Commentary

Recombinant DNA Research: The Scope and Limits of Regulation

SHELDON KRIMSKY, PHD, AND DAVID OZONOFF, MD, MPH

Abstract: The paper provides an overview of public policy issues pertaining to the use of gene-splicing (recombinant DNA [deoxyribonucleic acid]) techniques in research and for industrial applications. Included is a discussion of the regulatory framework at the federal and institutional levels. The principal limitation of the current federal guidelines is its failure to provide mandatory coverage for private sector activities. Four municipalities and two states have passed their own legislation to remedy the situation. These enactments and their tie-in to the public health sector are examined. (*Am J Public Health* 69:1252–1259, 1979.)

Six years have now elapsed since the public health community first became aware that a group of molecular biologists were sufficiently uneasy about the potential hazards of their laboratory research to call for wider discussions and increased caution.[1] The concern that emerged at that time,* around June 1973, focused on a specialized technique for splicing together segments of deoxyribonucleic acid (DNA) from disparate sources, and then re-implanting these hybrid genes into a host organism, usually a bacterium, where they might then begin to function through the genetic apparatus of the host cell. This raised the possibility that a hybrid bacterium with a foreign gene might give rise to unforeseeable adverse effects. Some scientists feared, for example, that these novel agents might generate new pathways for the spread of disease, or that certain experiments could introduce animal tumor viruses into the human intestinal tract, with uncertain effects.[2,3] The intense and sometimes bitter debate that ensued over possible biohazards has been detailed in a number of recent books and articles.[4–10] The principal result of that debate has been the promulgation of federal guidelines to regulate research sponsored by the National Institutes of Health (NIH), and the passage of a handful of laws at the state and local levels. As research involving recombinant DNA techniques** becomes more prevalent, the public health community will need to be familiar with these regulations and their limitations.

Major Policy Issues

The public policy debate surrounding the recombinant DNA episode developed out of a controversy which drew its first breath from within the scientific community. Initially, the issues focused exclusively on the question of biohazards. It is here where most scientists wanted the issue to stay and where, for the most part, it has stayed.

Address reprint requests to Sheldon Krimsky, PhD, Acting Director, Program in Urban, Social and Environmental Policy, Tufts University, Brown House, Medford, MA 02155. Dr. Ozonoff is with the Public Health Program, Boston University School of Medicine. Dr. Krimsky is a member of the NIH Recombinant DNA Advisory Committee; Dr. Ozonoff is a public member of the Harvard University Institutional Biosafety Committee. This paper, submitted to the Journal February 26, 1979, was revised and accepted for publication June 15, 1979.

*Concerns over the use of recombinant DNA techniques were expressed in private communications among scientists as early as June 1971 at the Cold Spring Harbor Tumor Virus Workshop. The issues were first brought to the public's attention following the Gordon Conference on nucleic acids, held June 11–15, 1973; after polling the participants, a letter from the conference co-chairpersons was published[1] expressing the sentiments of those attending that new gene-splicing techniques may be hazardous.

**Recombinant DNA techniques produce recombinant DNA molecules, usually defined as molecules that consist of different segments of deoxyribonucleic acid (DNA) which have been joined together in cell-free systems and which have the capacity to infect and replicate in some host cell, either autonomously or as an integrated part of the host genome.

It could easily have been otherwise, however. As more people became informed about the implications of transplanting segments of DNA between organisms of different species, other concerns began to surface. Included among them: Could recombinant DNA techniques be used to engineer human genes? Could applications be found for biological warfare? Could the industrial production of new hybrid micro-organisms and their dissemination into the environment endanger the public health or even the ecosystem?

For several years scientists debated the issue among themselves and in the public arena: should the new research techniques be regulated and if so, by whom, by what authority, and to what degree? Three distinct positions emerged which we term the minimalist, the centrist, and the maximalist. The first called for a system of voluntary self-regulation, where responsibility for taking appropriate precautions in the use of recombinant hybrids is placed entirely with the principal investigator. The moderate, centrist position gave the principal funding agency (in this case NIH) authority to establish guidelines and oversee institutional compliance with them. The third approach looked toward federal legislation to regulate the use of recombinant DNA techniques uniformly, for all sectors of society. The system that prevailed was the centrist position as embodied in the NIH guidelines, described below. But this did not end the policy debate.

