RECOMBINANT DNA RESEARCH AND ITS APPLICATIONS

OVERSIGHT REPORT

BY THE

SUBCOMMITTEE ON SCIENCE, TECHNOLOGY, AND SPACE

OF THE

SENATE COMMITTEE ON COMMERCE, SCIENCE, AND TRANSPORTATION

together with
MINORITY VIEWS

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LETTER OF TRANSMITTAL

Hon. Howard Cannon,
Chairman, Committee on Commerce, Science, and Transportation,
U.S. Senate, Washington, D.C.

Dear Mr. Chairman:

I am submitting herewith an oversight report by the Subcommittee on Science, Technology, and Space on the regulation of recombinant DNA research and its applications, together with the minority views of Senator Harrison Schmitt, ranking minority member. The subcommittee's findings and recommendations for the regulation of recombinant DNA activities are based in the first instance on its hearings on November 2, 8, and 10, 1977. During these hearings 27 witnesses discussed the benefits and possible risks of research using recombinant DNA techniques, issues of scientific freedom and responsibility, the administration of the National Institutes of Health research guidelines, and the need to extend these controls to privately sponsored research projects.

The report is also the first systematic effort to examine the issues that are likely to arise in the regulation of future large-scale commercial applications of recombinant DNA techniques. Following the subcommittee's hearings, opinions were requested of the relevant Federal regulatory agencies, the Congressional Research Service, and several of the witnesses. Analysis of these views and recommendations are included in part II of this report; related documents are found in the appendix.

The subcommittee is grateful for the assistance of Dr. James M. McCullough, Senior Specialist in Life Sciences, and Donna C. Parratt, Legislative Attorney, both of the Congressional Research Service, and to Dr. Bernard Talbot, Office of the Director, National Institutes of Health, who reviewed the technical material in the report.

Sincerely,

Adlai E. Stevenson,
Chairman,
Subcommittee on Science, Technology, and Space.

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Appendix:

List of Witnesses, Hearings on the Regulation of Recombinant DNA Research Before the Subcommittee on Science, Technology, and Space, November 2, 8, and 10, 1977

List of Additional Statements and Submissions

Communications from:

Hon. Frank Press, Director, Office of Science and Technology Policy, January 27, 1978, with attachment (Letter to Gilbert S. Omenn, Assistant Director for Human Resources and Social and Economic Services, OSTP, from Peter Barton Hutt, Covington and Burling, January 6, 1978)

Hon. Joseph A. Califano, Jr., Secretary, Department of Health, Education, and Welfare, letter of February 27, 1978

Hon. Douglas M. Costle, Administrator, Environmental Protection Agency, December 9, 1977

Eula Bingham, Assistant Secretary for Occupational Safety and Health, Department of Labor, December 15, 1977

Hon. Bob Bergland, Secretary, Department of Agriculture, December 23, 1977

Hon. Brock Adams, Secretary, Department of Transportation, December 21, 1977

Jordan Baruch, Assistant Secretary for Science and Technology, Department of Commerce, May 26, 1978

Memoranda:

Regulation of Recombinant DNA Under Existing Statutory Authorities, by Marcia J. Cleveland, Staff Attorney, Natural Resources Defense Council, Inc., December 2, 1977

Regulation Under Current Law of the Products of Recombinant DNA Research, American Law Division, Congressional Research Service, December 7, 1977
SUMMARY OF FINDINGS AND RECOMMENDATIONS

The subcommittee finds that the use of recombinant DNA techniques is rapidly increasing scientific understanding of basic biological phenomena and is likely to have important applications in the manufacture of drugs and industrial enzymes, waste treatment, production of food crops, and treatment of genetically related diseases. In the absence of confirmed hazards, the benefits that have been and may be derived from research with recombinant DNA molecules justify its continuation and support by the Federal Government and the private sector.

As a result of apprehensions about its effects on health and the environment, however, recombinant DNA research has been subject to various restrictions, principally the 1976 guidelines governing research supported by the National Institutes of Health. Recent scientific data indicate that permissible experiments employing NIH-approved host organisms and vectors do not pose significant risks to laboratory workers, the public, or the environment. Uncertainty remains, however, about the safety of experiments with other materials and about the hazards that may be associated with future uses of the technology, including the large-scale production of organisms with recombinant DNA and their release into the environment for presumably beneficial purposes. These uncertainties, which will be resolved over the course of years, justify continued exercise of caution in both research and commercial applications of recombinant DNA techniques.

Current Federal guidelines requiring the use of precautionary measures are nevertheless deficient in several respects. The National Institutes of Health lack authority to monitor and enforce compliance with the guidelines by those engaged in research supported by private funds or other Federal agencies. It is doubtful, in any case, whether enforcement by the principal Government sponsor of recombinant DNA research is appropriate and will be effective. As presently written and administered, the guidelines do not fully insure the accountability of institutions and investigators. The relationship between Federal and State and local government regulations is unsettled and controversial. Procedures are unclear for revising the standards to reflect new scientific evidence relating to the possible hazards or absence of hazards associated with recombinant DNA research. The standards do not purport to deal with its prospective commercial applications and the concerns they raise.

