

**Chapter 11**

# **Regulation of Genetic Engineering**

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	<i>Page</i>
<b>Introduction . . . . .</b>	<b>211</b>
<b>Framework for the Analysis. . . . .</b>	<b>211</b>
<b>Current Regulation: the NIH Guidelines. . . . .</b>	<b>212</b>
<b>Substantive Requirements . . . . .</b>	<b>212</b>
<b>Administration . . . . .</b>	<b>212</b>
<b>Provisions for Voluntary Compliance . . . . .</b>	<b>215</b>
<b>Evaluation of the Guidelines . . . . .</b>	<b>216</b>
<b>The Problem of Risk . . . . .</b>	<b>216</b>
<b>The Decisionmaking Process. . . . .</b>	<b>221</b>
<b>Conclusion. . . . .</b>	<b>223</b>
<b>Other Means of Regulation . . . . .</b>	<b>224</b>
<b>Federal Statutes. . . . .</b>	<b>224</b>
<b>Law and Workmen's Compensation . . . . .</b>	<b>227</b>

<b>State and Local Law . . . . .</b>	<b>229</b>
<b>Conclusion . . . . .</b>	<b>230</b>
<b>Issue and options . . . . .</b>	<b>230</b>

## Tables

Table No.	<i>Page</i>
35. <b>Containment Recommended by National Institutes of Health . . . . .</b>	<b>213</b>
36. <b>Statutes That Will Be Most Applicable? to Commercial Genetic Engineering. . . . .</b>	<b>224</b>

# Regulation of Genetic Engineering

## Introduction

Although no evidence exists that any harmful organism has been created by molecular genetic techniques, most experts believe that some risk\* is associated with genetic engineering. One kind is relatively certain and quantifiable—that of working with known toxins or pathogens. Another is uncertain and hypothetical—that of the possible creation of a pathogenic or otherwise undesirable organism by reshuffling genes thought to be harmless. These may be thought of as physical risks because they concern human health or the environment.

Concern has also arisen about the possible long-range impacts of the techniques—that they may eventually be used on humans in some morally unacceptable manner or may change fundamental views of what it means to be human. These possibilities may be thought of as cultural risks, since they threaten fundamental beliefs and value systems.<sup>1</sup>

The issue of whether or not to regulate molecular genetic techniques—and if so, to what extent—defies a simple solution. Perceptions of the nature, magnitude, and acceptability of the risks differ drastically. Approximately 6 years ago, when the scientific community itself accepted a moratorium on certain classes of recombinant DNA (rDNA) research, some scientists considered the concern unnecessary. Today, even though the physical risks of rDNA research are generally considered to be less than originally feared—and the realization of its benefits much closer—some people would still prohibit it.

The Federal Government's approach to this issue has been the promulgation of the Guidelines for Research Involving Recombinant DNA Molecules (Guidelines), by the National Institutes of Health (NIH). (See app. III-C for information about what other countries have done

\*As used in this chapter, risk means the possibility of harm. The probability of that harm occurring may be extremely low and/or highly uncertain.

<sup>1</sup>H. Tristram Engelhardt, Jr., "Taking Risks: Some Background Issues in the Debate Concerning Recombinant DNA Research," *Southern California Law Review* 51:6, pp. 1141-1151, 1978.

with respect to guidelines for rDNA.) Three other available modes of oversight or regulation are current Federal statutes, tort law, and State and local law.

### *Framework for the analysis*

In deciding how to address the risks posed by genetic engineering, some of the important questions that need to be examined are:

- How broadly the scope of the issue (or problem) should be defined.
  - Who identifies the risks and their magnitude?
  - Who proposes the means for addressing the problem?
- The nature of the procedural, decisionmaking mechanism.
  - Who decides?
  - Who will benefit from the proposed action and who will bear the risk?
  - Will the risk be borne voluntarily or involuntarily?
  - Who has the burden of proof?
  - Should a risk/benefit analysis, or some other approach, be used?
- The available solutions and their adequacy.
  - Should there be full regulation, no regulation, or something in-between?
  - What actions and actors should be covered?
  - What is the appropriate means for enforcing a regulatory decision?
  - Which agency or other group should do the regulating?

Underlying these questions is the proposition, widely accepted by commentators on science policy, that scientists are qualified to assess physical risk, since that involves measuring and evaluating technical data. However, a judgment of safety (the acceptability of that risk) can only be made by society through the political process, since it involves weighing and choosing among values.<sup>2,3</sup> 456 Scientists are not nec-

<sup>2</sup>William W. Lowrance, *Of Acceptable Risk: Science and the Determination of Safety* (Los Altos, Calif.: William Kaufmann, Inc., 1976).

essarily considered to be more qualified to make decisions concerning social values than other well-informed persons; they may in fact be less qualified when the decision involves possible restrictions on scientific research because of the

(*op. cit.*)  
 W. Alvin W. Weinberg, "Science and Ethics," *Science*, April 10, 1973, pp. 327-332.  
 "Disputes Between Ethics and Science," *Science*, April 11, 1973, pp. 327-332.  
 Kantrowitz, "The Science Court Experiment," *Science*, April 11, 1973, pp. 332-333.  
 David L. David, "Risk and Responsibility," *Science*, vol. 205, no. 4380, 1979, pp. 277-280.

high value they place on unrestricted research and because of possible conflicts of interest. Moreover, according to this view, if society is to bear a risk, it should judge the acceptability of that risk and give its informed consent to it.<sup>7\*</sup>

(*op. cit.*)  
 Engelfardt, *op. cit.*; Lowy and *op. cit.*; *op. cit.*  
 ● [In practice, it may often be difficult to keep the two kinds of decisions separate, since the values of individual scientists may differ. Their interpretation of technical information and since scientists and makers may not have the technical competence to understand the risks.]  
 Weinberg, *op. cit.*; and *op. cit.*; *op. cit.*

## Current regulation: the NIH Guidelines

The Guidelines have been developing in stages over a period of approximately 6 years as scientists and policymakers have grappled with the risks posed by rDNA techniques. (This history, discussed in app. III-A, is crucial to understanding current regulatory issues, and it serves as a basis for evaluating the Guidelines.) They represent the only Federal oversight mechanism that specifically addresses genetic engineering.

### Substantive requirements

The Guidelines apply to all research involving rDNA molecules in the United States or its territories conducted at or sponsored by any institution receiving any support for rDNA research from NIH. Six types of experiments are specifically prohibited: 1) the formation of rDNA derived from certain pathogenic organisms; 2) the formation of rDNA containing genes that make vertebrate toxins; 3) the use of the rDNA techniques to create certain plant pathogens; 4) transference of drug resistance traits to micro-organisms that cause disease in humans, animals, or plants; 5) the deliberate release of any organism containing rDNA into the environment; and 6) experiments using more than 10 liters (1) of culture unless the rDNA is "rigorously characterized and the absence of harmful sequences established." A procedure is specified for obtaining exceptions

from these prohibitions. Five types of experiments are completely exempt.

Those experiments that are neither prohibited nor exempt must be carried on in accordance with physical and biological containment levels that relate to the degree of potential hazard. (See table 35.) Physical containment requires methods and equipment that lessen the chances that a recombinant organism might escape. Four levels, designated P1 for the least restrictive through P4 for the most, are defined. *Biological containment* requires working with weakened organisms that are unlikely to survive any escape from the laboratory. Three levels are specified. Classes of permitted experiments are assigned both physical and biological containment levels. Most experiments using *Escherichia coli K-12*, the standard laboratory bacterium used in approximately 80 percent of all experiments covered by the Guidelines, may be performed at the lowest containment levels.

### ADMINISTRATION

The Guidelines provide an administrative framework for implementation that specifies the roles and responsibilities of the scientists, their institutions, and the Federal Government. The parties who are crucial to the effective operation of the system are: 1) the Director of NIH, 2) the NIH Recombinant DNA Advisory Committee (RAC), 3) the NIH Office of Recombi-

**Table 35.—Containment Recommended by National Institutes of Health**

<b>Biological</b> —Any combination of vector and host must be chosen to minimize both the survival of the system outside of the laboratory and the transmission of the vector to nonlaboratory hosts. There are three levels of biological containment:	
HV1—	Requires the use of <i>Escherichia coli</i> K12 or other weakened strains of micro-organisms that are less able to live outside the laboratory.
HV2—	Requires the use of specially engineered strains that are especially sensitive to ultraviolet light, detergents, and the absence of certain uncommon chemical compounds.
HV3—	No organism has yet been developed that can qualify as HV3.
<b>Physical</b> —Special laboratories (P1-P4)	
P1—	Good laboratory procedures, trained personnel, wastes decontaminated.
P2—	Biohazards sign, no public access, autoclave in building, hand-washing facility.
P3—	Negative pressure, filters in vacuum line, class II safety cabinets.
P4—	Monolithic construction, air locks, all air decontaminated, autoclave in room, all experiments in class III safety cabinets (glove box), shower room.

SOURCE: Office of Technology Assessment.

nant DNA Activities (ORDA), 4) the Federal Interagency Advisory Committee on Recombinant DNA Research (Interagency Committee), 5) the Institution where the research is conducted, 6) the Institutional Biosafety Committee (IBC), 7) the Principal Investigator (PI), and 8) the Biological Safety Officer.

The *Director of NIH* carries the primary burden for the Federal Government's oversight of rDNA activities, since he is responsible for implementing and interpreting the Guidelines, establishing and maintaining RAC (a technical advisory committee) and ORDA (whose functions are purely administrative), and maintaining the Interagency Committee (which coordinates all Federal activities relating to rDNA). Under this arrangement, all decisions and actions are taken by the Director or his staff. For major actions, the Director must seek the advice of RAC, and he must provide the public and other Federal agencies with at least 30 days to comment on

proposed actions. Such actions include: 1) assigning and changing containment levels for experiments, 2) certifying new host-vector systems, 3) maintaining a list of rDNA molecules exempt from the Guidelines, 4) permitting exceptions to prohibited experiments, and 5) adopting changes in the Guidelines.