When faced with the possibility of federal regulatory actions, some scientists, favoring the minimalist position, put forward a constitutional argument that likened any controls on scientific research to an abridgement of their First Amendment rights or to a violation of their rights of free inquiry.[11–14] To counter this, constitutional experts and many other scientists distinguished between freedom of expression and freedom of action. They argued that First Amendment rights do not apply to activities of scientific inquiry which impose risks on society.

Meanwhile, in 1976–77 the maximalist position reemerged at the sub-federal level. Several states and local communities, concerned about the division that still existed within the scientific communtiy over the assessment of hazards of the new research program, and cognizant that private industry was not covered by the NIH guidelines, considered legislation of their own. This sparked a vigorous national debate that took place mainly within Congressional committees and in scientific journals.[15–19] A major issue was the rights of local communities to develop more restrictive regulations than those already in place at the federal level.

On one side were those who were concerned that local initiatives would lead to a patchwork of cumbersome and possibly ill-conceived regulations varying from state to state, and city to city. Both scientists and representatives of industry feared local ordinances would cripple research and development in some areas of the country while providing researchers in other locales a competitive advantage.

On the other side of the issue were those who supported the principle behind public participation in scientific and technological decision-making at the local as well as the national level. That principle received support under the present circumstances for two reasons. The first is that NIH is not set up as a regulatory agency and therefore local and state governments had reason for concern about how compliance with the regulations would be enforced. Secondly, despite a long debate on the pros and cons of federal legislation, privately funded laboratories are under no legal jurisdiction either for small scale research or for large scale production of recombinant DNA molecules.

A less publicized but increasingly important controversy concerned the rights of individuals or institutions to patent novel organisms. Since, in many instances, public funds have been used to develop the new techniques in molecular biology, some critics questioned whether individuals or institutions should be permitted to draw profits from industrial applications of such research. Profiting from publicly supported science is not a new issue, but somehow it took on a special meaning when the patenting of new life forms was at the center of the discussion.

Throughout the recombinant DNA debate, one is reminded of its structural similarity to other controversies of a health and environmental nature: disagreement among experts; some probability (with considerable variation in estimates) of a catastrophic event; the burdens that regulations would impose upon progress; the lack of validating results for numerous claims. To comply with the National Environmental Protection Act, NIH even issued an environmental impact assessment that accompanied its guidelines for gene-splicing experiments. Molecular biologists began to sound like industry spokespersons whose business was being threatened with regulation. They warned the public that regulating research would inhibit or delay valuable medical advances.

Yet despite these similarities the DNA controversy is unique in that the issues have focused predominantly on academic research. Little attention has been given as yet to the applications and potential industrial exploitation of the new technology. It is certainly an unusual outcome to have a potentially hazardous technology regulated for academic science and unregulated for the privately funded laboratory and the industrial sector. What follows gives the outline of this regulatory structure and points out some of its limitations.

Regulation at the Federal Level: The NIH

The NIH began to address the potential laboratory and public health hazards of recombinant DNA molecule research after a small number of eminent scientists published a letter in *Science* in July 1974.[20] That letter called upon all scientists to defer voluntarily certain classes of gene-splicing experiments until more was known about the risks. An international risk assessment conference, held at the Asilomar Conference Center in Pacific Grove, California, in February 1975, resulted in preliminary recommendations to the NIH.[21] Over the next year-and-a-half, those recommendations were refined and amended by the Recombinant DNA Molecule Advisory Committee (RAC), chartered by the Secretary of Health, Education, and Welfare in October 1974 to provide technical advice to the Director of NIH. The first guidelines to regulate the new research technique were issued in June 1976 by NIH.[22] After a second period of in-

tensive review amidst widespread public debate, HEW Secretary Joseph Califano announced in mid-December of 1978 that his agency was promulgating a new set of regulations[23] to supplant the earlier guidelines. These became effective on January 2, 1979.

