# A Need to Reinvent Biotechnology Regulation at the EPA

Henry I. Miller

The Environmental Protection Agency (EPA) has just announced final or preliminary policies for regulating various products that are genetically engineered and that have pesticidal properties (*1*, *2*). These represent the culmination of 10 years of effort to come to regulatory terms with the advent of recombinant DNA (rDNA) technology: a set of methods that have allowed researchers and plant breeders to control and transfer more precisely than ever before the genetic traits they find desirable. The intervening years and the stellar advances in the comprehension of the scientific bases of risk that have occurred during that period have allowed ample opportunity for scientific principles to drive regulatory policy (*3*). Yet, even in rules and policies announced in 1994, the EPA has cast into federal regulatory policy an anachronistic approach that targets the techniques used to create these organisms—that is, rDNA methods—rather than high-risk organisms or experiments likely to pose significant risk to public health or the environment. Although the technology has become ever more sophisticated, and although numerous experiments—including risk assessment experiments—continue to demonstrate that rDNA manipulation, per se, does not confer enhanced risk (*4*), the EPA has steadfastly discounted these findings. Instead, the EPA has held fast to its course of singling out these organisms for special consideration—consideration that turns into burdensome and unnecessary regulatory reviews (*3*, *5*).

Still, scientifically defensible and viable policy alternatives do exist. They have been implemented by government agencies such as the National Institutes of Health (NIH) and Centers for Disease Control (CDC) (*6*) and proposed by the National Research Council (*7*) and others (*8*).

## Flawed Policies: Regulating Processes Instead of Risks

The EPA has a lengthy history of policy formulation based on considerations other than scientific predictions or measures of risk related to environmental protection. For example, in the late 1980s, in response to a widespread media campaign waged primarily by the Natural Resources Defense Council, the EPA pressured apple growers to abandon the use of the plant growth regulator Alar, an agricultural chemical that permits apples to ripen uniformly and increases yield. EPA's capitulation to environmentalists' demands conflicted with the agency's own scientific findings (*9*, *10*). Environmentalists' demands appear likewise to have influenced the EPA's approach to regulating products of the new biotechnology.

The EPA's final rule for "genetically engineered" microbial biocontrol agents under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA, the "pesticide statute") was published on 1 September 1994 (*1*). While this regulation represented an opportunity for scientific principles to drive regulatory policy, the EPA, with the active collaboration of other parts of the administration, adopted a highly centralized, intrusive approach that once again targets techniques rather than high-risk organisms, environmental results, or outcomes. For example, under the new regulation the EPA is to regulate innocuous organisms such as *Pseudomonas syringae* or *Rhizobia* that contain the *Escherichia coli lacZY* genes as a metabolic marker or luciferase as a visual marker, just because rDNA techniques have been used. It is interesting that the EPA rule does not identify the use of rDNA techniques forthrightly as its regulatory trigger. Rather, the rule uses circumlocutions: It targets "deliberate genetic modification," but then defines "deliberate" as "directed," and finally equates "directed" with the use of molecular techniques. In the end, the rule still regulates phenotypically identical organisms differently, if different genetic techniques are used.

For a decade the EPA has offered proposals in which the scope of biotechnology regulation—that is, which products or experiments are subject to regulatory requirements—targets the newest and most precise molecular genetic manipulation techniques. Yet, broad scientific consensus [reviewed in (*3*)] holds that process or technique per se does not correlate with environmental risk. For example, in its 1989 report, "Field Testing Genetically Modified Organisms," the U.S. National Research Council (NRC) concluded that "no conceptual distinction exists between genetic modification of plants and microorganisms by classical methods or by molecular techniques that modify DNA and transfer genes"; and that, therefore, the use of the new, gene-splicing techniques should not constitute a trigger for regulation (*7*). The NRC report also observed that, compared to the imprecision of classical techniques of gene transfer or modification, "with organisms modified by molecular methods, we are in a better, if not perfect, position to predict the phenotypic expression [of organisms in field trials]." On the basis of such consensus observations, it could even be argued that if there were a rationale for a disparity in regulatory requirements according to genetic manipulation techniques, the newer, more precise and more predictable molecular methods should elicit less intensive and stringent oversight than their traditional counterparts.

