Regulatory Tangle Snarls Agricultural Research in the Biotechnology Arena

For scientists, the immediate future remains uncertain while debate rages on the safety of field testing altered organisms and on how much federal regulation is required

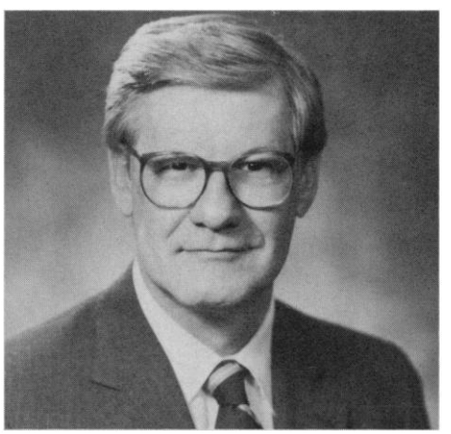
In June the Office of Science and Technology Policy (OSTP) published new guidelines to coordinate the regulation of biotechnology by federal agencies. To an extent they meet demands by university researchers and biotechnology companies for the government to undo the regulatory maze that has slowed some experiments. But for many researchers, especially those developing new plants, microbes, and other agricultural products, the new rules may produce more controversy than relief.

At issue is the safety of deliberately releasing genetically altered organisms into the environment and the extent to which such releases ought to be regulated. The scientific community, to varying degrees, is divided on what level of risk assessment is necessary for field tests, and on rules exempting certain types of organisms from intense federal review. The controversy extends to the environmental community and Congress, where five subcommittee chairmen in the House Science and Technology and Agriculture committees are siding with ecologists who favor close federal scrutiny of proposed releases.

Congressional calls for caution may aid activists such as Jeremy Rifkin and add to tensions at the local level where protests against a few field experiments have flared. The hundreds of comments on the new guidelines that have been filed with OSTP, Environmental Protection Agency (EPA), Department of Agriculture (USDA), Food and Drug Administration, and other federal agencies in recent weeks also demonstrate that debate on deliberate release is likely to get hotter.

Numerous regulatory ambiguities and conflicts remain, including getting federal agencies to agree on what constitutes a release into the environment. There are significant inconsistencies between EPA and USDA on the level of review that organisms proposed for field experiments will receive. Under general guidelines issued by OSTP, organisms would be excluded from regulation or subject to minimal review if they:

- Are created with genetic material from two or more genera that are highly characterized and contain only noncoding sequences. New organisms formed from different genera are subject to regulation when their behavior is not well understood;
- Belong to a species that has some pathogenic strains, but are generally recognized in the research community or in industry as being nonpathogenic;
- Contain genetic material from a donor pest that is highly understood and does not affect the regulatory functions of a nonpathogenic host organism;
- Are an "opportunistic" pathogen (organisms that do not act as pathogens except in unusual circumstances), or are derived from opportunistic pathogens;
- Result from the deletion or the addition of genetic material in organisms of the same genus.



Richard D. Godown *faults USDA's list of plant pests.*

Robert K. Colwell, a zoologist at the University of California at Berkeley and an officer of the Ecological Society of America, says the proposed exemptions and limits on regulatory reviews are too broad in many instances. "In our judgment," he says, "it seems likely that genetically engineered 'opportunistic' pathogens (or organisms receiving genetic material from them) will become virulent under certain environmental conditions."

As a case in point, he cites *Pseudomonas syringae*, the bacterial species which would be used in "ice-minus" experiments proposed by Steven Lindow of the University of California at Berkeley and by Advanced Genetic Sciences (AGS). The experiment calls for deleting a gene from a naturally occurring strain of the bacterium. The effect is to prevent the formation of a protein that encourages frost to form on strawberries, potatoes, and other crops. Colwell notes, however, that the same species also contains strains that are "serious pathogens." Scientific reviews of the ice-minus bacterium indicate it is not likely to be a pest, a finding, he concedes that will hold true in many other field experiments with genetically altered microorganisms.