For other specified actions, the Director need only inform RAC, the IBCs, and the public of his decision. The most important of these are: 1) making minor interpretive decisions on containment for certain experiments; 2) authorizing, under procedures specified by RAC, large-scale work (involving more than 101 of culture) with rDNA that is rigorously characterized and free of harmful sequences; and 3) supporting laboratory safety training programs. Every action taken by the Director pursuant to the Guidelines must present '(no significant risk to health or the environment. "

RAC is an advisory committee to the Director on technical matters. It meets quarterly. Its purpose, as described in its current charter of June 26, 1980 (and unchanged since its inception in October 1974), is as follows:

The goal of the Committee is to investigate the current state of knowledge and technology regarding DNA recombinant, their survival in nature, and transferability to other organisms; to recommend guidelines for the conduct of recombinant DNA experiments; and to recommend programs to assess the possibility of spread of specific DNA recombinant and the possible hazards to public health and to the environment. This Committee is a *technical committee, established to look at a specific problem.* (Emphasis added.)

The charter and the Guidelines also assign it certain advisory functions that have changed over time.

The RAC is composed of not more than 25 members. At least eight must specialize in molecular biology or related fields; at least six must be authorities from other scientific disciplines; and at least six must be authorities on law, public policy, the environment, public or occupational health, or related fields. In addition,

representatives from various Federal agencies serve as nonvoting members.

ORDA performs administrative functions, which include reviewing and approving IBC membership and serving as a national center for information and advice on the Guidelines and rDNA activities.

The *Interagency Committee* was established in October 1976 to advise the Secretary of the then Department of Health Education and Welfare (HEW) [now Health and Human Services (DHHS)] and the Director of NIH on the coordination of all Federal activities relating to rDNA. It has thus far produced two reports. Its first, in March 1977, concluded that existing Federal law would not permit the regulation of all rDNA research in the United States to the extent considered necessary and recommended new legislation, specifying the elements of that legislation.<sup>10</sup> The second, in November 1977, surveyed international activities on regulating the research and concluded that, while appropriate Federal agencies should continue to work closely with the various international organizations, no formal governmental action was necessary to produce international control by means of a treaty or convention.<sup>11</sup> It is currently considering issues arising from the large-scale industrial applications of rDNA techniques.

Under the Guidelines, essentially all the responsibility for overseeing rDNA "experiments lies with those sponsoring or conducting the research. The Institution must implement general safety policies,<sup>\*</sup> establish an IBC, which meets specified requirements, and appoint a Biological Safety Officer. The *Biological Safety Officer*, who is needed only if the Institution conducts experiments requiring P3 or P4 containment, (see table 35) oversees safety standards. The initial responsibility for particular experiments lies

<sup>10</sup> *Interim Report of the Federal Interagency Committee on Recombinant DNA Research: Research Elements-for Legislation*, Mar. 15, 1977, pp. 9-10.

<sup>11</sup> *Report of the Federal Committee on Recombinant DNA on International Activities*, April 1977, pp. 13-15.

<sup>\*</sup>These include conducting surveillance that it determines to be necessary ensuring the Biological Safety officers, Principal Investigator, laboratory staff.

with the PI, the scientist receiving the funding. This person is responsible for determining and implementing containment and other safeguards and training and supervising staff. In addition, the PI must also submit a registration document that contains information about the project to the IBC, and petition NIH for: 1) certification of host-vector systems, 2) exceptions or exemptions from the Guidelines, 3) and determination of containment levels for experiments not covered by the Guidelines. Furthermore, all of the above have certain reporting requirements designed so that ORDA is eventually informed of significant problems, accidents, violations, or illnesses.<sup>\*\*</sup>

The IBC is designed to provide a quasi-independent review of rDNA work done at an institution. It is responsible for: 1) reviewing all rDNA research conducted at or sponsored by the institution and approving those projects in conformity with the Guidelines; 2) periodically reviewing ongoing projects; 3) adopting emergency plans for spills and contamination; 4) lowering containment levels for certain rDNA and recombinant organisms in which the absence of harmful sequences has been established; and 5) reporting significant problems, violations, illnesses, or accidents to ORDA within 30 days.<sup>\*\*\*</sup> The IBC must be comprised of no fewer than five members who can collectively assess the risks to health or the environment from the experiments. At least 20 percent of the membership must not be otherwise affiliated with the institution where the work is being done, and must represent the interests of the surrounding community in protecting health and the environment. Committee members cannot review a project in which they have been, or expect to be, involved or have a direct financial interest. Finally, the Guidelines suggest that IBC meetings be public; minutes of the meetings and submitted documents must be available to the public on request.

● The PI is required to report this information within 30 days to his or her Institution. The Biological Safety officer must report the information to the Institution and the ORDA unless the PI has done so. The Institution must report within 30 days to the ORDA unless the PI or the Institution has done so.

<sup>\*\*</sup> "It is the responsibility of the PI to report if the PI or Institution has done so."

The requirements imposed on an institution and its scientists are enforced by the authority of NIH to suspend, terminate, or place other conditions on its funding of the offending projects or all projects at the institution. Compliance is monitored through the requirements for notification mentioned above.

#### PROVISIONS FOR VOLUNTARY COMPLIANCE

Organizations or individuals who do not receive any NIH funds for rDNA research are not covered by the Guidelines. These include other Federal agencies, institutions and individuals funded by those agencies, and corporations.

Federal agencies other than NIH that conduct or fund rDNA research have proclaimed their voluntary compliance with the Guidelines. \* Staff scientists have been so informed by memoranda. As for outside investigators, this policy has been implemented through the grant application process. Instructions in grants applications contain policy statements regarding compliance with the Guidelines, and applicants are sometimes contacted to ascertain their knowledge of the Guidelines. Information has been requested for certain experiments, and IBC membership has been reviewed. From time to time, the agencies have consulted with NIH on matters that need interpretation.

Part VI of the Guidelines is designed to encourage voluntary compliance by industry. It creates a parallel system of project review and IBC approval analogous to that required for NIH-funded projects, modified to alleviate industry's concerns about protection of proprietary information.

The Freedom of Information Act requires Federal agencies, with certain exceptions, to make their records available to the public on request. One of the exceptions is for trade secrets and proprietary information obtained from others. Part VI contains several provisions for protecting this information. Perhaps the most important is a process whereby a corporation

may request a presubmission review of the records needed to register its projects with NIH. The DHHS Freedom of Information Officer makes an informal determination of whether the records would have to be released. If they are determined to be releasable, the records are returned to the submitting company. The Guidelines also require that NIH consult with any institution applying for an exemption, exception, or other approval about the content of any public notice to be issued when the application involves proprietary information. As a matter of practice, such applications are also considered by RAC in nonpublic sessions.

Large-scale experiments (more than 10<sup>1</sup> of culture) with rDNA molecules are prohibited unless the rDNA is "rigorously characterized and the absence of harmful sequences established." Such experiments are actually scale-ups of potential industrial processes. Those meeting this standard may be approved by the Director of NIH under procedures specified by RAC. \* At its September 1979 meeting, RAC adopted procedures for review that require the applicant to submit information on its laboratory practices and containment equipment. Subsequently, recommendations were developed for large-scale uses of organisms containing rDNA. These were published in the Federal Register on April 11, 1980. Besides setting large-scale containment levels, they require the institution to appoint a Biological Safety Officer with specified duties, and to establish a worker health surveillance program for work requiring P3 containment. At its September 1980 meeting, RAC modified its review procedures so that the application need only specify the large-scale containment level at which the work would be done, without providing details on containment equipment. RAC will continue to review the biological aspects of the applications in order to determine that rDNA is rigorously characterized, that the absence of harmful sequences is established, and that the proposed containment is at the appropriate level.

\*These agencies are the National Science Foundation, the Department of Agriculture, the Department of Energy, the Veterans Administration, and the Centers for Disease Control. Two others which have expressed interest in this research but are not currently sponsoring any projects, are the Department of Defense and the National Aeronautics and Space Administration.

at is not the company proposing the scale-up, that determines if the material to be used is "rigorously characterized and the absence of harmful sequences established."

for Research Involving Recombinant Molecules, sec. 3.

### ***Evaluation of the Guidelines***

Two basic issues must be addressed. The first is how well the Guidelines confront the risks from genetic engineering, which may not have a definitive answer in view of the uncertainty associated with most of the risks. Consequently, it is also necessary to consider a second issue—whether confidence is warranted in the decisionmaking process responsible for the Guidelines.

#### **THE PROBLEM OF RISK**

The Guidelines are designed to address the risks to public health and the environment from either rDNA molecules or organisms and viruses containing them. The underlying premise is that research should not be unreasonably restricted. This is essentially a risk-benefit approach; at the time that the original Guidelines were drafted, it represented a compromise between the extremes of no regulation and of no research without proof of safety. Physical and biological containment levels were established for various experiments based on estimated degrees of risk. The administrative mechanism created by the Guidelines is that of a Federal agency—NIH—advised by a diverse body of experts—RAC. Scientific advice on the technical aspects of risk assessment is provided by technical experts on RAC; public input is provided by experts in nontechnical subjects and by the right of the public to comment on major actions, which are published in the Federal Register. Compliance is accomplished by a combination of local self-regulation and limited Federal oversight, with the ultimate enforcement resting in the Federal funding power.

Since their initial appearance, the Guidelines have evolved. As scientists learned more about rDNA and molecular genetics, two trends occurred. First, containment levels were progressively lowered. Major revisions were made in 1978 and 1980; minor revisions were often made quarterly, as proposals were submitted to the RAC at its quarterly meetings, recommended by RAC, and accepted by the Director. By now, approximately 85 percent of the permitted experiments can be done at the lowest physical and biological containment levels. Second, the degree of centralized Federal over-

sight has been substantially reduced to the point where almost none remains. Under the 1976 Guidelines, all permitted experiments ultimately had to be reviewed by the IBC and ORDA before they could be started; the 1978 Guidelines no longer required preinitiation review of most experiments by ORDA, although ORDA continued to maintain a registry of experiments and to review IBC decisions. Under the November 1980 revision to the Guidelines, there will be no Federal registration or review of experiments for which containment levels are specified in the Guidelines. About 97 percent of the permitted experiments fall into this category.

