be more readily biodegradable.

Another key argument with the premise of singling out plants genetically modified for enhanced resistance to pests is that *all* plants have natural pest resistance characteristics. Selection pressures over evolutionary time have favored the spread of genes in natural populations that code for characteristics unattractive or harmful to insects. Furthermore, such characteristics have been selected in breeding programs throughout the history of agriculture. In short, making a distinction between recombinant DNA modified plants and naturally occurring or agriculturally bred plants that are pest resistant is arbitrary, not science-based. If the “pesticidal plant” premise is disallowed, there is then an argument that EPA-OPP is not automatically the best home for regulatory review of such plants. When specific new compounds are introduced into crop plants, food safety testing through FDA, rather than regulations based on the spraying of pesticides, may or may not be more relevant to human safety.

The OPP has not yet finalized the approach that it will take to implement oversight of ‘‘pesticidal plants, ” particularly at a large scale, and USDA-APHIS has been taking the lead at the field trial stage. Companies and universities have moved ahead and conducted tests. Clearly, however, the unclarified status of the OPP's approach to large-scale commercialization worries companies. Moreover, treating all crop plants as pesticides would take an immense toll in State government time and personnel; yet States cannot plan because they have not as yet received guidance from EPA as to what is coming.

Informal suggestions have been made that since USDA-APHIS already takes the lead in field tests of plants genetically modified for enhanced pest resistance, has appropriately trained personnel, and has a clearly articulated approach and established implementation procedures, it could take on oversight authority for large-scale release as well. Whether or not this matches the intent of the original Coordinated Framework, conferring this authority on USDA/APHIS could be compatible with the framework’s product emphasis and would consolidate oversight of plant biotechnology within an efficient, functioning system with a track record of accomplishment in this arena. Perhaps maintaining consultation with EPA personnel would ensure diversity of perspectives on complicated cases.

Delay in EPA Regulatory Development

EPA-Office of Pesticide Programs (OPP)

The OPP’s progress toward implementation of oversight of biotechnology under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) has been patchy. A system has been developed for the oversight of microbial pesticides, whether derived through genetic engineering or not; implementation in this arena is reasonably straightforward. Staff expertise and procedure fairly readily can be adapted to “new” biotechnology. On the other hand, as indicated above, plant expertise is lacking and no clear vision of oversight implementation has been articulated for review of "pesticidal plants," particularly not for large-scale introductions. It is unclear at this time when clarification of oversight might be made; therefore, it is difficult to project a timeframe for regulatory development. It may be that assistance, or perhaps the provision of a model, from another agency could break the logjam.

EPA-OTS (Office of Toxic Substances)

Under the Toxic Substances Control Act (TSCA), new draft regulations have emerged after a prolonged hiatus since the time when earlier draft regulations failed. (See ch. 8.) It is not yet clear whether the new draft regulations will survive. A principal point of controversy is that all microorganisms other than genetically modified ones are eliminated from oversight. Thus, it seems the regulations automatically ascribe special risk to biotechnology processes, contrary to the recommendations by the National Research Council and others. In addition, some proposed regulations subject academic research to the same procedures as industrial research. This has the potential of limiting nonindustrial research done in this area. Clearly defined mechanisms for exempting specific classes of biotechnology-derived microorganisms from TSCA review might soften the impact of the new regulations, but such actions are not evident at this time. By treating biotechnology as an inherently risky process, the regulations send a negative message about biotechnology to the public, as well as to industry and academia, and may well inhibit nonpesticidal uses of genetically modified microorganisms in agriculture and other applications. For example, the emerging industry of bioremediation based on the biodegradation or breakdown of toxic chemicals by microorganisms may be stifled by the TSCA regulations.

Comparison With APHIS Process, Personnel, Structure

EPA’s regulatory logjam might be remedied by adopting the model provided by USDA-APHIS. USDA-APHIS’s track record with field tests has been widely commended. Industry representatives have testified to that effect; en-

vironmentalists appear to have conceded that the system works well at the field trial stage although they remain concerned over large-scale introductions.

