BIOTECHNOLOGY

Is *Safety* All That Matters?

BY SUSAN OFFUTT AND FRED KUCHLER

Recent debate over the uses of biotechnology has centered on the application of recombinant DNA (rDNA) techniques in the development of products for agriculture. Frost-inhibiting bacteria, soil-dwelling microbes with insecticidal properties, growth hormones, and plant and animal vaccines using live, biologically novel organisms are examples of rDNA products for farm use. Proposals for deliberate release of genetically engineered microbes, plants, and animals in the open have raised questions about the potential for risk to human health and the environment. The dimension of the risk is still an unknown.

Federal regulatory agencies are at the center of this controversy because they interpret their legislative mandate as vesting them with responsibility for scrutinizing both the processes and products of biotechnologies. In the case of agriculture, controversy has erupted over wide-area use of products intended to alter the environment to suit farmers' needs. But in the case of medical technologies, regulators have accepted large-scale production of human insulin and growth hormone, substances whose clinical properties in remedying health defects are understood. So far, the scope of regulatory issues facing agricultural biotechnology products has been broader than that facing medical products.

Regulations: Too Slow For Some, Too Fast For Others

Government regulators are criticized by some people for moving too slowly and by others for acting too hastily in approving field testing of gene-altered products. Biotechnology researchers in academia and industry are frustrated by what they perceive as unnecessarily cumbersome procedures to gain approval for initial tests of gene-altered products outside controlled laboratory conditions. For example, plant pathologist Steven Lindow waited over three years for the go-ahead to field test Frostban, a frost-inhibiting microbe. The level of regulatory concern over the safety of the release is seen as unwarranted. Not surprisingly, government regulation is often perceived as serving only to postpone the marketing of profitable products.

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On the other hand, at least some members of the public prefer even closer examination of proposals for release. Those who argue for caution in regulatory decisionmaking demand two distinct types of information. First, they ask whether there are any conditions under which free release could cause harm to human health or the environment. Second, they voice concerns about the ethical and socioeconomic ramifications of the proposed product or technology. Some regional dairy-

Susan Offutt and Fred Kuchler are agricultural economists with the Resources and Technology Division of the Economic Research Service, USDA.

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men's associations, fearing for their members' financial solvency, argue against allowing the use of bovine growth hormone (bGH) to boost milk production.

Because there is limited opportunity for recalling a product once it is approved for use, concerned groups—often led by highly visible activists—feel compelled to raise non-safety related issues at the early stages of regulatory oversight. When their lawsuits based on alleged procedural impropriety are successful, regulatory approval is thereby delayed. While delay does not necessarily imply ultimate disapproval, it allows more time for public discussion.

Recalling Biotechnology May Not Be Easy

There are good reasons for asking questions about new organisms prior to their release. Regulatory experience with pesticides and animal drugs shows that it is rarely easy to recall agricultural input products, even when scientific evidence shows materials to be an environmental or human health hazard. Regulatory battles over the insecticide toxaphene lasted more than a decade. The animal growth promotant DES was used in cattle feeding in violation of FDA regulations. Once a new technology is fully integrated into standard farm management practices, both farmers and manufacturers have financial interests in maintaining its availability.

A possible impediment to the effective recall of biotechnology products is the ability of many genetically engineered micro-organisms to survive and thrive in the open environment. Indeed, if organisms are to make modifications in ecological systems to suit farmers' purposes, they must be viable in the open. As long as all possible interactions between genetically engineered organisms and their new environment are not fully understood, the possibility for environmental damage and the subsequent need for recall must be taken seriously.

Economic Climate Fuels Debate

The burden of commodity surpluses and rising government farm support costs intensifies the level of the debate over the use of biotechnologies in agriculture. From this perspective, the safety issue becomes subsidiary; almost any new technology that promised to raise agricultural output under conditions of oversupply would be the target of close inspection. In the past year, two gene-altered microbes have been released—one legally, one not—with no apparent ill effects. Yet, neither the safety nor the ethical and socioeconomic issues related to these organisms have been resolved.

The Uses of rDNA: Why Worry?

The basic point of rDNA techniques is to insert a gene into an organism such that desirable characteristics are expressed more abundantly than would have occurred naturally. The promise of rDNA is that more precision and more variety can be gained in making the gene transfer than was previously allowed with conventional plant and animal breeding techniques. However, this capability also means that plants, animals, and micro-organisms that do not exist now will be created. The inability to predict with certainty the behavior of these new organisms is the foundation for safety concerns.