Preinitiation review of experiments by RAC has been an important part of the oversight mechanism. Expert review encourages experimental design to be well thought out and provides a means for catching potential problems, e.g., one application reviewed by RAC never mentioned that the species to be used as a DNA donor was capable of manufacturing a potent neurotoxin; it was turned down after a RAC member familiar with the species brought this fact to the Committee's attention.<sup>13</sup>

The burdens imposed on rDNA activities by the Guidelines appear to be reasonable in view of continuing concerns about risk. Less than 15 percent of permitted experiments require preinitiation approval by the local IBC's, which usually meet monthly. Preinitiation approval of experiments by NIH is required only for: 1) experiments that have not been assigned containment levels by the Guidelines; 2) experiments using new host-vector systems, which must be certified by NIH; 3) certain experiments requiring case-by-case approval; and 4) requests for exceptions from Guideline requirements. The lowest containment levels place minimal burdens on the experimenter. (see table 35). For industrial applications, NIH approval must be received not only when the project is scaled-up beyond the 10-1 limit, but also for each additional scale-up of the same project. Many representatives of industry consider these subse

<sup>13</sup> M. <sup>13</sup>R "Trouble on 'rubble on the RAC: Splits Over Downgrading of *E. coli* Containment," *Bioscience*, *Riv* 29, pp. vol 762, December 1979.



quent approvals to be unnecessary and burdensome.

Information about whether the Guidelines have been a disadvantage for U.S. companies in international competition is scanty. Examples include the approximately 1-year headstart two European groups were given while the cloning of hepatitis B virus was prohibited, the advantage some European companies had in using certain species of bacteria for cloning under conditions that were prohibited in the United States, and the delays some pharmaceutical companies faced because they had to build better containment facilities.

The present Guidelines are a comprehensive, flexible, and nonburdensome way of dealing with the physical risks associated with rDNA research while permitting the work to go forward. That is all they were ever intended to do.

The Scope of the Guidelines.—In many respects, the Guidelines do **not** address the full scope of the risks of genetic engineering. They cover one technique, albeit the **most** important; they do not address the admittedly uncertain, long-term cultural risks; they are not **legally** binding on researchers receiving funds from agencies other than NIH; and they are not binding on industry.

Other genetic techniques present risks similar to those posed by rDNA, but to a lesser degree. Recombinant DNA is the most versatile and efficient technique; it uses the greatest variety of genetic material from the widest number of sources with reasonable assurance of expression by the host cell. Cell fusion of micro-organisms, which **also** involves the uncertain risk of recombining the genetic material of different species, is significantly less versatile and efficient than rDNA but mixes more genetic material. In addition, the parental cells may contain partial viral genomes that could combine to form a complete genome when the cells are fused. Transformation, a technique known for decades, similarly involves moving pieces of DNA between different cells. However, it is significantly less versatile and efficient than cell fusion, and it is generally considered to be virtually risk-free. Thus, cell fusion is in a gray area

between the other two techniques; yet no risk assessment has been done, and no Federal oversight exists.

Another limitation in the scope of the guidelines—and in the process by which they were formulated—is that long-range cultural risks (as distinguished from policy issues related to safety) were never addressed. As noted by the Director of NIH:<sup>14</sup>

NIH has been addressing the policy questions involving the safety of this research, **not** the 'potential future application . . . to the altering of the genetic character of higher forms of life, including man' . . .

Perhaps it was inappropriate to do more. Such ethical issues might be considered premature in view of the level of the development of the technology. The desire among many molecular biologists to move ahead with the research meant that experiments were being done; therefore the immediate potential for harm **was to** health and the environment. Thus, it was arguably necessary to develop a framework to deal with the risks based on what was known at the time. On the other hand, the broader questions of where the research might eventually lead and whether it should be done at all have been raised in the public debate. They have not been formally considered by the Federal Government.

Another limitation in the scope of the Guidelines is their nonapplicability to research funded or performed by other Federal agencies. However, agencies supporting such research are complying with the Guidelines as a matter of policy. There appears to be little reason for questioning these declarations of general policy. In practice, problems might arise if a mission is perceived to be at odds with the Guidelines or because of simple bureaucratic defense of territory—e.g., when the 1976 Guidelines were promulgated, two agencies—the Department of Defense (DOD) and the National Science Foundation (NSF) preserved the right to deviate for reasons of national security or differing interpreta-

<sup>14</sup>3. Dec. 22, 1978; Dec. 22, 1978, . 330(7. ulv 33067, 1978.

tions, respectively. \* DOD no longer claims an exception for national security.<sup>15</sup> NSF took its position when it approved funding for an experiment using a particular species of yeast that had not been certified by NIH, relying on an ambiguously worded section<sup>16</sup> in the Guidelines to assert that it could certify the host. subsequent revisions explicitly stated that these hosts had to be certified by the Director of NIH<sup>17,18</sup> and removed many similar ambiguities.

In the final analysis, NIH has indirect leverage over the actions of other agencies through its funding. All non-NIH funded rDNA projects at an institution which also receives NIH funds for rDNA work must comply with the Guidelines; otherwise NIH funds may be suspended or terminated.

While the procedures of other agencies for administering compliance are significantly less formal than those created by the Guidelines for NIH, they do rely heavily on NIH for help and advice, and they coordinate their efforts through the Interagency Committee and their nonvoting membership on RAC. So far, this voluntary compliance by the agencies appears to be working fairly well.

The most significant limitation in the scope of the Guidelines is their nonapplicability to industrial research or production on other than a voluntary basis. This lack of legal authority raises concerns not only about compliance but also about NIH's ability to implement a voluntary program effectively.

whether every company working with rDNA will view voluntary compliance to be in its best interest depends on a number of factors. In the past, certain short-sighted actions by even a few companies in a given industry has led to

\*For a statement of the DOD position, see the minutes of the November 23, 1976, meeting of the Federal Interagency Committee. At that time, DOD had no active or planned rDNA projects. NSF's statement of its intention to "preserve some level of independence of decision" was expressed in an internal NIH memorandum dated February 24, 1978, from the Deputy Director for Science, to the Director, he E

John H. Dr. John III., Assistant Secretary of Defense for Health Affairs, personal communication, Nov. 18, 1980.

<sup>16</sup>"Fungal or Similar Low Host-Vector Systems," 27902, 27920, 29027, 1976.

<sup>17</sup>4 Dec. 22, 1978, Sec. 2, 197 of the III-C Guidelines. 1s45 6724, 15 F.R. 6724, Jan. 9, 1980; of the 198

well-documented abuses and a host of Federal laws to curtail them. However, at least two constraints are operating in the case of the biotechnology industry. First, the possibility of tort lawsuits is an inducement to comply with the Guidelines, which would probably be accepted as the standard of care against which alleged negligence would be evaluated. (This concept is discussed in greater detail in the section on Tort Law and workman's compensation.) second, the threat of statutory regulation, which the companies have sought to avoid, always exists. Other factors are also at work. Except for the 10-1 limitation, for which cases-by-case exceptions must be sought, the large-scale containment recommendations of April 11, 1980, are not excessively burdensome, at least for pharmaceutical companies. The requirements are similar to measures that must currently be taken to prevent product contamination. In addition, the public debate should have made each company aware of the problems and the need for voluntary compliance before it invested substantially in biotechnology; expensive controls will not have to be retrofitted. However, one definite concern is that new companies attracted to the field will perceive their interests differently. Because they did not actually experience the period when legislation seemed inevitable and because they will be late entries in the race, they may be inclined to take shortcuts.

Besides the concern about whether industry has sufficient incentive to comply, there are a number of other reasons for questioning the effectiveness of the voluntary program. First, until very recently no member of RAC was an expert in industrial fermentation technology-yet the committee has been considering applications from industry for large-scale production since September 1979. \* This drawback was demonstrated at its March 1980 meeting, when the committee expressed uncertainty over what Federal or State safety regulations presently cover standard fermentation technology em-

• At its September 1980 meeting, RAC passed the following resolution, which has been accepted by the Director of Dir...

Members of the chosen to provide expertise in fermentation engineering, fermentation, and on large-wide production.

A fermentation technology expert was appointed in January 1981.

s. 77373, 15 F.R. 77373, N

ployed by the drug industry. Various members expressed concern in the March and June 1980 meetings about the Committee's continuance to make recommendations on the applications without a firm knowledge of large-scale production.

second, the provisions in part VI of the Guidelines, which allow prior review of submitted information by the DHHS Freedom of Information Act Officer, give an industrial applicant the option of withholding potentially important information on the grounds of trade secrecy, even when DHHS disagrees. Third, because some RAC members have been opposed to discussing industrial applications in closed session (needed to protect proprietary information), they have chosen not to participate in those sessions. Thus, some diversity of opinion and expertise has been lost. Fourth, monitoring for compliance after the scale-up applications are granted is limited. Some early applications were granted on the condition that NIH could inspect facilities, and at least one inspection was made. Under procedures adopted at the September 1980 meeting, a company's IBC will be responsible for determining whether the facilities meet the standards for the large-scale containment level assigned by RAC. A working group of RAC may visit the companies and their IBCs from time-to-time but only for information gathering purposes, rather than for regulatory actions. Fifth, even if noncompliance were found, no penalties can be imposed.

The members of RAC, acutely aware of the problems with voluntary compliance by industry, have been deliberating about them for almost 2 years. At a meeting in May 1979, they decided, by a vote of nine to six with six abstentions, to support the principle of mandatory compliance with the Guidelines by non-NIH funded institutions. However, the Secretary of HEW (Joseph Califano) decided to continue with the development of voluntary compliance provisions<sup>20</sup> which were adopted as Part VI of the Guidelines in January 1980. Actual RAC review of submissions from the private sector for large-scale work began in September 1979. At a meeting in June 1980, RAC debated the effectiveness

<sup>20</sup> of 1979, p. 7 of 79, pp. 6-7, 1979, p. 16, in *Recombinant DNA Research*, vol. 5, (Wash., D. C.: HEW, 1980), p. 165.

of NIH's quasi-regulation of industry. A primary concern was whether the RAC would be viewed as giving a "stamp of approval" to industrial projects, when, in fact, it has neither the authority nor the ability to do so. One member, lawyer Patricia King, stated:<sup>21</sup>

Voluntary compliance is the worst of all possible worlds. . . . You achieve none of the objectives of regulation and none of the benefits of being unregulated. All you're saying is 'I give a stamp of approval to what I see here before me without any authority to do anything.'