Nevertheless, Colwell and the ecological society insist that it is wrong to assume categorically that the field experiments with certain species do not pose risks—whether they involve organisms containing material derived from pathogenic strains, nonpathogenic combinations across species, or simple gene deletions. This view is shared by some influential members of Congress. Says Representative, James H. Scheuer (D–NY), chairman of the subcommittee on natural resources, agriculture, research, and environment, "Right now no one can say with any certainty what's going to happen [ecologically]."

Long before OSTP issued its guidelines, congressional dissatisfaction with its approach to regulating biotechnology was evident. Representative Don Fuqua (D–FL), the retiring chairman of the House Science and Technology Committee, introduced a bill (*Science*, 28 March, p. 1501) to strengthen the regulatory mechanisms at EPA and USDA. Although the bill went nowhere, Bruce Mackler, general counsel for the Association of Biotechnology Companies, expects to see similar bills in 1987.

The potential for congressional intervention also is evident in comments submitted to OSTP by Representatives Scheuer, George E. Brown, Jr. (D–CA), and Harold L. Volkmer (D–MO), who chair three science subcommittees, and Berkley Bedell (D–IA) and Leon E. Panetta (D–CA), who chair subcommittees on agriculture. They argue that "until more is known about the effect on the environment . . . opportunistic pathogens and organisms containing any

alteration of noncoding regulatory sequences should, as a rule, receive the highest level of review."

Anne K. Vidaver, president of the American Phytopathological Society and a plant pathologist at the University of Nebraska, rejects this argument. "We do not believe that a recipient organism receiving genetic material from a plant pest should automatically be defined as a plant pest, or pathogen," says Vidaver. Under this stipulation, even widely used bacteria such as *Escherichia coli* would be subject to regulation when they contain material from a pathogen. She agrees with the proposal that opportunistic pathogens should be exempt from intense reviews "in view of the low risk."

Predictions of monster microorganisms being let loose to alter the landscape, says Vidaver, are "based on fears that are not supported by fact." New organisms created by biotechnology should be regulated, she says, in the context of a gene's function rather than its source. In their present form, the proposed regulations, says Vidaver, will hinder research. For example, the regulations could require a permit for some epidemiological and competition studies conducted with organisms developed through traditional chemical and radiation mutation methods. Depending on how long it takes to obtain a permit, planning research could become difficult, she says.

Equally stifling, says Richard D. Godown, executive director of the Industrial Biotechnology Association (IBA), is USDA's list of organisms that are or contain potential plant pests. It is excessive, he says, and "will trigger many needless reviews." The list should be narrowed, and the department should create a mechanism granting exemptions to investigators. Similarly, EPA needs to modify plans for reviewing microorganisms designed to act as pesticides in agriculture and for organisms used in fermentation and other industrial processes, IBA contends.

For researchers and companies working in the agricultural arena, the prospect of ongoing regulatory turmoil is troubling. Near-term revenues from designer plants and microbes are not critical to the survival of large companies in the agriculture sector such as Pioneer Hi-Bred International, a major seed supplier. But for smaller companies, getting over regulatory hurdles and bringing a few products to market may be essential. Kathy Behrens, an analyst with Robertson, Coleman & Stevens of San Francisco, says a prolonged debate could cause investors to lose interest in small, start-up companies.

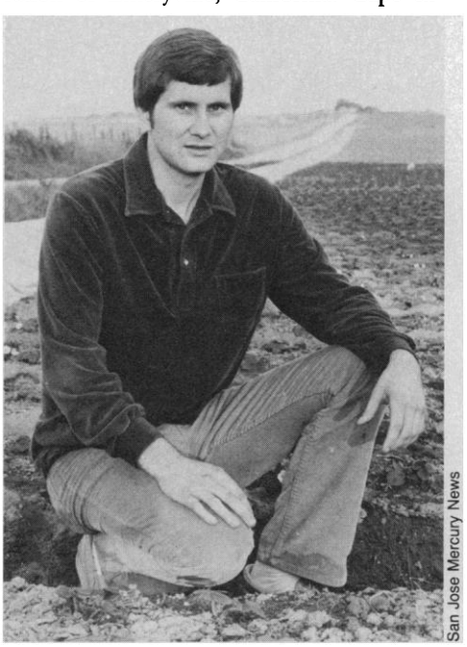
The Commerce Department and industry executives see other consequences, too.