The EPA's pursuit of policies that regulate the technique rather than product risks is one manifestation of the agency's documented neglect of science advice applied to policy formulation, a deficiency that has been criticized by eminent extramural scientific panels (*5*, *11*). An expert panel commissioned by EPA Administrator William Reilly reported in 1992 that (i) "The science advice function—that is, the process of ensuring that policy decisions are informed by a clear understanding of the relevant science—is not well defined or coherently organized within EPA." (ii) "In many cases, appropriate science advice and information are not considered early or often enough in the decision-making process." (iii) While "EPA should be a source of unbiased scientific information . . . EPA has not always ensured that contrasting, reputable scientific views are well explored and well documented." And most damning of all, that (iv) "EPA science is perceived by many people, both inside and outside the Agency, to be adjusted to fit policy. Such 'adjustments' could be made consciously or unconsciously by the scientist or the decision-maker" (*11*). Moreover, EPA's biotechnology policies have conflicted with official federal policy (developed with EPA's agreement) that regulation of biotechnology products should be "risk-based," "scientifically sound," and focused on "the characteristics of the biotechnology product and the environment into which it is being introduced, not the process by which the product is created" (*5*, *12*). The EPA statements of policy have often used the appropriate buzzwords while subverting the concepts (*3*).

The EPA has ignored bona fide risk considerations in favor of the unsubstantiated fears expressed by special interest groups. One of EPA's convoluted arguments holds that "newness," in the narrow, literal sense, is highly correlated to risk, and that because rDNA techniques can easily be used to create new gene combinations, rDNA manip-

The author is Robert Wesson Fellow of Scientific Philosophy and Public Policy, Hoover Institution, and Consulting Professor, Institute for International Studies, Stanford University, Stanford, CA 94305–6010, USA.

ulations therefore "have the greatest potential to pose risks to people or the environment" (*13*). The result of this reasoning is extensive, expensive, case-by-case screening of all or a major subset of small-scale field trials of rDNA-manipulated microorganisms, while tests of similar—or even phenotypically identical—organisms manipulated by other techniques are exempted. Thus, EPA's policy would require governmental review of largely innocuous organisms but would exempt field trials of "naturally occurring" organisms (and those manipulated by chemical or radiation mutagenesis or by transduction, transformation, or conjugation) that could foul waterways or pose other environmental risks. EPA's long-standing (pre-biotechnology) policy was to exempt small-scale field trials of microorganisms and chemicals (*5*, *14*). Except for microorganisms manipulated with rDNA techniques, that policy remains essentially intact. (EPA's exemption in the new rule of recombinant organisms whose genome has only undergone deletion or rearrangement represents scant improvement.)

## Dubious Decisions

In the mid 1980s, the EPA astonished the scientific and regulatory communities by classifying as a pesticide the ubiquitous and innocuous recombinant "ice-minus" variant of the bacterium *Pseudomonas syringae*. The bacterium was to be sprayed on potatoes and strawberries in an attempt to prevent frost damage. (The EPA reasoned that the wild-type *P. syringae* is a pest because its ice-nucleation protein serves as a nidus for ice crystal formation and that a mutant strain intended to displace it is therefore a pesticide. This convoluted rationale could lead the EPA to regulate outdoor trash cans as a pesticide because litter is an environmental pest.) There was unanimity among scientists within and outside the EPA about the safety of the test. Nevertheless, because the organism was rDNA-manipulated, the field trial was subjected to an extraordinary and burdensome review (*15*). And even after EPA approval was granted, the agency's wrongheaded actions continued; ostensibly in order to perform research on risk, EPA officials attired in moon suits conducted elaborate and superfluous monitoring of the actual field trials (*16*, *17*).