Most of the speakers expressed the desire that the various agencies in the Interagency Committee be responsible for such regulation. However, the Interagency Committee, which has been studying the problem since January 1980, has yet to decide what it can do. Thus, many of its members see RAC as filling a regulatory void until the traditional agencies take action.

Some regulatory agencies have begun to deal with specific problems within their areas of interest. The Occupational Safety and Health Administration will decide its regulatory policy on the basis of a study of potential risks to workers posed by the industrial use of rDNA techniques being conducted by the National Institute of Occupational Safety and Health (NIOSH). In a letter to the Director of NIH dated September 24, 1980, Dr. Eula Bingham, then Assistant Secretary for Occupational Safety and Health of the Department of Labor, estimated this process would take approximately 2 years. The Environmental Protection Agency (EPA) has awarded several contracts and grants to assess the risks of intentional release of genetically engineered micro-organisms and plants into the environment. And the Food and Drug Administration (FDA) has begun to develop policy with respect to products made by processes using genetically engineered micro-organisms. (Further details on agency actions are discussed in the section, *Federal Statutes*.)

**Compliance.**—The primary mechanism in the Guidelines for enforcing compliance is local self-regulation, with very limited Federal over-

<sup>21</sup> Susan Wright, Recommended NA Policy: Large-Scale Processing," *Environment*, vol. 22, September 1980, pp. 29,32.

sight. Penalties are based on NIH's power to restrict or terminate its funding.

The initial responsibility for compliance lies with the scientist doing the experiments. A researcher's attitude toward the risks of rDNA techniques and the necessity for the Guidelines appear to be an influential factor in the degree of compliance. A science writer who worked for 3 months in a university lab in 1976 noted sloppy procedures and a cavalier attitude, stating: "Among the young graduate students and post-doctorates it seemed almost chic not to know the NIH rules."<sup>22</sup> On the other hand, in the case of a recent violation of the Guidelines, it appears as if the investigator's graduate students were the first to raise questions.<sup>23 24</sup> Competitiveness is another important factor. Novice scientists must establish reputations, secure tenure in a tight job market, and obtain scarce research funds; established researchers still compete for grants and certainly for peer recognition. This competitive pressure could provide strong incentives to bend the Guidelines; on the other hand, it might be channeled to encourage compliance if it is believed that NIH will in fact penalize violations by restricting or terminating funding.

The first level of actual oversight occurs at the institution. An argument can be made that reliance on the PI and an IBC (that might be composed mostly of the PI's colleagues) provides too great an opportunity for lax enforcement or coverups. On the other hand, spreading responsibility among the institution, the PI, the IBC, and, in the case of more hazardous experiments, the Biological Safety Officer might reduce the chance of violations being overlooked or condoned. This responsibility is enhanced by the reporting requirements borne by each of these parties, designed so that ORDA learns of "significant" problems, accidents, violations, and illnesses. What is "significant" is not defined.

Public involvement at the local level acts as an additional safeguard. Twenty percent of the

L. 22) Janet "Recombinant Lab for DNA and rDNA 95 and in It," *Smithsonian*, vol. 8, June 1977, p. 62.

23) (Another "Another of [in] Guide] NIH) Guidelines ' 286, 14, 1980, p. 649.

24) Discussion. "DNA Rec Forces Resignation," *Signati* vol. 287, Sept. 18, 1980, p. 179.

IBCs members must be unaffiliated with the institution. IBC documents, including minutes of meetings, are publicly available, but meetings are not required to be held in public. On the other hand, the probable inability of the members who represent the public to understand the technical matters might limit their effectiveness.

How successful has compliance been? Three known violations have occurred. In each, no threat to health and the environment existed. In each, there was some confusion as to why the violations occurred. NIH is presently investigating the third violation. For the first two, it accepted explanations of misunderstandings and misinterpretations of the Guidelines. However, a Senate oversight report concluded:<sup>25</sup>

While undoubtedly most researchers have observed the guidelines conscientiously, it is equally clear that others have substituted their own judgments of safety for those of NIH.

No firm conclusions can be drawn on the question of compliance. The reporting of only a few violations could be evidence that the compliance mechanism embodied in the Guidelines has been working well. Or it could mean that some violations are not being discovered or reported.

The November 1980 amendments to the Guidelines substantially changed procedures designed to monitor compliance by abolishing a document called a Memorandum of Understanding and Agreement (MUA). It had been required for 15 to 20 percent of all experiments, those thought to be potentially most risky. The MUA, which was to be filed with ORDA by an institution, provided information about each experiment, and it was the institution's certification to NIH that the experiment complied with the Guidelines. By having the MUAs, ORDA could monitor for inconsistencies in interpreting the Guidelines, actual noncompliance, and the consistency and quality with which IBCs functioned nationwide. The amendments continued a trend begun in January 1980, when approximately 80 percent of the experiments,

25) "Recombinant DNA Research and Its Applications," *Oversight Report*, Subcommittee on Science, Technology, and Space of the Senate Committee on Commerce, Science and Transportation, Aug. 1978, p. 17.

those done with *E. coli* K-12, were exempted from the MUA requirement.

The abolition of the MUA essentially abolished centralized Federal monitoring of rDNA experiments. The only current Guideline provision that serves this kind of monitoring function is the requirement that the institution, the IBC, or the PI notify ORDA of any significant violations, accidents, or problems with interpretation. Limited monitoring of large-scale activities continues. Under NIH procedures (which are not part of the Guidelines) for reviewing applications for exemptions from the 10-1 limit, the application must include a copy of the registration document filed with the IBC. The manufacturing facilities may also be inspected by NIH, not for regulatory purposes, but to gather information for updating its recommended large-scale containment levels; The abolition of the MUA is consistent with traditional views that Government should not interfere with basic scientific research. Whether or not it will reduce either the incentive to comply with the Guidelines or the likelihood of discovering violations remains to be seen.

#### THE DECISIONMAKING PROCESS

Another way to evaluate the Guidelines besides considering their substantive requirements is to look at the process by which they were formulated. In a situation where there is uncertainty and even strong disagreement about the nature, scope, and magnitude of the risks, it is difficult to judge whether or not a proposed solution to a problem will be a good one. Society's confidence in the decisionmaking process and in the decisionmakers then becomes the issue. As David L. Bazelon, Chief Judge of the U. S. Court of Appeals for the District of Columbia, has stated:<sup>26</sup>

When the issues are controversial, any decision may fail to satisfy large portions of the community. But those who are dissatisfied with a particular decision will be more likely to acquiesce in it if they perceive that their views and interests were given a fair hearing. If the decision-maker has frankly laid the competing considerations on the table, so that the public knows the worst as well as the best, he is unlike-

<sup>26</sup> L. Bazelon, "Coping With Technology Through the Such Process," 62 *Harvard Law Review* 817,825, June 1977.

ly to find himself accused of high-handedness, deceit, or cover-up. We simply cannot afford to deal with these vital issues in a manner that invites public cynicism and distrust.

The manner in which the Guidelines themselves evolved has been controversial. (For a detailed discussion see app. III-A.) Initially, the scope and nature of the problem was defined by the scientific community; NIH organized RAC along the lines suggested by the NAS committee letter referred to in app. III-A. One of the goals of RAC was to recommend guidelines for rDNA experiments; it was not charged with considering broader ethical or policy issues or the fundamental question of whether the research should have been permitted at all. The original Guidelines were produced by a committee having only one nonscientist.

In late 1978, the Secretary of HEW significantly restructured RAC and modified the Guidelines in order to increase the system's accountability to the public, to "provide the opportunity for those concerned to raise any ethical issues posed by recombinant DNA research" and to make RAC "the principal advisory body . . . on recombinant DNA policy."<sup>27</sup> However, it has remained in large part a technically oriented body. Its charter was not changed in this respect; the Guidelines themselves state that its advice is "primarily scientific and technical," and matters presented for its consideration have continued to be mostly technical. One area where RAC has played a significant policy role, however, is in dealing with the issue of voluntary compliance by industry.

It could be argued that the system did provide for sufficient public input into the formulation of the problem\* and that no other formulation was realistic. The two meetings in 1976 and 1977 of the NIH Director's Advisory Committee and the hearing chaired by the general counsel of HEW in the fall of 1978 provided the opportunity for public comment on the overall Fed-

<sup>27</sup> California Association of Scientists, "Notice of Revised Guidelines for Recombinant DNA Research," 43 *Science* 60080-60081, Dec. 22, 1978.

\* The problem was conceived in terms of how to permit the search to be done while limiting the physical risks to an acceptable level. Other formulations were possible, the broadest being how to limit the risks, including cultural ones, to an acceptable level. Such a formulation could have resulted in a prohibition of the research.

eral approach to the controversy, including whether or not the problem had been too narrowly phrased. Similarly, Congress had the opportunity in 1977 to reevaluate the entire institutional response, taking into account any moral objections to the research in addition to those concerning safety. Yet the principal bills were based on the proposition that the research continue in a regulated fashion.

A related issue is the one of burden of proof. Should the proponents of a potentially beneficial technology be required to demonstrate minimal or acceptable risk even if that risk is uncertain or even hypothetical? Or should its opponents be required to demonstrate unacceptable risk? If the proposition is accepted that those who bear the risks, in this case the public as well as the scientists, must judge their acceptability, then the burden must be on the proponents. The scientific community clearly accepted this burden. The moratorium proposed by the NAS committee in July 1974 called for a suspension of certain types of rDNA experiments until the risks could be evaluated and procedures for adequately dealing with those risks could be developed. The Guidelines prohibited some experiments, specified containment levels for others, and required certification of host-vector systems. All actions approved by the Director of *ERTC* including the lessening of the restrictions imposed by the original Guidelines, have had to meet the requirement of presenting "no significant risk to health or the environment."

Two other criticisms have been directed against RAC, particularly in its early days. The first concerned inherent conflicts of interest. RAC's members were drawn from molecular biology and related fields. One of the early drafts of the Guidelines was criticized as being "tailored to fit particular experiments that are already on the drawing boards."<sup>28</sup> However, only a few of the members were actually working with rDNA.<sup>29</sup> A more serious criticism was the lack of a broad range of expertise. Although

the risks had been expressed in terms of potential hazards to human health and the environment, the original RAC had no experts in the areas of epidemiology, infectious diseases, botany or plant pathology, or occupational health. It did have one expert in enteric organisms, *E. coli* in particular.