Marjorie Sun is on leave from *Science* as a Vannevar Bush fellow in journalism at the Massachusetts Institute of Technology for the academic year.

Even large companies, such as Monsanto and Pioneer Hi-Bred, may shelve or abandon some research if obtaining permits takes too long. Worse yet, says Edwin B. Shykind, science adviser at Commerce's International Trade Administration, "We could see foreign companies buying up infant products and technology and transferring it out of the country."

Such dire forecasts are not accepted universally. Joseph G. Perpich, a vice president of Meloy Laboratories and a former member of the National Institutes of Health's Recombinant DNA Advisory Committee, is optimistic. The 3-year delay encountered by Lindow "is not going to be normal," he says. "Agricultural products will now move through [USDA] rapidly."

USDA officials, in fact, expect to process more than 200 applications for field experiments from researchers in the coming year. Nicholas Frey, director of research at Pioneer Hi-Bred, agrees that the regulatory mechanism can work effectively—if the agencies are given time. Not all executives share this view. "I am not optimistic," says Ronald E. Cape, chairman of Cetus Corporation of Emeryville, California. Cape expects that the industry will continue to encounter opposition from activists and members of Congress.



Glen Church *challenged AGS's field experiment.*

The ruckus over the regulation of biotechnology has yet to produce a ground swell of public protest. Predictably, though, social activist Jeremy Rifkin, who has played a central role in delaying the ice-minus experiments, also is bringing a court challenge against the guidelines. He says the process by which the guidelines were developed contravened federal regulations and the National Environmental Policy Act (*Science*, 1 August, p. 516). Until the court renders a decision, a cloud will hang over the legal standing of the Administration's action.

Also, rumblings emanating from Congress and the involvement of mainstream environmental groups such as the Natural Resources Defense Council (NRDC) and the Environmental Defense Fund (EDF) suggest that Rifkin will not be alone. These groups are examining the adequacy of risk assessment related to experiments and favor more review than that proposed by OSTP.

Environmentalists also are questioning whether EPA and USDA have adequate legal authority to regulate biotechnology. Margaret G. Mellon of the Environmental Law Institute, says USDA has little to rely on except the National Environmental Policy Act in attempting to protect the environment. This statute simply requires that actions be examined for their environmental impact, but provides scant regulatory authority. "What the department needs are marching orders from Congress to protect broad environmental interests, rather than just those of agriculture," says Mellon.

Representative John Dingell (D–MI), chairman of the House Energy and Commerce Committee, as well as House Science and Technology Committee members also see legal gaps in statutes that may hinder these agencies' ability to process experiment proposals and perform in court. As a result, legislation may be introduced in the House and Senate next spring to strengthen laws such as the Toxic Substances Control Act and Federal Plant Pest Act.

Whether opposition to field trials will be widespread is hard to predict. Ten years ago, there were similar protests across the country concerning the conduct of recombinant DNA technology experiments at university and industrial research laboratories. In most instances, protests faded away fairly rapidly after local review boards were established. The research, however, was being conducted in contained facilities.

As field experiments near, state legislatures, town managers, and unions may join with local citizens and activists in demanding more information about experiments.

Where they are not fully informed or have fears about the potential effects, there may be efforts to halt tests. For example, Glenn Church, a Salinas, California, Christmas tree farmer, fired off a letter to the Monterey County Board of Supervisors last January after reading in his local newspaper that Advanced Genetic Sciences would not divulge the location of its proposed test of a frost-inhibiting bacterium (*Science*, 14 March, p. 1242). He later contacted Rifkin for help.

After a public hearing, the AGS experiment was delayed by local officials, and subsequent revelations of an unauthorized experiment at the company's Oakland headquarters led EPA to suspend its field test permit. Church and a Tulelake, California, telephone company worker, who recently obtained a court order blocking Lindow's experiment, have since organized a statewide alliance to monitor future field tests.