Personnel with relevant technical and legal training have implemented USDA oversight authority effectively (see ch. 7), and in a science-based, risk-based manner. The review process is carried out in a straightforward manner. Furthermore. that process and criteria by which applications will be assessed are clearly delineated and accessible to anyone with an interest in how the system works. Experience gained through early field trials is applied to review of later field trials and now is being applied to large-scale introductions. Flexibility, combined with a willingness to learn with experience and change over time, has characterized USDA's mode of operation. The EPA could make good use of all of these regulatory features: use of highly trained personnel with relevant scientific expertise: a clearly delineated and visible process for implementation; and an overall structure with the capacity to evolve over time based on experience gained.

Competitiveness Factor

The delay in EPA regulatory development needs to be addressed because it could impair American competitiveness in the agricultural industry (as well as the environmental industry). Certainly, industry progress should not be facilitated blindly, regardless of risk. Equally important, however, it should not be needlessly blocked in cases where risk is negligible or can be managed. Regulations that are not risk-based send a negative message to industry that can readily stifle innovation. Furthermore, unpredictability itself can have a real impact on corporate strategies; lack of confidence in the eventual settling of the regulatory situation may decrease the uptake of innovative, competitive technologies by American companies.

TSCA Applicability to Living Organisms

Questions arise when a law written for chemicals, specifically TSCA, is stretched to cover living organisms. Essentially, the traditional role of "gap filler" played by TSCA is being extended to planned introductions of microorganisms used for purposes other than as pesticides. (See ch. 7.) Approval for the introduction of microorganisms rests on determination that they will not in some way harm human health or the environment. Microorganisms are not themselves toxic; neither are they likely to be applied in the volumes typical of chemical applications. Instead of persisting as do many synthetic chemical compounds. living organisms are biodegrada ble. However, because they potentially can reproduce themselves and spread in the environment, their use brings up concerns different from those aroused by chemicals.

TSCA could be stretched to cover microorganisms. However, biologically trained staff will have to be given the authority to develop the procedures and requirements of the office. Managers will have to acknowledge the difference between microorganisms and chemicals, and support their biologically trained staff accordingly, when different treatments are necessary. Shifts in regulatory paradigms will have to occur if EPA is to adapt laws, premises, and procedures designed for chemicals to living organisms. EPA's ability to do so appropriately has been questioned.

On the other hand, acceptance of EPA's new regulatory role under TSCA has grown with the passage of time. EPA has yet to prove that it can implement oversight of more than a handful of field trials under TSCA.

A different issue regarding EPA authority under TSCA is that of who is affected. TSCA is a statute explicitly designed to regulate activity conducted "for commercial purposes. Academic research has therefore always been exempt from TSCA oversight. The new draft rules for microorganisms, however, greatly expand the regulatory ''net. Presumably, one rationale (an unusually broad interpretation) for including academic research is that sometimes universities engage in technical transfer or patent filing; or receive research money from companies. Scientifically, the effects of microorganisms placed in the environment by a professor are no different from the effects of those same microorganisms placed in the environment by an industry scientist. However, many question the legal precedent that could be set by extending TSCA's scope to noncommercial research and worry that the draft rules could have a negative impact on academic research. It has been estimated that an application for a single field trial of genetically modified microorganisms could cost between $180,000 and $623,000 (2). Even a cost at the lower end of this scale is more than most universities or research grants will be able to cover, particularly in these difficult economic times. While companies have personnel and budget items dedicated to coping with regulatory processes, universities by and large do not have regulatory policy officials, nor do they even have budget items for the cost of filing applications to regulatory agencies.

Academic research thus could shift away from topics that entail placing organisms in the environment, possibly giving industry a "lock" on this research arena. In spite

of the fact that objective basic research has always played an essential role in this country's development of science and technology. Furthermore, free communication of the results of such research is necessary for the building of a knowledge base to be used in future risk assessments. The absence of academic scientists and their open publication of their research results therefore could represent a significant cost to risk assessment and management.