These shortcomings were eventually remedied by expanding RAC's membership to allow the appointment of other experts, including some from nontechnical fields such as law and ethics. In addition to providing knowledge of other fields, these members served as disinterested advisors, since they had no direct interest in expediting the research. Thus, the Government dealt with the problem of conflicts of interest by offsetting the interested group with other groups. In view of the need for the technical expertise of the molecular biologists, this approach seems reasonable; nevertheless the matter could probably have been handled more expeditiously. Although the April 1975 amendment to the RAC charter added experts from such fields as epidemiology and infectious diseases, the charter did not require plant experts until September 1976 (shortly after the passage of the original Guidelines) and occupational health specialists until December 1978. In addition, while two nontechnical members were added in 1976 (one before and one after passage of the Guidelines), their number was not increased until secretary Califano reconstituted the Committee in late 1978.

The present makeup of RAC is fairly diverse. As of September 1980, nine of its members specialized in molecular biology or related fields, seven were from other scientific disciplines, and eight were from the areas of law, public policy, the environment, and public or occupational health.<sup>30</sup> Moreover, since December 1978, representatives of the interested Federal agencies have been sitting as nonvoting members. In January 1981, an expert on fermentation was added.

Wade, "Recombinant DNA: . . . Sets Strict Rules to Launch New Technology," *190Science* 1175,1179, 1975.

Elizabeth . . . a member of . . . at that time, . . . communication, Sept. 11, 1980.

Bernard . . . Special Assistant to the Director, . . . personal communication, Sept. 18, 1980.

One conflict of interest not solved by expanding the diversity of the RAC's membership is institutional in nature. NIH, the agency having primary responsibility for developing and administering the Guidelines, views its mission as one of promoting biomedical research. Although the Guidelines are not regulations, they contain many of the elements of regulations. They set standards, offer a limited means to monitor for compliance, and provide for enforcement, at least for institutions receiving NIH grants to do rDNA work; thus, they may be considered quasi-regulatory. Regulation is not only foreign but antithetical to NIH's mission. The current Director stated publicly at the June 1980 RAC meeting that the role of NIH is not one of a regulator, a role that must be avoided. Under these circumstances, perhaps another agency, or another part of DHHS, might be more appropriate for overseeing the Guidelines, since the attitudes and priorities of promoters are usually quite different from that of regulators.

If RAC has always been essentially a technical advisory body, who then has made the value decisions concerning the acceptability of the risks presented by rDNA and the means for dealing with them? The final decisionmaker has been the Director of NIH, with the notable exception in the case of the 1978 Guidelines, which contained the significant procedural revisions needed to meet Secretary Califano's approval.<sup>31</sup> The Director did have access to diverse points of view through the Director's Advisory Committee meetings and the public hearings held before the 1978 Guidelines. (See app. III-A.) In addition, major actions were always accompanied by a statement discussing the relevant issues and explaining the basis for the decisions; after the 1978 revisions, major actions had to be proposed for public comment before decisions were made. In theory, it may have been preferable for the public to have been substantially involved in the actual formation of the original Guidelines rather than simply to have reacted to a finished product. However, this probably would have slowed the process at a time when the, strong desire of the molecular biologists to

use the rDNA techniques could have threatened the notion of self-regulation. Today, there appears to be reasonable opportunity for public input through the process of commenting on proposed actions.

### **Conclusion**

The Guidelines are the result of an extraordinary, conscientious effort by a combination of scientists, the public, and the Federal Government, all operating in an unfamiliar realm. They appear to be a reasonable solution to the problem of how to minimize the risks to health and the environment posed by rDNA research in an academic setting, while permitting as much of that research as possible to proceed. They do not in any way deal with other molecular genetic techniques or with the long-term social or philosophical issues that may be associated with genetic engineering.

The Guidelines have been an evolving document. As more has been learned about rDNA and molecular genetics, containment levels have been significantly lowered. Also, the degree of Federal oversight has been substantially lessened. Under the November 1980 Guidelines, virtually all responsibility for monitoring compliance is placed on the IBCs. NIH's role will involve primarily: 1) continuing interpretation of the Guidelines, 2) certifying new host-vector systems, 3) serving as a clearinghouse of information, 4) continuing risk assessment experiments, and 5) coordinating Federal and local activities.

The most significant short-term limitation of the Guidelines is the way they deal with commercial applications and products of rDNA techniques. Although large-scale containment levels and related administrative procedures exist, there are several reasons for questioning the effectiveness of the voluntary compliance concept. The most serious problem has been the lack of expertise in fermentation technology on RAC. In addition, since the Guidelines are not legally binding upon industry, the NIH lacks enforcement authority, although there has been no evidence of industrial noncompliance. Finally, because of its role as a promoter of bio-

<sup>31</sup> *op. cit.*

medical research, NIH cannot be expected to act aggressively to fill this regulatory void.

As a model for societal decisionmaking on technological risks, the system created by the Guidelines could serve as a valuable precedent. It does a reasonable job of combining substantive scientific evaluation of technical issues with

procedural safeguards designed to accommodate social values and to limit conflicts of interest. The only major criticism is that procedural safeguards and public input were not significant factors when the rDNA problem was first addressed.

## other means of regulation

There are three other means available for regulating molecular genetic techniques and their products—current Federal statutes, tort law and workmen's compensation, and State and local laws. These all may be used to remedy some of the limitations of the Guidelines.

### *Federal statutes*

The question of whether existing Federal statutes provide adequate regulatory authority first arose with respect to rDNA research. In March 1977, the Interagency Committee concluded that while a number of statutes\* could provide authority to regulate specific phases of work with rDNA, no single one or combination would clearly reach all rDNA research to the extent deemed necessary by the Committee. Furthermore, while some could be broadly interpreted, the Committee believed that regulatory action taken on the basis of those interpretations would be subject to legal challenge.<sup>32</sup> This was the basis for their conclusion that specific legislation was needed and was one of the reasons behind the legislative effort discussed in app. III-A.

With respect to commercial uses and products of recombinant and other genetic techniques, a much more certain basis for regulation exists. Many of the Federal environmental, product safety, and public health laws are directed toward industrial processes and products. To a

large extent, the genetic technologies will produce chemicals, foods, and drugs—as well as pollutant byproducts—that will clearly come within the scope of these laws. However, there may be limitations in these laws and questions of their interpretation that may arise with respect to the manufacturing process, which employs large quantities of organisms, and when there is an intentional release of microorganisms into the environment—e.g., for cleaning up pollution. For a list of pertinent laws, see table 36.)

The Federal Food, Drug, and Cosmetic Act (FEDCA) and section 351 of the Public Health Service Act (42 U.S.C. 262) give FDA authority over foods, drugs, biological products (such as vaccines), medical devices, and veterinary medicines. This authority will also apply to those products when they are made by genetic engi-

**Table 36.—Statutes That Will Be Most Applicable to Commercial Genetic Engineering**

1. Federal Food, Drug, and Cosmetic Act (21 U.S.C. §301 et. seq.)
2. Occupational Safety and Health Act (29 U.S.C. §651 et. seq.)
3. Toxic Substances Control Act (15 U.S.C. §2601 et. seq.)
4. Marine Protection, Research, and Sanctuaries Act (33 U.S.C. §1401 et. seq.)
5. Federal Water Pollution Control Act, as amended by the Clean Water Act of 1977 (33 U.S.C. §1251 et. seq.)
6. The Clean Air Act (42 U.S.C. §7401 et. seq.)
7. Hazardous Materials Transportation Act (49 U.S.C. §1801 et. seq.)
8. Solid Waste Disposal Act, as amended by the Resource Conservation and Recovery Act of 1976 (42 U.S.C. §6901 et. seq.)
9. Public Health Service Act (42 U.S.C. §301 et. seq.)
10. Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C. §136 et. seq.)

SOURCE: Office of Technology Assessment.

\*The Committee concentrated on the following statutes: 1) the Occupational Safety and Health Act (29 U.S.C. §651 et. seq.); 2) the Toxic Substances Control Act (15 U.S.C. §2601 et. seq.); 3) the Hazardous Materials Transportation Act (49 U.S.C. §1801 et. seq.); and 4) the Public Health Service Act (42 U.S.C. §301 et. seq.).

<sup>32</sup>John Barrett, *Interagency Interactions on Recombinant DNA Research: Suggested Elements for Legislation*.



neering methods. However, interpretive questions arising out of the unique nature of the technologies—such as the type of data necessary to show the safety and efficacy of a new drug produced by rDNA techniques—will have to be resolved by the administrative process on a case-by-case basis.

FDA has not published any statements of official policy toward products made by genetic engineering. Since it has different statutory authority for different types of products, it is likely that regulation will be on a product-by-product basis through the appropriate FDA bureau. Substances produced by genetic engineering will generally be treated as analogous products produced by conventional techniques with respect to standards for chemistry, pharmacology, and clinical protocols; however, quality controls may have to be modified to assure continuous control of product purity and identity. In addition, for the time being, the Bureau of Drugs and the Bureau of Biologics will require a new Notice of Claimed Investigational Exemption for a New Drug and a new New Drug Application for products made by rDNA technology, even if identity with the natural substance or with a previously approved drug is shown. This policy is based on the position that drugs or biologics made by rDNA techniques have not become generally recognized by experts as safe and effective and therefore meet the statutory definition of a “new drug.”<sup>33\*</sup>

FFDCA also permits regulation of drug, food, and device manufacturing. Certain FDA regulations, called Good Manufacturing Practices, are designed to assure the quality of these products. FDA may have to revise these to accommodate genetic technologies; it has the authority to do so. It probably does not have the authority to use these regulations to address any risks to workers, the public, or the environment, since FFDCA is designed to protect the consumer of the regulated product.

<sup>33</sup> Report of the Industrial Practices Subcommittee of the Federal Interagency Advisory Committee on Recombinant DNA Research, Dec. 16, 1980, p. 3.

\*Sec. 201(p) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. §321(p)) defines a new drug as “any article the composition of which is such that such article is not generally recognized among experts qualified by scientific experience and training as safe and effective for use in man.”