Regulatory Structure

Notwithstanding the fact that NIH has had no experience in the area of regulation, it responded to the concerns of some members of the scientific community and quickly developed a formidable administrative framework for overseeing its sponsored research involving recombinant DNA molecules.* This framework consists of the Recombinant DNA Advisory Committee (RAC), the Office of Recombinant DNA Activities (ORDA), and the Federal Interagency Advisory Committee (FIAC). In addition to these bodies at the federal level, the NIH guidelines also require local biosafety committees for those institutions receiving funding for recombinant DNA work. Institutions conducting such research under moderate or high physical containment [see Appendix], must also have a biological safety officer.

The Recombinant DNA Advisory Committee is the principal technical advisory group to the Director of NIH and the Secretary of HEW. In the past this group has had the responsibility for drawing up drafts of the guidelines and more recently for recommending substantial revisions which downgraded the containment requirements for most experiments. Now that the new guidelines have been issued, the RAC will continue to offer advice on changes in the regulations which reflect new knowledge about risks. The membership of the RAC has recently been enlarged to include, besides those chosen to provide scientific expertise, individuals knowledgeable in legal, social, environmental, or occupational issues.**

Representatives from such federal agencies as the Food and Drug Administration (FDA), the Environmental Protection Agency (EPA), and the Occupational Safety and Health Administration (OSHA) can participate in all deliberations and sub-committee work, but have no vote on RAC decisions. To date these agencies have made no substantial input in RAC deliberations.

The federal agencies, however, have their own committee to advise the NIH Director: the Federal Interagency Advisory Committee (FIAC). This body will continue to address the impact of the guidelines on the activities of other federal agencies and, if it feels compelled, it can request a meeting of the RAC to consider their concerns. The FIAC has completed studies on patent policies and the legal options for regulating non-NIH funded projects.

The Office of Recombinant DNA Activities is the administrative arm of NIH. ORDA's principal functions are to help institutions interpret the guidelines; review and approve the membership of the Institutional Biosafety Committees (IBCs); maintain a communications network between NIH, institutions, and the public; and generally to see to the housekeeping functions required of any regulatory body.

When new knowledge about risks justifies changes in physical or biological containment, the Director of NIH may issue revisions in the guidelines. In initiating such revisions, the Director has at his disposal the advisory opinions of the RAC and the more broadly based Director's Advisory Committee (DAC).*** This latter body, which predates NIH's role in recombinant DNA research, is consulted by the Director on a wide range of policy matters.

In the latest version of the guidelines, NIH has delegated many of the oversight responsibilities to the institutions which carry on the research by requiring them to establish their own Institutional Biosafety Committees. The function of these local bodies is to review all recombinant DNA research at the institution and assure and certify that the guidelines are being followed. Through ORDA, NIH oversees these decisions and initiates interpretations of the guidelines when clarification is needed. The IBC can issue approval of certain types of experiments without prior approval of NIH, and even has some limited authority to lower containment levels under specified conditions. The decision on the part of NIH to decentralize much of the oversight for gene-splicing activities has given the IBC a central role in the regulatory process. Consequently, the make-up of this committee was the subject of considerable public comment when the new guidelines were proposed in July 1978. For several years, HEW has required institutions receiving its funding and doing experiments with human subjects to have Institutional Review Boards (IRBs). Their purpose is to assess protocols of the research, weigh the risks and benefits of the study, and assure itself that the rights of the human subjects are being safeguarded. As with the IRBs, the IBCs are intended as a means for establishing peer review at the institutional level, with a provision for some outside participation to ensure accountability to a broader population. Under the new guidelines, the IBCs are to consist of no less than five members. Two members, or 20 per cent of the total, whichever is greater, are to be persons not affiliated with the institution. Moreover, they should represent the interests of the surrounding community with respect to health and environmental protection. The NIH suggests that appropriate public members might include officials of state or local public health or environmental protection agencies, members of other local governmental bodies, or persons active in medical occupational health or environmental concerns in the community. The guidelines state that the composition of the committee should include those who understand the recombinant DNA technology and who have expertise in laboratory safety or public health. Ironically, there is a recommendation, but no requirement, that laboratory technicians be represented on the IBCs.

*The NIH is the largest public benefactor of biomedical research in the United States. Its role as regulator of a technique integral to some research programs that it promotes has been cited as a case of conflict of interest by some of its critics.[24, 25]

**At least 20 per cent of RAC's membership must represent those areas of concern. This policy was first realized at the February 15-17, 1979 meeting of the RAC.