It is noteworthy that the researcher proposing the experiment had previously performed field trials with spontaneous mutants of *P. syringae* that were phenotypically identical to the recombinant ice-minus organism and that these trials had required no government review or notification of any kind. Data from these field trials were also submitted as part of the proposal to test the recombinant ice-minus strain. Regulators were similarly unconcerned about field trials with the wild-type *P. syringae* tested for the ability to enhance the production of artificial snow at ski resorts. The use of rDNA techniques was—and continues to be—the EPA's preferred regulatory trigger.

In 1985, the Monsanto Company proposed a scientifically interesting and potentially important small-scale field trial, using a soil bacterium, *Pseudomonas fluorescens*, to control a voracious corn-eating insect. The bacterium, harmless both before and after its modification with rDNA manipulation, contained a well-characterized gene cloned from another, equally innocuous bacterium. The EPA refused to permit the field trial in spite of the conclusion of the EPA's own Scientific Advisory Panel and other federal agencies that there was virtually no likelihood of significant risk and in spite of the recommendation to allow the experiment to proceed (*5*). Two aspects of this situation are noteworthy. First, analogous to the ice-minus experiments, the Monsanto field trial would not have been subject to any government regulation at all had it involved a phenotypically identical organism crafted with "conventional" (and less precise) genetic techniques. Second, Monsanto's response to the EPA's refusal was to dismantle its research program on microbial biocontrol agents (*18*, *19*). It is difficult to calculate the overall societal cost of such disincentives at a time of growing demand for nonchemical pest control, but it is likely to be substantial (*3*, *5*).

## Plants as Pesticides

The EPA's process- or technique-based approach to regulating microbial biocontrol agents is only one example of scientifically flawed regulation under FIFRA—and of negative impact on R&D that aims to improve agriculture and the environment. The EPA has begun a process that would require the regulatory review of a whole category of products that until now have been perceived as requiring no regulation at all: whole plants genetically modified (with rDNA techniques) for enhanced pest resistance (*2*).

Plant varieties have long been selected by nature and humans for improved resistance or tolerance to external factors that inhibit their survival and productivity. These factors include insects, disease organisms, herbicides, and environmental stresses. All plants contain resistance traits, otherwise they would not survive. Thus, the issue is not one of the presence or absence of pesticidal properties, but one of degree. Moreover, there is no evidence to suggest that the degree of pest resistance is correlated with risk to the environment.

Genetic improvement of crops for pest resistance is likely to be less environmentally hazardous and more socially acceptable than the manufacturing and spraying of chemical pesticides. Plant breeders, farmers, and consumers possess extensive experience with crops and foods that have been genetically modified for pest resistance. In recent decades, so-called "alien" genes have been transferred widely across natural breeding boundaries by chromosome substitution or by embryo rescue techniques to yield commonly available food plants including oats, rice, black currants, pumpkins, potatoes, tomatoes, wheat, and corn (*20*). Most often, the desired improvement has been pest resistance, such as resistance to nematode and bacterial canker resistance in tomato, or to late blight and leaf roll in potato (*20*). These are, in fact, "genetically engineered" (although not rDNA-manipulated) plants, but they are not sequestered in laboratories or test plots by regulatory mandates. Their produce is commonly available at the local supermarket or farm stand.

The EPA's proposal to regulate plants with "pesticidal" properties introduced by means of rDNA technology (*2*) also stands in stark contrast to the conclusions and recommendations of groups such as the National Academy of Sciences (*21*), the NRC (*7*), and the National Biotechnology Policy Board (*5*). The EPA is moving deliberately toward case-by-case regulation of rDNA-manipulated pest- or disease-resistant plants and would again ignore genuine risk considerations. Thus, for example, regulated field trials would include those with wheat or corn in which a gene for chitinase or one of the other newly discovered disease-resistance genes has been added by rDNA manipulation; but they would exclude a poorly characterized hybrid between a tomato and toxic, inedible members of the "deadly nightshade" family, to which it is related. The EPA would exempt from review these hybrids created by means of traditional techniques because it views these hybrids as resulting from processes similar to those that occur in nature. It is ironic that the EPA's policies discriminate specifically against the new molecular techniques just as these methods are yielding a "bumper crop of disease resistance genes" that may be "the biggest thing since the discovery of chlorophyll" (*22*).