The statute most applicable to worker health and safety is the Occupational Safety and Health Act, which grants the Secretary of Labor broad power to require employers to provide a safe workplace for their employees. This power includes the ability to require an employer to modify work practices and to install control technology. The statute creates a general duty on employers to furnish their employees with a workplace “free from recognized hazards that are causing or are likely to cause death or serious physical harm,” and it requires employers to comply with occupational safety and health standards set by the Secretary of Labor. According to a recent Supreme Court case, a standard may be promulgated only on a determination that it is “reasonably necessary and appropriate to remedy a significant risk of material health impairment.”<sup>34</sup> Because these fairly stringent requirements limit the Act’s applicability to recognized hazards or significant risks, the statute could not be used to control manufacturing where the genetic techniques presented only hypothetical risks. However, it should be applicable to large-scale processes using known human toxins, pathogens, or their DNA.

The Secretary of Labor is also directed to account for the “urgency of the need” in establishing regulatory priorities. How the Department of Labor will view genetic technologies within its scale of priorities remains to be seen. NIOSH, the research organization created by this statute, has been studying rDNA production methods to determine what risks, if any, are being faced by workers. It has conducted fact-finding inspections of several manufacturers, and it is planning a joint project with EPA to assess the adequacy of current control technology. In addition, a group established by the Center for Disease Control (CDC) together with NIOSH will be making recommendations on: 1) the medical surveillance of potentially exposed workers, 2) the central collection and analysis of medical data for epidemiological purposes, and 3) the establishment of an emergency response team.<sup>35</sup>

<sup>34</sup> *Union Department Department, AFL-CIO v. American Institute*, 100 S. Ct. 2844, 2863, 1980.

<sup>35</sup> Report of the Industrial Practices Subcommittee of the Federal Interagency Advisory Committee on Recombinant DNA Research, Dec. 16, 1980, op. cit., p. 6.

The Toxic Substances Control Act (TSCA) was intended by Congress to fill in the gaps in the other environmental laws. It authorizes EPA to acquire information on "chemical substances" in order to identify and evaluate potential hazards and then to regulate the production, use, distribution, and disposal of those substances.

A "chemical substance" is defined under section 3(2) of this Act as "any organic or inorganic substance of a particular molecular identity," including "any combination of such substances occurring in whole or in part as a result of a chemical reaction or occurring in nature."\* This would include DNA molecules; however, it is unclear if the definition would encompass genetically engineered organisms. In promulgating its Inventory Reporting Regulations under TSCA on December 23, 1977, EPA took the following position in response to a comment that commercial biological preparations such as yeasts, bacteria, and fungi should not be considered chemical substances:<sup>36</sup>

The Administrator disagrees with this comment . . . . This definition [of chemical substance] does not exclude life forms which may be manufactured for commercial purposes and nothing in the legislative history would suggest otherwise.

However, in a December 9, 1977, letter responding to a Senate inquiry, EPA Administrator Douglas M. Costle stated:<sup>37</sup>

[A]lthough there is a general consensus that recombinant DNA molecules are "chemical substances" within the meaning of section 3 of TSCA, it is not at all clear whether a host organism containing recombined DNA molecules fits—or was intended to fit—that definition . . . . If such organisms are subject to TSCA on the grounds that they are a "combination of . . . substances occurring in whole or in part as a result of a chemical reaction," the Agency might logically have to include all living things in the definition of "chemical substance"—an inter-

"Substances subject solely to FFDCA or the Federal Insecticide, Fungicide, and Rodenticide Act are excluded from this definition.

F. R., 64572, 64584, Dec. 23, 1977.

to 371 of E. Stevenson, Chairman, Subcommittee on Science, Technology, and Space, U.S. Senate Committee on Commerce, Science, and Transportation, in *Report, Joint Hearing on the Department of Health and Its Applications, 95th Congress, August 1978*, GUS

pretation which I am confident the Congress neither contemplated nor intended.

If EPA were to take the broader interpretation, and if that were to survive any legal challenge, TSCA would have great potential for regulating commercial genetic engineering by regulating the organisms. Under section 4 of this Act, EPA can adopt rules requiring the testing of chemical substances that "may present an unreasonable risk"\* to health or the environment when existing data are insufficient to make a determination. Under section 5, the manufacturer of a new chemical substance is required to notify EPA 90 days before beginning production and to submit any test data available on the chemical's health or environmental effects. If EPA decides that the data are insufficient for evaluating the chemical's effects and that it "may present an unreasonable risk" or will be produced in substantial quantities, the chemical substance's manufacture or use can be restricted or prohibited. Under section 6, EPA can prohibit or regulate the manufacture or use of any chemical substance that "presents, or will present an unreasonable risk of injury to health or the environment."

As with the Occupational Safety and Health Act, the scientific evidence probably does not support a finding that most genetically engineered molecules or organisms present an unreasonable risk. On the other hand, the standard in section 5—may present an unreasonable risk—and the requirement for a premanufacturing notice would permit EPA to evaluate cases where genetically engineered micro-organisms were proposed to be released into the environment.

Several other environmental statutes will apply, mainly with respect to pollutants, wastes, or hazardous materials.\*\* The Marine Protec-

\*The term "unreasonable risk" is not defined in the statute. However, the legislative history indicates that its determination involves balancing the probability that harm will occur and the magnitude and severity of that harm, against the effect of the proposed regulatory action and the availability to society of the benefits of the . . . .  
31 1341, 31 1341, 2d 1341, 1976, pp. 13-15.

\*\*Two consumer protection statutes were considered . . . were determined to be virtually inapplicable. These were: the Federal Hazardous Substances Act, 15 U.S.C. § 1195 (et. seq.); and the Consumer Product Safety Act, 15 U.S.C. § 2051 (et. seq.).

tion, Research, and Sanctuaries Act prohibits ocean dumping without an EPA permit of any material that would “unreasonably degrade or endanger human health, welfare, or amenities, or the marine environment, ecological systems, or economic potentialities.”<sup>39</sup> “Material” is defined as “matter of any kind or description, including . . . biological and laboratory waste . . . and industrial . . . and other waste.”<sup>40</sup> The Federal Water Pollution Control Act regulates the discharge of pollutants (which include biological materials) into U.S. waters, and the Solid Waste Disposal Act regulates hazardous wastes. The Clean Air Act regulates the discharge of air pollutants, which includes biological materials. Especially applicable is section 112 (42 U.S.C. 7412), which allows EPA to set emission standards for hazardous air pollutants—those for which standards have not been set under other sections of the Act and which “may reasonably be anticipated to result in an increase in mortality or an increase in serious irreversible, or incapacitating reversible, illness.” The Hazardous Materials Transportation Act covers the interstate transportation of dangerous articles, including etiologic (disease-causing) agents. The Secretary of Transportation may designate as hazardous any material that he finds “may pose an unreasonable risk to health and safety or property” when transported in commerce in a particular quantity and form.<sup>41</sup>

Section 361 of the Public Health Service Act (42 U.S.C. §264) authorizes the Secretary of HEW (now DHHS) to “. . . make and enforce such regulations as in his judgment are necessary to prevent the introduction, transmission, or spread of communicable diseases . . . .” Because of the broad discretion given to the Secretary, it has been argued that this section provides sufficient authority to control all rDNA activities. \* Others have argued that its purpose is to protect only human health; for regulations to be valid, there would have to be a supportable finding of a connection between rDNA and

human disease. In any event, HEW declined to promulgate any regulations.

The following conclusions can therefore be made on the applicability of existing statutes. First, the products of genetic technologies—such as drugs, chemicals, pesticides,\*\* and foods—would clearly be covered by statutes already covering these generic categories of materials. Second, uncertainty exists for regulating either production methods using engineered micro-organisms or their intentional release into the environment, when risk has not been clearly demonstrated. Third, the regulatory agencies have begun to study the situation but, have not promulgated specific regulations. Fourth, since regulation will be dispersed throughout several agencies, there may be conflicting interpretations unless active efforts are made by the Federal Interagency Committee to develop a comprehensive, coordinated approach.

### ***Tort law and workmen’s compensation***

Statutes and regulations are usually directed at preventing certain types of conduct. While tort law strives for the same goal, its primary purpose is to compensate injuries. (A tort is a civil wrong, other than breach of contract, for which a court awards damages or other relief. ) By its nature, tort law is quite flexible, since it has been developed primarily by the courts on a case-by-case basis. Its basic principles can easily be applied to cases where injuries have been caused by a genetically engineered organism, product, or process. It therefore can be applied to cases involving genetic technologies as a means of compensating injuries and as an incentive for safety-conscious conduct. The most applicable concepts of tort law are negligence and strict liability. (A related body of law—workmen’s compensation—is also pertinent. )

Negligence is defined as conduct (an act or an omission) that involves an unreasonable risk of harm to another person. For the injured party to be compensated, he must prove in court that: 1) the defendant’s conduct was negligent, 2) the

<sup>39</sup> 33  
• 33 • \$1412.  
1402(c).  
<sup>40</sup> 49 • 1803.

<sup>41</sup> On Nov. 11, 1976, the Natural Resources Defense Council and the Environmental Defense Fund petitioned the Secretary of HEW to promulgate regulations concerning “ ” under this Act.

•• Pesticides to the Insecticide Fungicide, et.

defendant's actions in fact caused the injury, and 3) the injury was not one for which compensation should be denied or limited because of overriding policy reasons.

Because of the newness of genetic technology, legal standards of conduct (e.g., what constitutes unreasonable risk) have not been articulated by the courts. If a case were to arise, a court would undoubtedly look first to the Guidelines. Even if a technique other than rDNA were involved, they would provide a general conceptual framework for good laboratory and industrial techniques. Other sources for standards of conduct include: 1) CDC's guidelines for working with hazardous agents; 2) specific Federal laws or regulations, such as those under the Public Health Service Act covering the interstate transportation of biologic products and etiologic agents; and 3) industrial or professional codes or customary practices, such as generally accepted containment practices in the pharmaceutical industry or in a microbiology laboratory. Compliance with these standards, however, does not foreclose a finding of negligence, since the courts make the ultimate judgment of what constitutes proper conduct. In several cases, courts have decided that an entire industry or profession has lagged behind the level of safe practices demanded by society. \* Conversely, noncompliance with existing standards almost surely will result in a finding of negligence, if the other elements are also present.