***With the broadening of RAC's membership to include more non-scientists, the DAC has played no official role in the decision-making process.

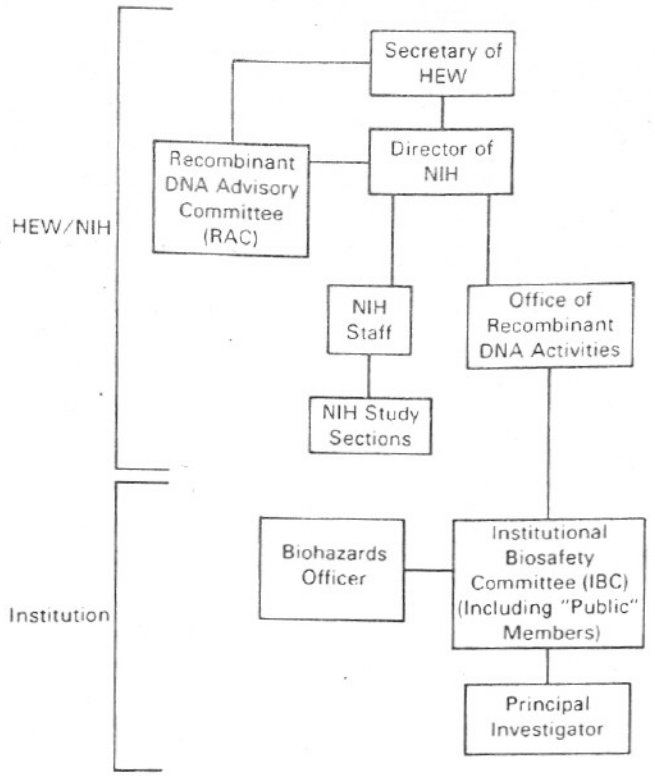

FIGURE 1—Recombinant DNA Regulatory Structure for NIH and Participating Institutions

In addition to a formally constituted IBC, institutions conducting research under moderate or high containment conditions must also have a biological safety officer (BSO). The idea of a biological safety officer was first introduced by the British in their guidelines for recombinant DNA molecule research. Under NIH regulations, the BSO must serve on the IBC; in addition, he or she is responsible for making periodic inspections of the laboratory, ensuring that safety standards are met, reporting serious illnesses—in general, overseeing the safety standards of the laboratory.

The key elements in the NIH-HEW administrative structure and its relationship to the IBCs at funded institutions are shown in Figure 1.

The regulatory system is intended to work in the following way. An investigator seeking NIH funding for work involving the production of recombinant molecules (or, alternatively, any researcher planning to undertake such work in an institution that already receives NIH funding for recombinant DNA work) must prepare a memorandum of understanding and agreement (MUA) to be filed with NIH through the local IBC. The MUA requires a description of the nature of the experiment, the sources of DNA used, the host-vector system, and the type of containment (biological and physical) [see Appendix] to be applied. There is also an assurance that the investigator will abide by the NIH guidelines. The MUA is reviewed at the institutional level by the IBC, which accepts or rejects the containment level. Once the MUA is approved by the IBC, it is finally forwarded to the program administrator in the appropriate section of the funding agency. (For new projects, the MUA is also reviewed by the Office of Recombinant DNA Activities, ORDA.)

Regulation at the Federal level: Non-NIH and Legislative

The administrative apparatus set by NIH to regulate recombinant DNA research appears quite substantial. Yet in spite of this, the NIH has no real enforcement capability. It must depend upon the reports of the biosafety officer or others in the laboratory to cite violations. If a breach in the guidelines is established, NIH has no sanctions available except limitation, suspension, or termination of a grant. Indeed this provides an actual disincentive to report. Moreover, recombinant DNA research that is privately supported is under no mandatory restrictions.* Some of the holes in this coverage have been plugged by obtaining the agreement of all federal agencies to require compliance with the NIH guidelines for all research that they fund. In addition, the Secretary of HEW has directed the FDA Commissioner to propose new rules which would require that any research done to satisfy FDA's regulatory requirements must conform to the NIH guidelines.[26] HEW Secretary Califano also wrote to EPA Administrator Douglas Costle, asking him to consider whether the EPA could regulate the remaining privately funded recombinant DNA activity under its mandate to protect the environment.[23] These are relatively new initiatives, however, and if successful at all, will take time to implement.