If under proposed TSCA rules the coverage of academic research is upheld, the agency will need to explore with university representatives a variety of mechanisms for mitigating negative impacts. An alternative application process may need to be developed by the agency, perhaps based on a form already developed that is meant to be streamlined. Other possibilities include giving oversight authority to Institutional Biosafety Committees or to funding agencies, further streamlining the academic's application process, or reimbursing the university for the costs of application.

Implications of Past Treatments of Small-Scale Planned Introductions for the Future of Commercial, Large-Scale Introductions

One key element in successful oversight of large-scale introductions is the effective communication of agency requirements to the applicant. As noted above, USDA-APHIS-BBEP has won kudos from applicants for the clarity of requirements for small-scale field tests. USDA now has drafted a users handbook on how to apply for large-scale introductions. EPA has received more critical reviews, although it has taken steps to outline the information needed from applicants for field testing. It seems likely that the requirements for approval of large-scale introductions will be clarified more quickly for USDA applicants than for applicants to EPA.

Another key element in the development of sound treatment for large-scale introductions is willingness to make use of input from a variety of perspectives. USDA-APHIS has sponsored meetings, among them three (to date) national conferences on Federal and State Regulation of Biotechnology, that are attended by participants from State and Federal Government, industry, universities, and public interest groups. This is one vehicle for ensuring the receipt of outside input. In addition, numerous handouts and other materials make the internal workings of APHIS more visible and, therefore, accessible to outsiders wanting to make comments. EPA personnel also make presentations at conferences, but with the exception of two transgenic plant workshops cosponsored by the agency, they tend to take a less proactive role in fostering a public presence to encourage communication.

Perhaps the key component in facilitating safe large-scale introductions is a clear direction, a set of operating principles, a map with guidelines. USDA preparation of a draft users' handbook for treatment of large-scale introductions is a specific example of a way in which an agency can send clear signals. Certainly, USDA has shown that it is willing to build on its experience with small-scale field tests to begin to come to grips with large-scale introductions in a way that is accessible to applicants. Given its track record, EPA-OPP may be able to move to large-scale introductions of microbial pesticides in a similarly straightforward manner. Whether it can do so for large-scale introductions of plants with enhanced pest resistance properties remains unclear. The recent circulation of draft rules by the Office of Toxic Substances has been a positive step toward clarifying future directions; even as they generate controversy, clarification should eventually be achieved.

With the concerns attendant on any new technology today, it makes particular sense for agencies to monitor the impacts of planned introductions, particularly if potential problems have been identified. Judging by their track records with small-scale field tests, both USDA and EPA seem amenable to appropriate use of monitoring in larger scale introductions.

Effective regulatory treatment of planned introductions is certainly enhanced by competent, technically trained personnel working in a structure designed to facilitate science-based risk assessments, reviews, and decisionmaking. USDA has put together a staff of scientists focused on planned introductions; the structure in which they work has made it possible for the group to learn from experience and to modify the system so that relatively unfamiliar or risky applications can receive the most attention. EPA's OPP can draw on microbiologically trained personnel, but does not have the plant specialist staff of USDA. EPA's OTS has had so few biotechnology applications, all but one of which were from the same company, that it is hard to extrapolate as to the effectiveness of personnel or structure for future cases.

Clearly, sound, effective oversight of large-scale planned introductions will make a difference to the future of agricultural biotechnology and thus to the future of agriculture. (See ch. 7.) Review processes that protect human health and the environment while still facilitating safe introductions will benefit the competitiveness of American agriculture by ensuring the uptake of new techno-

logical tools. The American economy will be harmed, on the other hand, by unnecessary blocking of these new technological tools through:

- reviews based on criteria that are not science or risk-based;
- unclear directions within regulatory agencies;
- inadequate communication of requirements;
- minimal learning from experience and from input from outside perspectives; or
- insufficiently trained personnel in a structure not conducive to building on experience and streamlining procedures while maintaining safety.

As the era of large-scale introductions opens, the challenge before EPA as well as USDA is to strike the appropriate balance of protecting the American public's health and environment while allowing the American public to benefit from significant advances in agriculture.