Causation may be difficult to prove in a case involving a genetically engineered product or organism. In the case of injury caused by a pathogenic micro-organism—e.g., it may be difficult to isolate and identify the micro-organism and virtually impossible to trace its origin, especially if it had only established a transitory ecological niche. In addition, it might be difficult to reconstruct the original situation to determine if the micro-organism simply escaped despite

example, see: *The T. J.*, 60 S.W.2d 737 (2d Cal. 1932), concerning tugboats; and *Robinson v. Carey*, 519 P. 2d 981 (1974), where the court held that the general practice among ophthalmologists of not performing glaucoma tests on patients under 40 (because they had only a one in 25,000 chance of having the disease) would not prevent a finding of negligence when such patient developed the disease.

precautions or if culpable human action was involved. On the other hand, if a micro-organism or toxin is identified, it may be so unique because of its engineering that it can be readily associated with a company known to produce it or with a scientist known to be working with it. \*\*

The law recognizes that not every negligent act or omission that causes harm should result in liability and compensation—e.g., the concept of “foreseeable” harm serves to limit a defendant's liability. The underlying social policy is that the defendant should not be liable for injuries so random or unlikely as to be not reasonably foreseeable. This determination is made by the court. In the case of a genetically engineered organism, extensive harm would probably be foreseeable because of the organism's ability to reproduce; how that harm could occur might not be foreseeable.

Unlike negligence, strict liability does not require a finding that the defendant breached some duty of care owed to the injured person; the fact that the injury was caused by the defendant's conduct is enough to impose liability regardless of how carefully the activity was done. For this doctrine to apply, the activity must be characterized as “abnormally dangerous.” To determine this, a court would look at the following six factors, no one of which is determinative:<sup>42</sup>

1. existence of a high risk of harm,
2. great gravity of the harm if it occurs,
3. inability to eliminate the risk by exercising reasonable care,

<sup>42</sup> several companies were working with the micro-organism, it could be impossible to prove which company produced the particular ones that caused the harm. A recent California Supreme Court case, *Robinson v. Abbott Laboratories*, 26 Cal. 4th 588, 1980, could provide a way around this problem if the new theory of liability that it establishes becomes widely accepted by courts in other jurisdictions. The Court ruled that women whose mothers had taken a drug that allegedly caused cancer in their daughters, could proceed to trial against manufacturers of the drug, even though most of the plaintiffs would not be able to show which particular manufacturers produced the drug. The Court said that when the defendant manufacturers had a substantial share of the product market, liability, if found, would be apportioned among the defendants on the basis of their market share. A particular defendant could escape liability only by proving it could not have made the drug. *Robinson v. Abbott Laboratories*, 26 Cal. 4th 588 (1976).

4. extent to which the activity is not common,
5. inappropriateness of the activity to the place where it is done, and
6. the activity's value to the community.

Given the current consensus about the risks of genetic techniques, it would be difficult to argue that the doctrine of strict liability should apply. However, in the extremely unlikely event that a serious, widespread injury does occur, that alone would probably support a court's determination that the activity was abnormally dangerous, regardless of its probability. In such cases, the courts have generally relied on the principle of "enterprise liability"—that those engaged in an enterprise should bear its costs, including the costs of injuries to others.<sup>43</sup>

For either negligence or strict liability, the person causing the harm is liable. Under the legal principle of *respondent superior*, liability is also imputed from the original actor to people or entities who have a special relationship with him—e.g., employers. Thus, a corporation can be liable for the torts of its scientists or production workers. Similarly, a university, an IBC, a Biological Safety Officer, and a PI would probably be liable for the torts of scientists and students under their direction.

Another body of law designed to compensate injuries deserves brief mention. Workmen's compensation is a statutory scheme adopted by the States and—for specific occupations or circumstances—by the Federal Government to compensate injuries without a need for showing fault. The employee need only show that the injury was job-related. He is then compensated by the employer or the employer's insurance company. It would clearly apply to genetic engineering.

Tort law and workmen's compensation will be available to compensate any injuries resulting from the use of molecular genetic techniques, especially from their commercial application. Tort law may also indirectly prevent potentially hazardous actions, although the de-

terrent effect of compensation is less efficient than direct regulation—e.g., the threat of lawsuits will not necessarily discourage high-risk activities where problems of proof make recovery unlikely, where the harm may be small and widespread (as with mild illness suffered by a large number of people), or where profits are less than the cost of prevention but greater than expected damage awards and legal costs.

Tort law has two other limitations. First, tort litigation involves high costs to the plaintiff, and indirectly to society. Second, it cannot adequately compensate the victims of a catastrophic situation where liability would bankrupt the defendant.

### ***State and local law***

Under the 10th amendment to the Constitution, all powers not delegated to the Federal Government are reserved for the States or the people. One of those is the power of the States and municipalities to protect the health, safety, and welfare of their citizens. Thus, they can regulate genetic engineering.

The reasons espoused in favor of local regulation are based on the traditional concept of local autonomy; those most likely to suffer any adverse affects of genetic engineering should control it. Also, local and State governments are usually more accessible to public input than the Federal Government. Consequently, judgments on the acceptability of the risks will more precisely reflect the will of the segment of the public most directly affected.

A number of arguments have been made against local as opposed to Federal regulation. The primary one is that regulation by States and communities would give rise to a random patchwork of confusing and conflicting controls. In addition, States and especially localities may not have the same access as the Federal Government to the expertise that should be used in the formulation of rational controls. Finally, any risks associated with rDNA or other techniques are not limited by geographic boundaries; therefore, they ought to be dealt with nationally. The above arguments reflect the position that regulation of genetic technologies is a na-

<sup>43</sup> See, e.g., "Enterprise Liability and the Law: Legal Aspects of Recombinant DNA Research," in *The Recombinant DNA Debate*, Jackson and Stich (eds.) (Englewood Cliffs, N. J.: Prentice-Hall, Inc. 1979), pp. 219, 223.

tional issue that can be handled most effectively at the Federal level.

A few jurisdictions have used their authority in the case of rDNA. \* The most comprehensive regulation was created by the States of Mary-

● Cambridge, Mass., established a citizens' study group that recommended that researchers be subject to some additional restrictions beyond those of the Guidelines. These were embodied in an ordinance passed by the City Council on Feb. 1977. The City Council passed an ordinance requiring private research to conform to the Guidelines. Similar ordinances or resolutions were passed by Princeton, N.J., Amherst, Mass., and

land and New York.<sup>45</sup> Currently, there is little, if any, effort on the State or local level to pass laws or ordinances covering rDNA or similar genetic techniques, and there is little activity under the existing laws.

of Maryland, art. 43, §§ 898-910  
Laws of New York, Health  
art. 32-A, § 1701 (1980)

## Conclusion

The initial question with respect to regulating genetic engineering is how to define the scope of the problem. This will depend largely on what groups are involved in that process and how they view the nature, magnitude, and acceptability of the risks. Similarly, the means of addressing the problem will be determined by how it is defined and who is involved in the actual decisionmaking process. For these reasons, it is important that regulatory mechanisms combine scientific expertise with procedures to accommodate the values of those bearing the risk so that society may have confidence in those mechanisms.

Currently, genetic techniques and their products are regulated by a combination of the

Guidelines, Federal statutes protecting health and the environment, some State or local laws, and the judicially created law of torts, which is available to compensate injuries after they occur. In most cases, this system appears adequate to deal with the risks to health and the environment. However, there is some concern regarding commercial applications for the following reasons: 1) the voluntary applicability of the Guidelines to industry, 2) RAC's insufficient expertise in fermentation technology, 3) the potential interpretive problems in applying existing law to the workplace and to situations where micro-organisms are intentionally released into the environment, and 4) the absence of a definitive regulatory posture by the agencies.

## Issue and Options

### ISSUE: How could Congress address the risks associated with genetic engineering?

A number of options are available, ranging from deregulation through comprehensive new regulation. An underlying issue for most of these options is: What are the constitutional constraints placed on congressional regulation of molecular genetic techniques, particularly when they are used in research? (This is discussed in app. III-B.)

### OPTIONS:

A: Congress could maintain the status quo by letting NIH and the regulatory agencies set the Federal policy.

This option requires Congress to determine that legislation to remedy the limitations in current Federal oversight would result in unnecessary and burdensome regulation. No known harm to health or the environment has occurred under the current system, and the agencies generally have significant legal authority

and expertise that should permit them to adapt to most new problems posed by genetic engineering. The agencies have been consulting with each other through the Interagency Committee, and the three agencies that will play the most important role in regulating large-scale commercial activities—FDA, OSHA, and EPA—have been studying the situation.

The disadvantages of this option are the lack of a centralized, uniform Federal response to the problem, and the possibility that risks associated with commercial applications will not be adequately addressed. Certain applications, such as the use of micro-organisms for oil recovery are not unequivocally regulated by current statutes; broad interpretations of statutory language in order to reach these situations may be overturned in court. Conflicting or redundant regulations of different agencies would result in unnecessary burdens on those regulated. In addition, some commercial activity is now at the pilot plant stage, but the responsible agencies have yet to establish official policy and to devise a coordinated plan of action.

**B: Congress could require that the Federal Interagency Advisory Committee on Recombinant DNA Research prepare a comprehensive report on its members' collective authority to regulate rDNA and their regulatory intentions.**

The Industrial Practices Subcommittee of this Committee has been studying agency authority over commercial rDNA activities. Presently, there is little official guidance on regulatory requirements for companies that may soon market products made by rDNA methods. -e.g., companies are building fermentation plants without knowing what design or other requirements OSHA may mandate for worker safety. As was stated by former OSHA head, Dr. Eula Bingham, it will take at least 2 years for OSHA to set standards, if the current NIOSH study shows a need for them.<sup>46</sup>

A congressionally mandated report would assure full consideration of these issues by the agencies and expedite the process. It could in-

clude the following: 1) a section prepared by each agency that assesses its statutory authority and articulates what activities and products will be considered to come within its jurisdiction, 2) a summary section that evaluates the adequacy of existing Federal statutes and regulations as a whole with respect to commercial genetic engineering, and 3) a section proposing any specific legislation considered to be necessary.