There have been attempts to accomplish the same ends by way of federal legislation for some time, beginning with a national debate over the adequacy of the 1976 guidelines. Early in 1977, Congressional activity directed at regulating gene transplantation research began to intensify. Five federal bills had been introduced by March of that year. In the midst of House and Senate hearings on these bills, the Federal Interagency Advisory Committee (FIAC) released a report examining the existing legislative authority by which the Secretary of HEW might attempt to regulate research in the private sector. The review included the following public laws: the Occupational Safety and Health Act, the Toxic Substances Control Act, the Hazardous Materials Transportation Act, and Section 361 of the Public Health Service Act. The FIAC concluded that "no single legal authority, or combination of authorities, currently exists which would reach all recombinant DNA research . . ."[27] The legal reasoning with respect to Section 361 of the Public Health Service Act is especially interesting. That section empowers the HEW Secretary to ". . . make and enforce such regulations as in his judgment are necessary to prevent the introduction, transmission, or spread of communicable diseases from foreign countries into the States or possessions or from one

*NON NIH-funded rDNA research is covered by the Guidelines if performed at an institution that receives any NIH support for rDNA research.

State or possession to any other State or possession . . ." According to some legal experts, to apply Section 361 there must be a reasonable presumption that what is being regulated can cause human disease. Since the risks that have been attributed to recombinant DNA research are hypothetical and remain unconfirmed, they aver, the Secretary's authority does not, strictly speaking, derive from the Public Health Service Act.

In recognizing the importance of having all recombinant DNA work regulated, Secretary Califano has supported new legislation.[27] One bill received a favorable vote from the House Subcommittee on Health and the Environment and its parent Committee on Commerce, despite intense lobbying efforts against it on the part of many scientists and their host institutions. But at that point a new wave of opposition to federal intervention emerged. As of August 1979, federal legislation appears unlikely.

There are two important consequences of the stalemate of federal legislation. The first is that, at present, there is no authority to regulate the private sector. Industry is on the threshold of applying the techniques of genetic engineering for the production of a wide range of biologicals in quantities that would be prohibited by the NIH guidelines. (The guidelines prohibit work with cultures containing recombinant DNA molecules greater than 10 liters. An exemption from the 10 liter limitation may be issued by the Director of NIH.)

The second consequence is that there is nothing to prevent states and local communities from establishing stricter guidelines than those issued by the NIH. A federal pre-emption clause which would have prevented multiple regulations did appear in the one Congressional bill that was voted out of committee, but never got to the floor. While Congress debated whether legislation to regulate DNA research was warranted, two states and four municipalities acted.

State and Municipal Regulation

Ordinances regulating the use of recombinant DNA techniques have been passed in Cambridge and Amherst, Massachusetts; the borough of Princeton, New Jersey; and Berkeley, California. Legislation has also been enacted in the states of New York and Maryland.‡

The Cambridge initiative[28] was the first of these, and drew world-wide attention. Passed on February 7, 1977, it represented the first enactment in the United States placing non-NIH funded genetic manipulations under regulatory control of a civil authority. The issue was brought to the Cambridge City Council by a unique set of circumstances: 1) a newspaper feature article describing a new moderate risk biological facility being constructed at Harvard University; 2) local scientists, among them members of Harvard's biology department, who protested having gene-splicing experiments in a densely populated city; and 3) a mayor who placed the DNA issue on the agenda of the City Council. The controversy over gene-splicing in Cambridge was resolved after a community lay-citizen board studied the arguments for five months, held hearings, and even ran a court-like adversary proceeding where scientists on both sides of the issue debated the issues. The citizen committee (Cambridge Experimentation Review Board) unanimously agreed that the research should proceed, but built an institutional structure that was eventually adopted by the City Council. A city biohazards committee (CBC) was created, made up of residents unaffiliated with the research or with the institutions supporting it and headed by the city's chief public health official. The purpose of the CBC is twofold: to link the city's public health apparatus to the institutional biosafety committees, and to provide assurance that privately funded work is properly regulated.