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Applications of rDNA to the problems of farming will create new input and output possibilities, as well as enhance old ones. New crop and animal varieties resistant to a range of environmental stresses, including droughts, floods, and temperature extremes, can be conceived. The ability of the farmer to detect and control disease in the barn, field, and storage bin will be improved. The dependence of modern systems on chemical pesticides and fertilizers may be reduced. The food value of commodities may be raised. The potential for application of rDNA (and related techniques such as cell fusion and embryo transfer) in these areas is great. The popular press has done a good job communicating these possibilities to the general public; the nature of the risks involved has been less well understood.

Biological Risks: Anticipating Problems

The genetically engineered plants, animals, and microbes that will accomplish these works will likely have no counterparts existing in nature. Such organisms either appeared and did not survive the process of natural selection or simply never existed. The concern over the behavior of these novel organisms, once released, is centered primarily on microbes. Plants and animals are thought to be easier to track, thereby facilitating prediction and control of any adverse environmental effects.

In trying to anticipate the future, scientists look to the experience of the past with the introduction of exotic species, the appearance of novel traits in natural populations, and the outcome of conventional breeding programs. So, for example, the lessons of the ravages of the gypsy moth, of the evolution of insecticide-resistant insects, and of the creation of leaner hogs may provide clues about new organisms' behavior in comparable situations. Scientists have noted that exotic species are frequently, but inadvertently introduced into new habitats. Most such introductions fail; an organism cannot always adapt to variation in the environment (temperature, humidity, competing and complementary flora and fauna). There is, however, a small probability of an organism finding a new niche and upsetting an ecology. Kudzu vine in the southern U.S. and rabbits in Australia are good examples of survival of exotic species outside their native homes.

With gene-altered micro-organisms, however, there are additional concerns; these microbes may have capabilities that increase the difficulty of prediction of the consequences of deliberate release. With some biotechnology products, such as soil-dwelling microbes given insecticidal properties, a large number of organisms would be released. These organisms would be capable of reproducing and might spread outside their original target area. Nucleic acids, added to give an organism new capabilities, may migrate to other, non-target organisms via plasmids or viruses. Given these possibilities, deliberate release could lead to unintended effects on other species and on the functioning of the ecosystem. Human health concerns arise if further genetic modifica-

tions of the organisms convert nonpathogens to pathogens or affect the behavior of existing agents of disease. In contrast, organisms altered through the deletion of a gene might not even survive in the wild, and, in any case, would have no additional genetic material to trade.

In agriculture, rDNA techniques can be used in a number of ways to conjure up a variety of products. Not all applications present the same potential for harm to human health and the environment. In the case of a single gene deletion, used, for example, to create a swine pseudorabies vaccine, some scientists would argue the danger of harm to human health or the environment is remote. However, the hazards of gene-added microbes are more problematic. Researchers have criticized the regulatory rules' failure to distinguish among levels of potential for harm in specifying the requirements for approval of field testing. Argument continues over the content of these more appropriate rules and procedures.

How Regulation Got That Way

Originally, responsibility for oversight of federally funded genetic engineering research was placed with a committee under the auspices of the National Institutes of Health (NIH). As use of the techniques broadened beyond human medicine, other federal agencies became involved. With the regulatory rules set by the White House in June 1986, NIH will continue to monitor research activities. However, responsibilities for oversight of specific applications were placed with other units of the government. USDA will regulate gene-altered animal vaccines and plants. The Environmental Protection Agency (EPA) has general responsibility for the oversight of genetically engineered microbes. However, this task will be shared with USDA when agricultural crops are involved. Animal drugs and human health care products are under the purview of the Food and Drug Administration (FDA). The Occupational Safety and Health Administration (OSHA) will look after genetically engineered products in the work place.

Confusion, delay, and disobedience have been the result of using both previous and current rules. USDA was sued for its failure to consult its own biotechnology advisors in issuing a license for a gene-deleted swine pseudorabies vaccine. Both NIH and EPA granted and later rescinded experimental use permits before Frostban was tried in the open. Most recently, a Montana State University researcher ignored EPA requirements and injected elm trees with a gene-deleted vaccine against Dutch elm disease. These incidents have received extensive media attention; the regulatory system has appeared to be in disarray.

Federal agencies have had difficulty in evaluating safety risks of biotechnologies in a timely fashion. Now regulators face the additional demand that they consider the ethical and socioeconomic impacts of product approval. For example, the FDA is charged with evaluating bovine Growth Hormone (bGH) (considered an animal drug) for use in hiking milk output from dairy cows. Although it is not currently obvious that there are any health risks to humans from drinking milk from bGH-treated cows, what is definitely contentious is the impact bGH may have on the dairy sector. Both the effects on the physical production system (e.g., stress on cows) and socioeconomic conditions (e.g., the future of

The Genie Escapes

As Aladdin well knew, and as the Rust brothers of Texas discovered, once a genie escapes from its bottle, it is impossible to recapture. In 1928, John and Mack Rust developed a spindle picker for cotton that allowed a single machine to do the work of 80 fieldhands. The Rusts' interest in mechanizing the harvest had been borne out of their first-hand experience as children working in their family fields.