States and the Federal Regulatory Process

The USDA has an extensive network of partner State organizations throughout the country, and has been able to bring appropriate State government officials into the review process for planned introductions (ch. 7). In addition to identifying appropriate contacts and sending them copies of applications for that State, USDA has integrated the State-level review into its own review "timeline. " State officials are respected for the germane local issues and environmental knowledge they can contribute. In addition, USDA has underscored its partnership relationship with the States by holding three annual national Conferences on Federal and State Regulation of Biotechnology at which information and views were shared, communication improved, and issues raised. USDA can be regarded as a model for the inclusion of States as partners in oversight of planned introductions.

EPA under FIFRA has somewhat of an analogous relationship to the States, in that State officials implement Federal rulings regarding monitoring, labeling, and other treatment of pesticides. The lack of clarity in OPP as to future handling of plants genetically modified for enhanced pest resistance, however, has significant ramifications for the States. State officials charged with implementing FIFRA and setting up the procedures for handling "pesticidal plants" have complained of being in the dark about EPA policy with regard to these products. Mechanisms to improve communication between the Federal officials setting policy and the state personnel who will have to implement it are needed as soon as possible. (See ch. 7.)

Federal officials under TSCA barely have initiated relationships with State agencies. and there is no explicit legal directive for TSCA to involve State officials. There is no tradition of connection between specific State environmental department personnel and the Office of Toxic Substances, yet States are interested in being involved in biotechnology-related policy and implementation. A joint biotechnology meeting for State and EPA regional personnel, to explore ramifications of the draft TSCA rules, would be a positive step toward building relationships with the States.

Potential Conflict of Interest Within USDA

USDA occasionally has been accused of conflict of interest in that it both funds research to promote agriculture and regulates agriculture. (See ch. 7.) USDA officials point out that the Department of Health & Human Resources also has within it both the research-funding National Institutes of Health and the regulatory Food and Drug Authority. More specifically, however, USDA-APHIS-BBEP has several important "checks" built into the system that greatly decrease the chances for conflict of interest. One significant check is provided by the openness of the system; the workings of BBEP are highly visible. Information is readily accessible through presentations, widely available printed materials, and responses to inquiries.

Another check is provided by the inclusion of States in the permit process. State officials watching out for the well-being of their own State provide external yet informed monitoring of APHIS decisions. In addition to being monitored continually by State officials, the APHIS system is sufficiently open that specters of conflict of interest can in all probability be laid to rest.

Risks of Genetically Modified Plants or Microorganisms Becoming Pests

Any novel organism potentially represents some level of risk to the environment, whether that organism is naturally occurring or genetically modified. Therefore, for any new variety, some risk assessment is appropriate.

The likelihood of a genetically modified plant or microorganism actually becoming a pest, however, is relatively low. (See ch. 8.) The track record of agriculture (in a sense, a form of long-term genetic engineering) has shown that current crops are not likely to become established as weeds. For the most part, long-established mechanisms for containment in agricultural systems have been highly successful in the United States. Moreover,

recombinant-DNA modified organisms, unlike wild, naturally occurring organisms, are *designed* to exist only in a specific environmental regime—the nurturing surroundings of a cultivated field.

Microorganisms modified for agricultural purposes are constrained somewhat similarly to plants, although they probably are not so dependent on cultivation for continued survival. However, the extensive agricultural experience with microorganisms (i.e., microbial pesticides) has not resulted in a pest problem. To become a pest organism, an agricultural plant or microorganism has to exist independently of cultivation—outside the planted field. Several steps are necessary to its success; each one, from dispersal to the production of viable, competitive offspring, is relatively unlikely to occur. (See ch. 8.) In general, the chances of a genetically engineered plant or microorganism becoming established as a pest are low, simply because each step of the process is fraught with difficulty.

Gene Transfer or Cross-Hybridization Between Genetically Modified Plants and Wild Plants

Cross-hybridization, the crossing of two plants of different species to produce fertile offspring, is a rare phenomenon. (See ch. 8.) While gene transfer between individuals of the same species is, of course, straightforward, gene transfer between different species is not; their genomes, or genetic compositions, are usually sufficiently different that they do not line up and match well for the key molecular and cellular events of reproduction, Even if a transferred gene were involved in such a cross, it would be cast onto an ‘‘alien’ genetic background—its expression could be problematic. Even if a viable first generation resulted from such a random crossing, as in the case of a horse crossed with a donkey producing a mule, that hybrid would most likely be sterile, so the new recombinant gene would not be passed along.