The three other municipalities that enacted ordinances—namely, Princeton, Berkeley, and Amherst[29–31]—followed the general framework of the Cambridge decision. Like Cambridge, Princeton created a new office for overseeing recombinant DNA activities. All such work in Princeton must be registered with a municipal biohazards enforcement officer. Also, the borough is empowered to select representatives to sit on the Institutional Biosafety Committees. In contrast, Berkeley and Amherst based their legislation on the existing authority of local public health officials.

In addition to the institutional framework established by the Cambridge and Princeton decisions, these communities placed conditions on the research beyond that set by NIH. This raised fear among some scientists that national legislation without local pre-emption would result in a nightmare mosaic of regulations. Eventually, however, when the 1978 guidelines were issued, most communities which had stipulated additional safeguards dropped them in favor of the new guidelines. This underscores the difficulty local communities face in maintaining a separate set of regulations. This difficulty is a natural result when funds, technical expertise, and enforcement capability are lacking.

In contrast to the municipalities, the concept of licensing is the basis of the state legislation passed in New York State and Maryland.[32,33] Both enactments require all research to be carried out in conformity to the NIH guidelines currently in effect. The chief public health officer of each state is the licensing authority, and facilities where such research is being done are subject to inspection by state public health officials. Both state laws on gene-splicing activities are built into their respective health codes, and both cite as justification the failure of the federal guidelines to require mandatory compliance by industrial and other private facilities. The New York State legislation[32] has its own pre-emption clause which prohibits local authorities from enacting any recombinant DNA ordinances.

The four local communities where laws were passed had an active scientific intelligentsia who brought the issues to the attention of politicians. In other areas where private facilities are tooling up for industrial applications of gene transplantation work and where stronger justification exists for some regulation, the absence of local scientific opposi-

‡Bills have also been introduced in the assemblies of California, Wisconsin, Massachusetts, New Jersey, and Illinois, while hearings have been held in San Diego, California; Shrewsbury, Massachusetts, and Ann Arbor, Michigan, with no legislation to date (August 1979).

tion is the main factor for the lack of any legislative initiative.

Conclusion

Scientists and others have been concerned that the regulation of recombinant DNA technology would set a dangerous precedent for controlling other types of basic research. While it is true that the technique arose in the context of the basic study of microbial genetics, the commercial applications of the research have been recognized with unusual clarity from the very outset. The efficient production of insulin, somatostatin, growth hormone, interferon, and blood clotting factors are among the many commercial applications that are now being contemplated.[34] Except in those communities or states where legislation already has been passed, any such commercial operations are now entirely unregulated except through voluntary compliance. This creates the paradoxical situation that many localities are likely to have the potentially less dangerous recombinant DNA research within their boundaries under regulation, with the potentially more hazardous applications currently under no mandatory controls.

This failure on the part of our federal government to regulate such activities in all sectors of society, in view of all that has been achieved in establishing safety standards, must stand out as a major flaw in the entire regulatory scheme. From the public health standpoint, therefore, the job is only partially complete. The crippling effect of regulation so feared by many scientists has not occurred, although admittedly some research may have been slowed down. Where there have been delays in recombinant DNA research, it may be a small price to pay for securing public confidence and giving meaning to the principle that those who generate risks must be accountable to those who must bear them. Meanwhile it would be advisable for officials responsible for public health on the local and state levels to become familiar with the industrial activities within their jurisdictions that are currently using recombinant DNA techniques.

APPENDIX

The Strategy of the NIH Guidelines

The purpose of the NIH guidelines is as simple as the details are complex. That purpose is to contain recombinant DNA molecules or organisms comprised of such molecules to the laboratory bench. In this way risks to the health of the laboratory worker, the surrounding community, and the environment itself can be minimized or eliminated. To accomplish this end, two types of isolation, or "containment" strategies, are embodied in the regulations. The first, designated as physical containment, consists of a combination of prescribed laboratory practices and physical barriers to contain experimental materials within the laboratory. The second containment strategy is called biological containment. This refers to using biological agents that will have little chance of surviving or spreading recombinant DNA molecules outside of a restricted laboratory environment. A basic strategy of the guidelines is to match the degree of physical and biological containment assigned to particular gene transplantation experiments with the potential hazard of the experiment.