This EPA proposal was vetted by an extramural scientific advisory panel whose report warned that any such regulatory policy "will have a profound effect on future plant breeding programs" and that an unwise choice of regulatory scope will constitute a potent disincentive to research and

commercialization. Ironically, the panel was unable to make the connection between this observation and its ultimate recommendation to limit regulation to rDNA-manipulated plants. Ignoring both scientific considerations and the impending disincentives to research and development (which the quotation above suggests was of concern to them), the panel members based their recommendation largely on the dubious, 20-year-old precedent of the NIH rDNA Guidelines (now obsolete and no longer applicable to the oversight of plants) and on "a public perception that there are risks" (*2*). The latter assumption is not generally supported by reliable data (*23*).

The only other rationale offered by the panel was based on the erroneous assertions that only with rDNA techniques is it "possible to make novel genetic combinations never before possible," and that novelty is synonymous with risk [see above and (*2*)]. Extending this logic, the EPA would regulate the presently unregulated new genotypes produced by plant breeders who use conventional genetic techniques. Each year an individual breeder of corn, soybean, wheat, or potato tests in the field as many as 50,000 new genotypes [(*7*); see also (*15*)]. Many of these new variants result from interspecific or intergeneric wide crosses that transcend natural breeding barriers, and their genomes are, at best, poorly characterized. Not surprisingly, no one has suggested that these field trials require government review.

As discussed elsewhere, this application of flawed scientific assumptions or paradigms is partly a function of the manner in which the EPA handles its advisory process (*11*). Not infrequently on policy issues related to the new biotechnology, the EPA has maneuvered scientific advisory panels on predetermined courses; when scientists on those panels offered independent perspectives, they angered federal officials. For example, when University of California Professor Dennis Focht, an academic member of the EPA's Biotechnology Science Advisory Committee, observed in writing to the chairman that a policy decision to regulate on the basis of genetic technique rather than according to risk was founded on nonscientific considerations (*24*), he was subjected to a written rebuke from EPA Assistant Administrator Linda Fisher. A lawyer, she chided this distinguished scientist on his inability to "provide the Agency with [an] unbiased assessment of the scientific issues at hand," and, in effect, invited him to resign from the committee (*25*). This unseemly treatment of a scientific adviser is not an isolated incident (*26*). Incidents like this subvert the ability of scientists to contribute fully to public policy decisions.

## Policy Alternatives

It is ironic that during the decade of regulatory fumbling at the EPA, scientifically defensible risk-based models have been available. Regulatory and science agencies in the United States and other nations have devised a number of regulatory regimes on the basis of assumptions about the magnitude or the distribution of risk. For example, under the traditional U.S. Plant Pest Act regulations, permits are only required if the organisms under investigation are certain known plant pests; similar organisms, not known to be pests, are exempted. For example, *Agrobacterium tumefaciens* is classified as a pest under the Plant Pest Act, whereas closely related *Agrobacterium radiobacter* is exempt from regulation (*8*). The validity of these assumptions determines the integrity of the regulatory scheme; without them, we might as well flip a coin or exempt field trials proposed on certain days of the week.

The NIH and CDC, in establishing laboratory safety standards for handling pathogens, have used a similar approach. They have stratified microorganisms according to risk and specified combinations of microbiological practices, safety equipment, and facilities that are recommended for different risk categories (*6*). The risk-based proposal of Miller *et al.* for oversight of field trials likewise relies on scientific experts' stratification of organisms (*8*). The proposal describes an algorithm that is highly adaptable to the resources and needs of different forms of oversight and regulatory mechanisms and that can accommodate any organism, whether naturally occurring or genetically modified by old or new methods. Many national or international regulatory approaches employ inclusive lists of regulated articles such as plant pests or animal pathogens and operate within similar principles (*27*).