In any case, most crop species in the United States do not have indigenous weedy relatives with which they could cross-hybridize. Canola is the only major crop for which there are related weedy species in the United States. A recent conference on large-scale introduction of canola analyzed the ramifications of the potential for cross-hybridization and made recommendations for scientific and agronomic risk management. (See ch. 8.)

The possibility of cross-hybridization is greater in other countries, where crop species and related weedy species do coexist. Weedy species of rice, for example, can impose tremendous economic costs in the far East. Canola has many relatives in Europe. The developing countries, in particular, are the center of origin for many crop species. This means that related weedy species are especially likely to be found close to agricultural fields. Stocks of an ancestral line could conceivably be “contaminated” through cross- hybridization with any crop plant, including genetically modified plants.

As it exports agricultural biotechnology capabilities, the United States should offer advice to developing countries as to the management of risk from cross-hybridization. Agency regulatory staff have already begun this sort of communication, passing on information regarding scientific and agronomic mechanisms of risk management and encouraging their regulatory colleagues to employ such mechanisms. This advisory function needs to grow with the export of technology; also, companies, foundations, and international agencies need to integrate risk management transfer with their agricultural biotechnology technology transfer to developing countries.

Regulations on a Case-by-Case Versus a Generic Basis

Currently, review of applications for field trials is done on a case-by-case basis. This approach has been recommended for several reasons. (See ch. 8.) First, we are learning by doing as we handle a new technology, so one step at a time has seemed appropriate. Specifically, each field test is unique in terms of the transferred gene, the vector by which that gene is transferred, the recipient individual’s genetic background, the resulting combination of phenotypic characteristics, the likelihood of further gene flow, and the likely impact of the phenotypic characteristics on various components of particular target and nontarget environments. Risk assessment should focus on those unique aspects of a field trial that may present potential risks.

A rationale also exists for reviewing applications by grouping them into generic categories for which guidelines of “approvability” have been developed. Risk assessment review would certainly be more streamlined under this approach. As knowledge is gained, categories can be updated continually.

Key reports have stressed “familiarity” as an appropriate theme for risk assessment: if we are familiar with a component of an application package (a particular organism, or vector, or characteristic, for instance) we more readily can assess the level of risk it presents than if it is new. As we become more familiar with greater numbers of genetically engineered products (through research and field trials) it should become easier to predict

the levels of risk they present and to design effective management. Thus, as oversight for planned introductions of recombinant-DNA modified organisms into the environment naturally evolves, certain (more familiar) categories of features automatically may be designated low risk, or high risk depending on certain conditions. However, each feature might be double checked for any specific idiosyncratic risk it might present; the overall package of features also might be assessed to ensure that no interactive effect among the features produces a new level of risk. The recipient organisms and vectors, may be the first features of biotechnology introductions to be categorized by riskiness; the characteristics most likely to be transferred eventually might be broadly categorized. The interactions between the genetically modified organism and the local environment (including probability of gene flow) will always bear close scrutiny, even if general categories suggest just what needs to be examined to assess risk.

The evolution from case-by-case to generic categories as a basis for review is likely to occur naturally; it is dependent on the accumulation and analysis of knowledge gained in the early stages of dealing with a new technology. Risk assessment of planned introductions of recombinant-DNA modified organisms now is undergoing this evolutionary process.

POLICY OPTIONS

ISSUE: The tools of biotechnology offer great potential to American agriculture; regulatory treatment of any agricultural products derived with such tools will play a dominant role in any related gains or losses in economic competitiveness. Science- and risk-based regulation of products can ensure safety without unnecessarily impeding the economy.

Option: Congress could direct Federal regulatory agencies to make science-based, risk-based regulation of biotechnology products (not process) a unifying policy across agencies.