Physical Containment

There are four levels of physical containment, designated P_1, P_2, P_3 and P_4. As one moves from a P_1 facility to a P_4 facility, there are additional laboratory safety procedures and substantial changes in the physical construction of the facility. The P_1-containment level requires no special facilities, but does specify certain minimum laboratory practices, such as prohibition of mouth pipetting and eating where experiments are in progress. As one ascends the scale of physical containment, there are additional safety protocols for laboratory work. Beginning with the P_2-containment level, some minimal requirements are cited for special equipment. Biological safety cabinets (exhaust hoods) with filtered exhausts are required to contain certain aerosol-producing operations, such as blending or centrifugation, when this is done with organisms that contain recombinant DNA molecules.

Beginning with the P_3 facility, special laboratory design is mandatory. Its requirements include restricted entry to the laboratory through a controlled access area, negative pressure ventilation systems, vacuum outlets protected by filters and liquid disinfectant traps, and sealed windows. The highest physical containment is represented by the P_4 level. This embodies the most advanced technologies and procedures for containment of highly contagious and pathogenic agents, including mandatory showering of personnel upon entrance or exit from the laboratory, individualized positive pressure suits for handling certain materials, and, where necessary, air locks, air filtering systems, and a biowaste treatment system for decontamination of all liquid effluent. A negative pressure gradient is maintained to prevent the outflow of particles in both P_3 and P_4 systems.

Under the new guidelines, almost all experiments involving recombinant DNA molecules require, at most, P_2 containment. P_2 laboratories are essentially normal laboratories with no special physical design that have locks on the door and where good microbiological technique is required.

Biological Containment

Operating in tandem with physical containment is the strategy of biological containment. This strategy aims to define various combinations of hosts (the organisms that receive the recombinant DNA molecule) and vectors (the vehicles that move the molecule into the host) which will minimize the possibility that organisms containing recombinant DNA molecules will escape the confines of the laboratory bench.‡‡

The lowest level of biological containment, designated EK_1, requires use of *E. coli* K12 as host, with designated

‡‡The biological containment parameter EK_1 is so designated because it pertains to the most commonly used host for gene transplantation work, *Escherichia coli* K12. It is actually a subset of the more general biological containment designation HV (host-vector). Since most work is still done with *E. coli*, we will continue to use the more specific terminology, EK_1, EK_2, EK_3. New HV systems using *Saccharomyces cerevisiae* (a yeast) and *Bacillus subtilis* (a gram-positive soil organism) have recently been certified by NIH.[35]

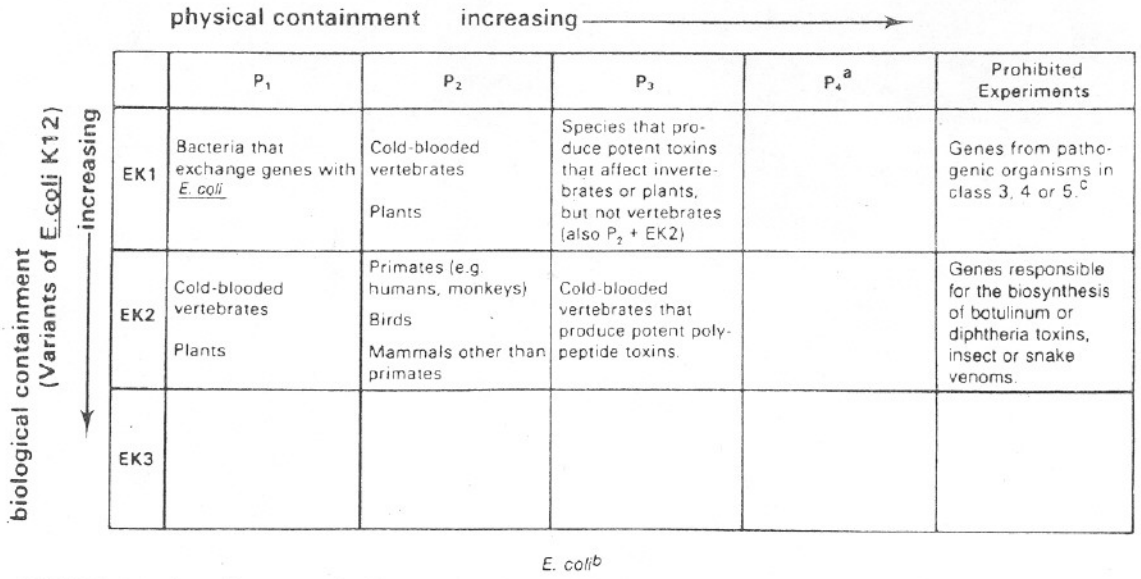

FIGURE A-1—Some Representative Classifications of Containment for Recombinant DNA Experiments as Cited in the NIH Guidelines, December 22, 1978