## Conclusions

The adoption by the EPA of risk-based approaches to oversight would have been a win-win proposition. The advantages would have been decreased direct government spending on regulation, stimulation of public and private sector R&D by removing the burden of regulatory disincentives, and reassurance to the public about the essential equivalence of new biotechnology to other more familiar techniques.

As it stands, however, the EPA's technique-based approach to biotechnology regulation is likely to exert a profoundly negative effect on agricultural research and on the commercialization of biological pest management strategies. Regulatory disincentives, increasingly enshrined in final regulations, will continue to deter researchers and companies from biological control strategies that could substitute safer genetically engineered microorganisms or plants for chemical pesticides. Innovations that may not provide sufficient financial return to offset the costs of testing and registration will be especially vulnerable (*28*). By limiting the available technological choices, the EPA's regulatory philosophy and policies are likely to damage, rather than protect, both the environment and agricultural research.

## REFERENCES AND NOTES


1. *Fed. Regist.* **59**, 45600 (1994).
2. Report of the Joint EPA FIFRA Scientific Advisory Panel and Biotechnology Science Advisory Committee Subpanel on Plant Pesticides, 10 February 1994.
3. H. I. Miller, in *Biotechnology*, D. Brauer, Ed. (VCH, Weinheim, Germany, in press).
4. B. W. Falk and G. Bruening, *Science* **263**, 1395 (1994).
5. National Biotechnology Policy Board Report, National Institutes of Health, Office of the Director, Bethesda, MD, 1992.
6. Anonymous, *Biosafety in Microbiological and Biomedical Laboratories* (Centers for Disease Control and National Institutes of Health, Department of Health and Human Services, Government Printing Office, Washington, DC, 1988).
7. *Field Testing Genetically Modified Organisms: Framework for Decisions* (National Academy Press, Washington, DC, 1989).
8. H. I. Miller, R. H. Burris, A. K. Vidaver, N. A. Wivel, *Science* **250**, 490 (1990).
9. M. Fumento, *Science Under Siege* (Morrow, New York, 1993), pp. 19–44.
10. Faced with a public relations barrage against Alar, EPA Assistant Administrator John Moore issued a statement asserting that "there is inescapable and direct correlation" between exposure to UDMH (the primary degradation product of Alar) and "the development of life-threatening tumors," and that therefore the EPA would soon propose barring Alar (EPA press release, 1 February 1989; and "EPA targets chemical used on apples," *Washington Post*, 2 February 1989, p. A4). (However, as EPA admitted separately, there were no data to support a finding of carcinogenicity.) Moore "urged" (this term has special magisterial meaning when the message comes from a high-level federal regulator) farmers who were using Alar to stop ("Hazard reported in apple chemical," *New York Times*, 2 February 1989, p. A1).
11. *Safeguarding the Future: Credible Science, Credible Decisions, The Report of the Expert Panel on the Role of Science at EPA* (EPA Document 600/9-91/050, March 1992).
12. *Fed. Regist.* **57**, 6753 (1992).
13. Anonymous, "Final rule on the testing of microbial pesticides," EPA background document accompanying the biotechnology microbial pesticides rule (*1*), EPA Office of Prevention, Pesticides and Toxic Substances, August 1994.
14. Important precedents are EPA's policies under FIFRA and Toxic Substances Control Act (TSCA), neither of which has traditionally required case-by-case reviews. Under FIFRA, all small-scale (less than 10 acres) field trials of microorganisms were considered automatically not to require EPA's review and were exempt from regulation. There was a similar but more vague exemption under TSCA of chemicals or microorganisms for "small quantities solely for R&D." While these approaches can hardly be said to be risk-based—they exempted both low-risk and other organisms alike—there was a certain logic, namely, that small-scale experiments generally are not of great safety concern. Under these exemptions, R&D was performed on thousands of microorganisms, for purposes as varied as pesticides, frost prevention, enhanced artificial snow–making, promoting the growth of plants, mining, oil recovery, bioremediation, and sewage treatment.