This would be a clear message to the executive branch that Congress expects a unified approach across Federal agencies based on the product not on the process. Communication through interagency groups would help to ensure a common approach based on scientifically determined product risk. This approach can help protect health and environment and, at the same time, should generate a comprehensible, workable regulatory apparatus for incorporating the tools of biotechnology into American agriculture. However, EPA will need to address staff needs to conduct technical risk-based reviews.

Option: Congress could direct appropriate agencies to review and regulate biotechnology as a process, rather than the products.

EPA-OTS has been accused of regulating the process of biotechnology, not the products, in its proposed rules, for example. It would be a clear signal that biotechnology is so unique that it must be scrutinized for each use. This would satisfy those concerned with the application of biotechnology to agricultural products. However, no scientific evidence exists to justify such an approach. If some agencies ignore the use of risk assessment of products and automatically penalize any efforts made using biotechnology, several impacts are likely to occur. Industries and universities would be likely to "agency-shop, ' orienting their efforts toward the agency with the clearest analytical assessment of science-based risks—that agency will be the least arbitrary and the most predictable, an approach certainly favored by industry. Research and industry activity in areas not regulated on the basis of science-based risk would diminish, at what may be a real cost to society. The agency regulating biotechnology as a process sends out an obvious negative message to industry and perhaps an equally important, if more subtle, message to the public. Regulations based on the assumption that biotechnology is inherently unpredictable and highly risky can lead to public reaction and political pressures that may be detrimental to the economic competitiveness of American agriculture.

ISSUE: Enhanced pest resistance is one of the most promising applications of the tools of the new biotechnology. Obstacles to its development could send a negative message to agribusiness, slowing its incorporation of biotechnology as a mechanism towards increased economic competitiveness.

Option: Congress could keep the oversight authority for plants genetically modified for enhanced pest resistance under EPA Office of Pesticide Programs (OPP), but direct EPA to strengthen OPP.

If oversight of “pesticidal plants” introduced at a large-scale is to be handled by OPP, several implementation steps would need to occur. Technical staff with plant expertise would need to augment current staff; clear definitions would have to be devised for review, given that some naturally occurring plants contain more ‘‘pesticidal compounds” than will the products of biotechnology;

communication with State-level implementors would need to be improved immediately; and a clear approach (even if wisely flexible over time) would have to be articulated, so that the public, industry, and academia would know where the agency stands and how it will implement its policy.

Option: Congress could direct USDA-APHIS to regulate large-scale introductions of plants genetically modified for enhanced pest resistance.

Since USDA-APHIS-BBEP has taken the lead for field tests of plants genetically modified for enhanced pest resistance, APHIS could handle large-scale introductions. This has the advantages of centralizing plant oversight and making effective use of an already well functioning technical staff and organizational unit. The chief disadvantage would be a departure from the Coordinated Framework, which ascribed authority to EPA-OPP.

Option: Congress could direct EPA to work with USDA to develop a similar model of operation and to report on progress to Congress within a specified period of time (e.g., 6 months).

Despite disadvantages of 'forcing' two very different offices to work closely together, this has the advantage of allowing USDA to handle any risk concerns related to planned introductions, while allowing EPA to continue to handle food safety concerns related to "pesticidal" toxins in the food supply. USDA has established a strong track record for taking the lead in field tests of pest-resistant plants; it is on the verge of establishing a track record in handling large-scale introductions generally. Building on this base such that USDA handles large-scale introductions of pest-resistant plants is a logical extension of capability and responsibility. Similarly, EPA has developed expertise in setting tolerance levels for pesticides in plants; after scientifically determining the relative risks of genetically engineered pest-resistant compounds compared to naturally occurring compounds, it could set tolerances in this case as well.

ISSUE: TSCA is a statute explicitly designed to regulate activity "for commercial purposes.>' Academic research, therefore, has been exempt from TSCA oversight. The proposed draft rules for microorganisms, however, greatly expand the regulatory "net." One rationale for including academic research is that sometimes universities engage in technical transfer or patent filing, or receive research funds from companies. Obviously, the effects of microorganisms being placed in the environment by a university scientist are no different from the effects of those same microorganisms being placed in the environment by an industry scientist. Concern exists, however, that the draft rules could have a negative impact on academic research.