[a]In the revised guidelines, no experiments were listed under P_4 containment, nor was there any cited requiring an EK_3 host.
[b]Many prokaryotes that exchange genes with *E. coli* are exempt from the NIH guidelines.
[c]See reference no. 36.

vectors chosen so as to restrict subsequent transmission of the recombinant molecule to other organisms. *E. coli* K12 is a common laboratory strain of a normal gut bacterium. It is believed to be less capable of survival outside the laboratory than the non-laboratory strains, and less able to colonize humans. EK_2 host-vector (HV) systems require the use of specially engineered *E. coli* K12 mutants and suitable vectors where the probability of survival of the organism outside the laboratory or transmission of the vector to another organism is less than one in 10^8. Even more stringent requirements are set down for EK_3 HV systems. To date, no EK_3 systems have been certified.

The Containment Space

The four physical containment parameters (P_1 to P_4) and the three grades of HV systems (EK_1 to EK_3 when *E. coli* K12 is the host) can be visualized as a two-dimensional containment space. Each recombinant DNA molecule transplant with *E. coli* K12 serving as a host is associated with a physical and biological containment coordinate. As an example, under the latest revised guidelines an experiment that would implant bird DNA into *E. coli* K12 requires a P_2 physical containment facility and an EK_2 host-vector system. Figure A-1 illustrates how a few select experiments are classified according to their physical and biological containment requirements. The complete mapping of experiments into the containment space can get very complex. In addition to the type of species serving as the donor of the genetic material, other considerations include: whether an entire gene or only segments are used in the transplant; whether the donor organism naturally exchanges genes with *E. coli;* whether the DNA is purified for a particular organism where the DNA is taken from. However, since many experiments are double-listed, e.g., they may be performed either at P_3 and EK_1 or P_2 and EK_2, laboratories may seek the higher biological containment and forego the expense of a P_3 physical containment facility.

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29. Chapter 26A, Secs. 1-13, added to The Code of the Borough of Princeton, effective March 9, 1978.
30. The Berkeley City Council passed ordinance No. 5010-N.S., Chapter 12.30, Secs. 1-10, entitled "Hazardous Biological Research," effective Oct. 21, 1977.
31. By a vote of the town meeting on Oct. 25, 1978, Amherst, MA added Article III, Sec. 10, to the town by-laws. It was approved by the Attorney General of Mass. on Feb. 8, 1979.
32. The New York State Assembly passed Article 32-A, Secs. 3220-23, amending the state public health law. It was signed into law by the Governor on July 20, 1978.
33. The Maryland Assembly added Article 43, Secs. 898-910 to the Annotated Code of Maryland, effective July 1, 1977.
34. Chase M: Industry sees a host of new products emerging from its growing research on gene transplants. The Wall Street Journal May 10, 1979, p. 48.
35. Department of Health, Education, and Welfare, National Institutes of Health: Recombinant DNA Research: Actions Under Guidelines. Federal Register, Vol. 44, pp. 21730-21736, April 11, 1979.
36. Center for Disease Control: Classification of Etiologic Agents on the Basis of Hazard, 4th Ed., Atlanta, GA: DHEW, CDC, July 1974.

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GLOSSARY OF ACRONYMS

BSO	Biological Safety Officer (institutional)
CBC	City Biohazards Committee (Cambridge)
DAC	Director's Advisory Committee (NIH)
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency
FIAC	Federal Interagency Advisory Committee
FDA	Food and Drug Administration
HEW	Health, Education, and Welfare
IBC	Institutional Biosafety Committees
IRB	Institutional Review Boards
MUA	Memorandum of Understanding and Agreement
NIH	National Institutes of Health
ORDA	Office of Recombinant DNA Activities (HEW/NIH)
OSHA	Occupational Safety and Health Administration
RAC	Recombinant DNA Advisory Committee (HEW/NIH)