15. A study funded by the EPA had already confirmed the substantial incidental release from "containment"—approximately $10^8$ organisms per day per technician—of recombinant organisms into the environment from standard research labs (Lincoln *et al.*, "Release and containment of microorganisms from applied genetics activities," under EPA grant R-808317-01, 1983). Thus, a vast and varied release "experiment," involving thousands of laboratories and millions of discrete new genotypes of recombinant microorganisms, had been in progress for more than a decade.
16. R. J. Seidler and S. Hern, *Special Report: The Release of Ice-Minus Recombinant Bacteria at California Test Sites* (Environmental Protection Agency, Environmental Research Laboratory, Corvallis, OR, March 1988).
17. Two of the major stated purposes of the monitoring "experiment" in (*8*) were (i) "to determine distributions of the GEMs [genetically engineered microorganisms] on and off the plot during the meteorological conditions encountered during the spray and post-spray periods"; and (ii) "to provide recommendations for evaluating fate and transport of recombinant organisms for future field releases." However, as described in the text, there were already available relevant field trial data on wild-type and spontaneous mutants of *P. syringae*, making (i) superfluous; and (ii) cannot be accomplished by such an experiment: even in the ideal case, the data would only be meaningful for *P. syringae* in the particular environments where the tests were conducted. For example, the data would have no application to soil bacteria or those transmitted by animal or insect vectors.
18. A. K. Naj, *Wall Street Journal*, 30 January 1989.
19. R. B. Stewart, in *The Genetic Revolution*, B. D. Davis, Ed. (Johns Hopkins Univ. Press, Baltimore, MD, 1991), pp. 219–220.
20. R. M. Goodman, H. Hauptli, A. Crossway, V. C. Knauf, *Science* **234**, 48 (1987).
21. *Introduction of Recombinant DNA–Engineered Organisms into the Environment: Key Issues* (National Academy Press, Washington, DC, 1987).
22. A. S. Moffatt, *Science* **265**, 1804 (1994).
23. S. L. Huttner, in (*3*), in press.
24. R. Hoyle, *Bio/Technology* **10**, 742 (1992).
25. L. J. Fisher, EPA Assistant Administrator, letter to Dennis Focht, 21 August 1992.
26. During the Alar episode, a different EPA official (another lawyer) attempted to intimidate members of an advisory panel because their opinion differed from his own [(*9*) and R. J. Bidinotto, *Reader's Digest* (October 1990), pp. 55–56]. "Apparently, the EPA officials had expected the SAP [Scientific Advisory Panel] to rubber-stamp its decision [that Alar or UDMH was a carcinogen]. When it did not, Uniroyal [the manufacturer of Alar] officials were jubilant. But after the meeting, Steven Schatzow, then director of EPA's Office of Pesticide Programs, herded SAP members into his office. The angry Schatzow demanded, 'How can you do this to us?' After a heated exchange with the scientists, he concluded, 'Look, I can't tell you what to do, but you might like to think about this one again.' The scientists were stunned by such flagrant interference, and all refused to back down" (*9*).
27. United Kingdom: "Categories of pathogens according to hazard and categories of containment," Advisory Committee on Dangerous Pathogens, Her Majesty's Stationery Office, London, 1989. Germany: "Rictlinien sum Schutz vor Gefahren durch in-vitro neukombinierte Nucleinsäuren," Bundesministerium für Forschung und Technologie, Bonn, ed. 5, 1986. Netherlands: "Aanbevelingen voor Veilig Microbiologisch Werk," Nederlandse Vereniging voor Microbiologie, Bilthoven, ed. 2, 1984. France: "Contribution à l'etablissement d'une liste de microorganismses pathogènes pour l'homme," AFNOR-Report PrX 42-040, Fascicule de Documentation, Paris, 1988. Europe-wide (European Federation of Biotechnology): *Appl. Microbiol. Biotechnol.* **30**, 541 (1989).
28. R. J. Cook, letter to the Environmental Protection Agency Public Response Section, Field Operations Division, 17 September 1992.
29. I thank J. van Brunt, S. Huttner, and D. Kennedy for helpful suggestions and Stanford University's Center for Risk Analysis for support.