Option: Congress could allow the proposed rule to stand, placing the same requirements on academic research as on industrial research.

Subjecting universities to the requirements placed on companies seems contrary to Congressional intent behind TSCA. It could have significant impacts on university research. Faced with the added bureaucracy and high costs entailed by this rule, the majority of university researchers might deliberately avoid planned introductions of genetically modified organisms. This would leave industry in charge of an area of research that could continue to benefit from objective, openly published study. Such a situation would inhibit the production of new knowledge for use in future risk assessments. However, it is an arbitrary decision to automatically exclude universities from oversight—the release of organisms that pose a risk should be regulated regardless of who conducts the release.

Option: Congress could direct EPA to develop an oversight mechanism by public scientists for planned introductions as an alternative to the proposed TSCA rule.

Universities could make use of their already existing system of oversight committees and institutional biosafety officers to regulate biotechnology field trials "in house. " Just as the Institutional Biosafety Committees (IBCs) review laboratory research involving recombinant DNA, they could review proposals for planned introductions (3). It would entail education of laboratory-oriented personnel as to the ecological considerations of field release, as well as possible expansion of committee membership to include appropriate disciplines. Serving on an IBC is a time-consuming effort for university personnel. Many feel that there are already too many university committees on which they must serve and that there time could be used more productively. Use of those committees to provide oversight is a possible trade off for the university between being able to conduct this research or not.

Option: Congress could direct EPA-OTS to develop special procedures to minimize or eliminate the

regulatory burden on universities, to ensure that public research continues in this area, and to report to Congress on the method selected and its results.

This option would still hold public scientists accountable but would be aimed at lessening the regulatory burden if the appropriate procedure is used. Several possible procedures exist. One possibility would be that the agency funding the research would take the responsibility for monitoring and reviewing the work. As part of the funding contract, the principal investigator agrees to follow EPA guidelines on management and to contact EPA if the need arises. This makes it possible for the funding agency to monitor the project and enforce regulations through the distribution of funds (1).

Another approach is to streamline the application for public researchers. For example, an abstract from a grant proposal would be sufficient to trigger important questions that arise about the project from EPA. Another possibility would be for EPA to set aside a budget that would reimburse universities for costs incurred in filing an application. However, even if a cost-savings mechanism is developed. a bureaucracy-minimizing mechanism will also be necessary if Congress desires to encourage public researchers and their home institutions to conduct the objective research that will contribute further to our knowledge base.

Option: Congress could amend TSCA to exclude universities or to provide alternative means to regulate academic research.

An argument can be made for including academic researchers. Obviously, genetically modified organisms released into the environment by a public researcher have the same effect as the same organism placed into the environment by an industry scientist. On the other hand, concern exists about the legal precedent that could be set by extending TSCA's scope to noncommercial research and that it could have a negative impact on research. An application fee for a single field trial costs between $180,000 and $600.000. Even the lower cost is more than most universities or research grants are able to cover. Even though companies have personnel and a budget to cope with regulatory processes. universities for the most part do not have regulatory policy offices or the budget for filing applications. Congress could make its intent for universities clear by stating it in legislative language through TSCA.

ISSUE: As large-scale planned introductions become imminent, companies are looking to the regulatory agencies for guidance as to how to proceed. Clear guidance is critical to commercial development of agricultural biotechnology.

Option: **Congress could** direct *EPA-OPP and OTS to clarify their regulatory approaches to large-scale introductions and report back to Congress within a specified period of time.*

The interagency work groups. as well as leadership of EPA, can orient efforts toward assisting EPA staff in clarifying the regulatory guidelines. A flexible approach, capable of evolution as additional data are gathered seems appropriate, and individual case discussions between EPA and applicants are useful. Clarifying regulatory guidelines would be particularly helpful to agribusiness working with "pesticidal plants" or microorganisms other than microbial pesticides. USDA-APHIS-BBEP could provide model mechanisms for clear communication of requirements, use of input from outside the agency, addition of technologically trained personnel, and creation of an effective structure as well as clarification of direction.