The Rusts hoped to eliminate the drudgery of hand-picking. But when they saw the massive displacement of low-wage labor that would result from adoption of their new picker, they feared they had succeeded too well. Their original humanitarian purpose would be subverted.

Although the spindle picker was widely sought, the Rusts attempted to restrict its use to cushion its impact on small farmers, sharecroppers, and day laborers. At first, they refused to sell the machines at all. Instead, the Rusts would rent to any cotton farmer who agreed to eschew child labor and to pay field workers at the same rate and for the same hours as before the spindle picker's introduction. Then, because laborers on cooperative farms were also owners, the Rusts tried to interest these operations in the picker. However, labor was anything but scarce during the Depression, and these overtures met with little response. To encourage adoption by small farmers, the Rusts tried, unsuccessfully, to convert the self-propelled machine to one that could be pulled by mules or a small tractor.

Finally, the Rusts decided to market the spindle picker. Still uneasy about the machine's throwing labor off the land, they declared that they would take out of the returns no more than ten times the wage of their lowest-paid employee. The remainder was to go to a fund set up to assist those forced to leave cotton farming and to promote cooperatives. However, this plan came to grief when financial difficulties shut down the Rusts' venture. Widespread use of the picker dictated the need for large scale production, and it was finally International Harvester, Allis-Chalmers, and Deere that successfully met the demands of a national commercial market.

As the Rusts learned, advances in technology often mean painful adjustment for the farming community. Once an innovation becomes available, it may not be possible to halt or control its adoption. And it is surely beyond the power of its originators to mitigate the social and economic consequences of its introduction.

For today's debate over biotechnologies, the lesson is that commercial availability of profitable products makes their spread just about inevitable. Recent experience has taught that it is difficult enough to recall products that are unsafe; recalling those with undesirable socioeconomic effects could hardly be expected to be easier. What has yet to be decided is whether the response will be to ban some innovations altogether or to develop social programs to compensate and ease the pain of adjustment.

small dairies) are in question. In response to legal action requesting that these questions be evaluated, FDA has postponed ruling on the commercial use of bGH; close observers suggest it may be 1990 before a decision is made.

Now What?

Biotechnology regulation is evolving now. The initial impasse, in which no field testing of rDNA organisms took place in the United States, has been resolved. Several kinds of gene-deleted microbes have been safely released, as many individuals in the scientific community had predicted. However, important safety and socioeconomic issues have yet to be confronted. New biotechnologies will continue to emerge. The safety and socioeconomic issues surrounding them will receive substantial attention even after the fate of bGH and other rDNA organisms under review are decided.

The institutional changes necessary to streamline the regulatory process, while at the same time safeguarding human and health and the environment, are being made. Eventually, scientists and regulators may be able to reach a consensus on what factors constitute reasonable review for safety's sake. However, questions about socioeconomic impacts and ethical implications of biotechnologies are not being addressed directly. The regulatory system at present is not set up to handle such issues.

The academic and industrial research communities are increasingly sensitive to the necessity for "advance work," in educating the public about the benefits and the risks of using biotechnologies. Recent polls show the public finds university scientists, public health officials, and environmental groups to be more credible than government regulatory officials. But public awareness and improved scientific literacy may not translate into public approval of unrestricted use of biotechnology. One basic question to be decided is whether socioeconomic and ethical considerations will become criteria for prohibiting commercial release of a product, even if it is deemed *not* to present risks to human health or the environment.

If more than a technology's safety is to be weighed in the regulatory process, Congressional guidance on the standards and content of any "socioeconomic" impact statements must be forthcoming. Regulators will not inject these considerations without Congressional guidance. On the other hand, if safety is thought to be the only appropriate criterion, then continued legal challenges can be expected. The vacuum created by lack of legislative guidance will be filled by arguments in the court system. Regulatory decisions of any type will be slow in coming. More complex issues, such as the advisability of animal patenting, loom on the horizon; a comprehensive technology policy would be ideal, yet probably elusive.

What can be done to improve the public's grasp of biotechnology's socioeconomic impacts? The need for thoughtful evaluation of technologies before organisms are released has never been greater. What must be evaluated is not just static productivity benefits derived from new technologies (greater product availability and lower consumer prices). Attention needs to be given to the costs of failing to adopt new technology and U.S. farmers' losing a competitive advantage to other countries. The number, size, and location of farms is likely to change with any new technology; differential effects among farmers must be examined. In the end, these socioeconomic considerations could drive the public's decisions about biotechnologies. C