Efforts are under way to find neutral forums to air scientific questions and work out disputes between various factions. The National Research Council, for example, will meet on 27 and 28 October in Millwood, Virginia, to consider whether it should delve deeper into the deliberate-release issue. Also, the Washington-based World Resources Institute (WRI) has sounded out Monsanto about starting a dialogue between factions. According to WRI's vice president for policy analysis, Andrew McGuire, the aim is to help find a common ground.

"There has to be compromise by environmentalists and by this industry," says Mackler of the Association of Biotechnology Companies, "otherwise we are not going to have an industry." Indeed, NRDC's director of scientific research, Khareem Ahmed, who wants assurances that proposed releases are examined systematically, notes that "biotechnology need not be as combative as other issues in the past."

Former EPA administrator William Ruckelshaus, who now represents a privately held Maryland biotechnology firm, Crop Genetics International, agrees that there is room for compromise. But he says scrapping the Administration's framework at this point is unwise because continued regulatory uncertainty could hurt American biotechnology companies in world markets. To get environmental activists to accept the current structure, he says, the Administration will have to make some concessions on its new guidelines and agree to strengthen weak statutes. ■ **MARK CRAWFORD**

California to Vote on AIDS Proposition

Academics and health officials are unusually vocal in speaking out against proposition they say rests on "facts" that are all wrong

San Francisco

CALIFORNIA is poised to be the first state in the nation to attempt to deal with AIDS by public referendum. On 4 November citizens will vote on a Draconian measure that would legally declare AIDS an "infectious, contagious, and easily communicable disease." Ballot Proposition 64, if passed, could force public health officials to establish camps to quarantine AIDS patients, as well as anyone who carries the AIDS virus. The measure would also flatly ban persons infected by the virus from attending or teaching in public schools or holding jobs that involve food handling.

Sponsored by a Lyndon LaRouche organization called PANIC (the Prevent AIDS Now Initiative Committee), Proposition 64 embodies all of the deepest fears about AIDS in one cold legislative package. PANIC, based in Los Angeles, had no trouble getting 683,000 California voters to sign the petition that put Proposition 64 on the ballot.

Opposition to the AIDS measure among health officials, physicians, and academics is strong and mounting. Stanford University president Donald Kennedy, medical school dean David Korn, Nobel Laureate Paul Berg, and W. K. H. Panofsky, former director of the Stanford Linear Accelerator Center, are among university professors who recently took out an ad in the local newspaper to voice their opposition. In a statement to the press, Korn, who also is the chairman of the National Cancer Advisory Board (a White House appointment), said, "As an individual who serves in a position of public responsibility, I am very cautious about making statements involving political issues. But this measure is not a matter of weighing the normal subtleties of public policy. It has been presented to the public based on patently inaccurate scientific information which unproductively feeds on public fears of a genuine health threat."

The deans and faculties of four California schools of public health have also banded together to defeat Proposition 64. They are the University of California public health campuses at Berkeley and Los Angeles, and the public health schools at Loma Linda and San Diego State universities. Berkeley dean Joyce C. Lashof, says it is the first time the state's schools of public health have ever taken a combined stand on any state initiative but says this one would be a "public health disaster." In a public report designed to influence voters, the schools have taken on the PANIC forces. "Contrary to its stated intent, Proposition 64 would have no public health benefits . . . but would instead impede ongoing, appropriate public health efforts by spreading both hysteria and misinformation about one of the most challenging diseases to confront public health and medicine in recent times," their 24-page policy paper states.

Health officials could be forced to quarantine AIDS patients and those who carry the virus.

PANIC is an offshoot of Lyndon LaRouche's National Democratic Policy Committee. In addition to defining AIDS as an "easily communicable disease," the PANIC proposition directs public health officials to assume that "the condition of being a carrier of HTLV-III (the AIDS virus) is an infectious, contagious, and communicable condition."

Because the proposition got on the ballot with an excess of 650,000 petition signatures and because, in itself, it does not use scare language, nearly every medical, public health, and civil rights organization in the state is afraid it could pass, despite a $3.5-