Option: Congress could direct EPA to continue on its present course.

This is basically a status quo option. It would mean a continuation of the lack of clarity of regulating policy for potential applicants at the large-scale stage. The absence of applications to EPA-OTS for environmental release under TSCA over the last year may illustrate industries' response to lack of predictability in the regulatory arena. It also undermines public confidence in the ability of regulatory agencies to regulate biotechnology.

Option: Congress could conduct oversight hearings of EPA and USDA reguarding regulatory policy for large-scale release.

Oversight hearings could assist the agencies in developing policy to meet congressional intent for regulating these products even though the regulatory agencies have stated that current laws are sufficient for regulation of products derived from biotechnology. This could help clarify differences in laws written primarily for chemicals instead of genetically modified organisms.

ISSUE: The institutions handling new technology, including biotechnology, need credibility. In the past, far less attention was paid to this issue; today several elements of what should be "standard operating procedure" can be emphasized by institutions to gain or maintain vital public trust. A balance between maintaining public interest and ensuring industry competitiveness must be achieved.

Option: Congress could direct EPA and USDA to emphasize: 1) increased input of public participation into their systems; 2) an open process; 3) scientifically sound procedures communicated clearly to other scientists; and 4) follow-up on appropriate cases.

Most systems are sounder when external input is factored into decisions. External advisory committees, hearings, and informal workshops are examples of mechanisms by which Federal agencies can obtain such input. EPA-OPP, for example, cosponsored workshops on transgenic plants to gain scientific advice as they deliberated on their approach to so-called "pesticidal plants, " and has used its scientific advisory board in deliberations over the draft TSCA rule. USDA-APHIS has held a variety of conferences and workshops, stressing public input and State officials' input. In fact, USDA-APHIS has made State input an integral part of its review process; EPA could wisely adopt this approach, in OPP and OTS. Input at the State level can provide important relevant ecological information, perhaps equally important, it serves as a credible system of external checks and balances on a Federal agency.

By developing scientifically sound procedures for data needs and communicating them clearly, an agency can build an accessible database and contribute to and benefit from the scientific community. USDA's Agricultural Research Service is complementing the work of APHIS by building a database on field tests. The draft TSCA rule refers to a similar accumulation of data, although specific implementation processes could be made clearer. Along with ARS, USDA-APHIS-BBEP, in particular, has highly trained staff in relevant areas to interact with outside scientists.

Parties concerned about a new technology want to know that potentially problematic cases are being subjected to followup. While USDA and EPA can and do impose monitoring requirements on field tests, both agencies could benefit from selectively implementing more extensive followup (perhaps by monitoring indicators identified for a possible worst-case scenario) on specific cases that might prove troublesome. This is, of course, time consuming. This approach should be used in a manner that does not put undue burdens on straightforward cases; but so that the public feels secure in the knowledge that problematic cases will be tracked past the time of introduction.

Option: Congress could require regulatory agencies to develop explicit plans for building public confidence and report those plans to Congress.

This option would give agencies maximum flexibility. It would allow for the evolution of regulation based on the experience of the agency. Moreover, this approach would allow for a true solution to be developed within the agency as opposed to it being imposed on the agency from outside. Reporting the plan to Congress would allow the public to express its opinion and to exert pressure on the agency to change those parts of the plan found to be to unacceptable. On the other hand, it is a time consuming effort for the agencies and Congress. With the large demands on Congress, some members could be concerned that it was not the best use of their time.

Option: If regulatory agencies fail to maintain public confidence, new law(s) or congressional oversight could be established to satisfy the public demand for accountability.

This option is relatively drastic and could have several disadvantages. Managing a system from the outside invites logistical and other difficulties. Moreover, the tendency with this approach would be to "freeze" procedures at a particular moment. This could hamstring the natural and positive evolution of regulation, such as the gradual extraction of generic principles from case-by-case reviews. More generally, this approach would be more in the nature of imposed management rather than a true solution developed within the agencies; as such its own credibility may be weakened. However, it is an option that could ensure accountability to the public if regulatory agencies are incapable of doing so themselves.

CHAPTER 9 REFERENCES

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