The principal disadvantages of this option are that it maybe unnecessary and impractical. The agencies are studying the situation, which must be done before they can act. Also, it is often easier and more efficient to act on each case as it arises, rather than on a hypothetical basis before the fact.

**C: Congress could require Federal monitoring of all rDNA activity for a limited number of years.**

This option represents a “wait and see” position by Congress and the middle ground between the status quo and full regulation. It recognizes and balances the following factors: 1) the absence of demonstrated harm to human health or the environment from genetic engineering; 2) the continuing concern that genetic engineering presents risks; 3) the lack of sufficient knowledge from which to make a final judgment; 4) the existence of an oversight mechanism that seems to be working well, but that has clear limitations with respect to commercial activities; 5) the virtual abolition of Federal monitoring of rDNA activities by the recent amendments to the Guidelines; and 6) the expected increase in commercial genetic engineering activities.

Monitoring involves the collection and evaluation of information about an activity in order to know what is occurring, to determine the need for other action, and to be able to act if necessary. More specifically, this option would provide a data base that could be used for: 1) determining the effectiveness of voluntary compliance with the Guidelines by industry and mandatory compliance by Federal grantees, 2) determining the quality and consistency of IBC decisions and other actions, 3) continuing a formal risk assessment program, 4) identifying vague

<sup>46</sup>Letter from Dr. Eula Bingham, Assistant Secretary for Occupational Safety and Health, to Dr. Donald Fredrickson, Director, NIH, Sept. 24, 1980.

or conflicting provisions of the Guidelines for revision, s) identifying emerging trends or problems, and 6) tracing any long-term adverse impacts on health or the environment back to their sources.

The obvious disadvantages of this option are the increased paperwork and effort by scientists, universities, corporations, and the Federal Government. Those working with rDNA would have to gather the required information periodically and prepare reports, which would be filed by the sponsoring institution with a designated existing Federal agency. A wide-range of information would be required for each project. The agency would have to process the reports and take other actions, such as preparing an annual report to Congress, to implement the underlying purposes of this option. Additional manpower would most likely be needed by that agency.

A statute implementing this option could include the following elements: 1) periodic collection of information in the form of reports from all institutions in the United States that sponsor any work with rDNA, 2) active evaluation of that information by the collecting agency, 3) annual reports to Congress, and 4) a sunset clause. Important information would include: 1) the sponsoring institution's name; 2) all **places** where it sponsors the research; and 3) a tabular or other summary that discloses for each project continuing or completed during the reporting period: the culture volume, the source and identity of the DNA and the host-vector system, the containment levels, and other information deemed necessary to effect the purposes of the act. The statute could also require employers to institute and report on a worker health surveillance program.

For this option to work, the monitoring agency would have to take an active role in evaluating the data. It should have the authority to require amendments to the reports when any part is vague, incomplete, or inconsistent with another part. It could also be required to notify the appropriate Federal funding agency of apparent cases of noncompliance with the Guidelines by their grantees. Finally, it should pre-

pare an annual report to Congress on the effectiveness of Federal oversight.

The choice of an agency to administer the statute would be important. The selection of NIH would permit the use of an existing administrative structure and body of expertise and experience. On the other hand, one of the regulatory agencies may take a more active monitoring role and be more experienced with handling proprietary information.

This approach is similar to a bill introduced in the 96th Congress, S. 2234, but broader in scope. The latter covered only institutions not funded by NIH, and did not contain provisions for requiring amendments to the reports or for notifying other agencies of possible noncompliance. The bill was broader in one respect because it would have required information about prospective experiments. This provision had been criticized because of the difficulty of projecting in advance the course that scientific inquiry will take. The goals of a monitoring program can be substantially reached by monitoring ongoing and completed work.

*D. Congress could make the NIH Guidelines applicable to all rDNA work done in the United States.*

The purpose of this option is to alleviate any concerns about the effectiveness of voluntary compliance. RAC itself has gone on record as supporting mandatory compliance with the Guidelines by non-NIH funded institutions, including private companies.

This option has the advantages of using an existing oversight mechanism, which would simply be extended to industry and to academic research funded by agencies other than NIH. Specific requirements on technical questions such as containment levels, host-vector systems, and laboratory practices would continue to be set by NIH in order to accommodate new information expeditiously; the statute would simply codify the responsibilities and procedures of the current system. There would be few transitional administrative problems, since the expertise and experience already exist at NIH. However, it would be necessary to appoint several experts



in fermentation and other industrial technologies to RAC if production, as well as research, is to be adequately covered. In addition, the recommendations for large-scale containment procedures would have to be made part of the Guidelines.

The major changes would have to be made with respect to enforcement. Present penalties for noncompliance—suspension or termination of research funds—are obviously inapplicable to industry. In addition, procedures for monitoring compliance could be strengthened. Some of the elements of option C could be used. An added or alternative approach would be to inspect facilities.

The main disadvantage of this option is that NIH is not a regulatory agency. Since NIH has traditionally viewed its mission as promoting biomedical research, it would have a conflict of interest between regulation and promotion. One of the regulatory agencies could be given the authority to enforce the Guidelines and to adopt changes therein. NIH could then continue in a scientific advisory role.

*E. Congress could require an environmental impact statement and agency approval before any genetically engineered organism is intentionally released into the environment.*

There have been numerous cases where an animal or plant species has been introduced into a new environment and has spread in an uncontrolled and undesirable fashion. One of the early fears about rDNA was that a new pathogenic or otherwise undesirable micro-organism could establish an environmental niche. Yet in pollution control, mineral leaching, and enhanced oil recovery, it might be desirable to release large numbers of engineered micro-organisms into the environment.

The Guidelines currently prohibit deliberate release of any organism containing rDNA without approval by the Director of NIH on advice of RAC. The obvious disadvantage of this prohibition is that it lacks the force of law. The release of such an organism without NIH approval would be a prima facie case of negligence, if the organism caused harm. However, it may be more desirable social policy to attempt to pre-

vent this type of harm through regulation rather than to compensate for injuries through lawsuits. Another possible disadvantage of the present system is that approval maybe granted on a finding that the release would present “no significant risk to health or the environment;” a tougher or more specific standard than this may be desirable.

A required study of the possible consequences following the release of a genetically engineered organism, especially a micro-organism, would be an important step in ensuring safety. This option could be implemented by requiring those proposing to release the organism to file an impact statement with an agency such as NIH or EPA, which would then grant or deny permission to release the organism. A disadvantage of this option is that companies and individuals might be discouraged from developing useful organisms if this process became too burdensome and costly.

*F. Congress could pass legislation regulating all types and phases of genetic engineering from research through commercial production.*

The main advantage of this option would be to deal comprehensively and directly with the risks of novel molecular genetic techniques, rather than relying on the current patchwork system. A specific statute would eliminate the uncertainties over the extent to which present law covers particular applications of genetic engineering, such as pollution control, and any concerns about the effectiveness of voluntary compliance with the Guidelines.

Other molecular genetic techniques, while not as widely used and effective as rDNA, raise similar concerns. Of the current techniques, cell fusion is the prime candidate for being treated like rDNA in any regulatory framework. It permits the recombination of chromosomes of species that do not recombine naturally, and it may permit the DNA of latent viruses in the cells to recombine into harmful viruses. No risk assessment of this technique has been done, and no Federal oversight exists.

The principal arguments against this option are that the current system appears to be working fairly well, and that the limited risks of the

techniques may not warrant the significantly increased regulatory burden and costs that would result from such legislation. Congress will have to decide if that system will remain adequate as commercial activity grows.

If Congress were to decide on this option, the legislation could incorporate some or all of options C, D, and E. The present mechanism created by the Guidelines could be appropriately modified to provide the regulatory framework. The modifications could include a registration and licensing system to provide information on what work was actually being done and a means for continuous oversight. One important type of information would be health and safety statistics gathered by monitoring workers involved in the production of products from genetically engineered organisms. Another modification could be a sliding scale of penalties for violations, ranging from monetary fines through revocation of operating licenses to criminal penalties for extreme cases.

It would not be necessary to create a new agency, which would duplicate some of the responsibilities of existing agencies. Instead, Congress could give these agencies clear regulatory authority by amending the appropriate statutes. Designating a lead agency would assure a more uniform interpretation and application of the laws.

***G. Congress could require NIH to rescind the Guidelines.***

This option requires Congress to determine that the risks of rDNA techniques are so insignificant that no control or oversight is necessary. Deregulation would have the advantage of allowing funds and personnel currently involved in implementing the Guidelines at the Federal and local levels to be used for other purposes. In fiscal year 1980, NIH spent approximately \$500,000 in administering the Guidelines; figures are not available for the analogous cost to academia and industry. Personnel hours

spent have not been estimated. Very few people work full-time on administering or complying with the Guidelines. NIH employs only six people full-time for this purpose, and some institutions employ full-time biological safety personnel. However, over 1,000 people nationally devote some effort to implementing the Guidelines—members of the IBCs and the scientists conducting the rDNA experiments who must take necessary steps to comply.

There are several reasons for retaining the Guidelines. First, sufficient scientific concern about risks exists for the Guidelines to prohibit certain experiments and require containment for others. Second, they are not particularly burdensome, since an estimated 80 to 85 percent of all experiments can be done at the lowest containment levels and an estimated 97 percent will not require NIH approval. Third, NIH will continue to serve an important role in continuing risk assessments, in evaluating new host-vector systems, in collecting and dispersing information, and in interpreting the Guidelines. Fourth, if the Guidelines were abolished, regulatory activity at the State and local levels could again become active. Finally, the oversight system has been flexible enough in the past to liberalize restrictions as evidence indicated lower risk.

***H. Congress could consider the need for regulating work with all hazardous micro-organisms and viruses, whether or not they are genetically engineered.***

Micro-organisms carrying rDNA, according to an increasingly accepted view, represent just a subset of micro-organisms and viruses, which, in general, pose risks. CDC has published guidelines for working with hazardous agents such as polio virus. However, such work is not currently subject to legally enforceable Federal regulations. It was not within the scope of this study to examine this issue, but it is an emerging one that Congress may wish to consider.