Research

The subcommittee believes that the NIH standards should be applied to all recombinant DNA research regardless of its locale or sources of financial support. This can be accomplished by legislation
or possibly by administrative action under the authority of section 361 of the Public Health Service Act, which in the past has been used to control a variety of infectious and some noninfectious agents. The Secretary of HEW has expressed a preference for a specific legislative mandate. If Congress does not act on legislation, however, the Secretary should reconsider using the authority of the Public Health Service Act.

In either case, recombinant DNA should be defined as broadly as it is defined in the current NIH guidelines. It is also assumed that the standards for research will be similar if not identical to those required by the guidelines, which prohibit certain presumably dangerous experiments, require certification of the safety of host-vector systems, and prescribe physical and biological containment measures for the conduct of permissible experiments. The administering agency should have authority to revise the standards periodically, provided that there is opportunity for public comment and examination of the supporting data. There should also be authority to exempt from the requirements those classes of experiments that are shown to pose no significant risk to health or the environment and to waive the ban on particular experiments whose results are necessary to assess the risks of recombinant DNA research. In all of these actions the administrator should have the advice of a group of qualified scientists and laypersons, including members of the present NIH Recombinant DNA Molecule Program Advisory Committee.

The subcommittee recommends that institutions be certified to conduct recombinant DNA research. The certificate should be conditional upon the appointment and conduct of an institutional biosafety committee to approve research projects, certify laboratory facilities, provide for the training of laboratory workers and researchers, monitor the health of persons exposed to recombinant DNA materials, and keep such records and make such reports as are deemed necessary. For informational purposes, research projects should be registered in advance with the administering Federal agency. Because it would be inappropriate to disqualify an entire institution in the event of violations by a single or a few researchers, the Federal administrator should have authority, subject to procedural safeguards, to suspend the activities of such offenders for a period of time. In cases of serious knowing violations of the standards, civil penalties would be appropriate. Federal agencies sponsoring or conducting recombinant DNA research would retain authority to terminate funding of activities being conducted in violation of the standards. Certification, registration, inspection and reporting responsibilities should be delegated to the Center for Disease Control or another agency apart from NIH. To protect the confidentiality of trade secrets and patentable inventions, there should be a procedure for notifying and consulting with researchers, both publicly and privately funded, prior to disclosure of information by the Government.

The subcommittee recommends that legislation contain a limited pre-emption provision barring States and communities from prohibiting recombinant DNA research or imposing physical and biological containment requirements exceeding the Federal standards. However,
the Federal agency should be empowered to waive Federal preemption if a State or local government presents convincing reasons in support of stricter standards. States and localities should also be permitted to take other actions to assure their citizens that the Federal standards are being observed. While this limited preemption could not be accomplished under section 361 of the Public Health Service Act, the subcommittee's recommendation does not differ significantly from the status quo; few communities have imposed requirements exceeding the standards incorporated in the NIH guidelines. Legislation should not expire earlier than 3 years after its enactment in order to have sufficient time to assess the effect of and need for Federal standards.

Commercial applications

The subcommittee recommends maximum use of existing statutory authorities to require premanufacturing and premarketing review, testing, quality controls in manufacture, and safe transportation and disposal of recombinant DNA products and materials. For example, regulation of pesticidal applications should remain with the Environmental Protection Agency, employee health and safety with the Occupational Safety and Health Administration, drugs and related products with the Food and Drug Administration, and transportation of materials with the Department of Transportation.

The Environmental Protection Agency has authority under the Toxic Substances Control Act to regulate uses of recombinant DNA molecules not covered by other statutes. The relatively few weaknesses in these laws should be corrected by use of supplementary authorities such as section 361 of the Public Health Service Act and the plant and animal quarantine laws or by amendment.

To avoid conflicting regulation by different agencies of recombinant DNA activities, there will be a need for effective coordination; memoranda of understanding or an Executive order should be used to clarify agencies' responsibilities. These agencies should also receive additional funds and personnel to carry out their duties, depending upon the rate of development of recombinant DNA technology.
INTRODUCTION

The ability to recombine DNA molecules of different organisms holds the promise of important benefits, both intellectual and material. Theoretically, it may also create hazards to human beings or the environment or interfere in unpredictable ways with hereditary processes. Exchanges of genetic material among organisms occur naturally, and no illnesses or other adverse effects have been associated with recombinants produced in the research laboratory. Nevertheless, many scientists and laypersons believe that the degree of uncertainty and the magnitude of the hypothesized risks justify restricting the use of recombinant DNA techniques.

American society, however, places great value on scientific and academic inquiry and has been reluctant to limit their freedom. Even where the risks of research are known, Government has not always acted to reduce them. The Atomic Energy Act imposes controls on the scientific use of radioactive substances, and restrictions are placed on the use of human subjects in experimentation; but pathogenic organisms and toxins have long been used in research, largely without Government interference or serious adverse effects on public health. Regulation of recombinant DNA technology represents public control of research procedures whose scientific utility is proven, whose social benefits may be significant, and whose dangers are not evident.

Understandably, Congress has found it difficult to reach an acceptable legislative resolution of these issues. The difficulty arises from conflicting values and perceptions in the absence of long experience with recombinant DNA techniques and knowledge of their effects. Legislative attempts to protect public health and the environment without impeding further research and development have met with criticisms from both sides of the controversy. Some charge that the proposed controls are inadequate; others argue that they represent unwarranted and dangerously restrictive Government control of scientific investigation.

Pursuant to its jurisdiction over "science, engineering, and technology research and development policy," the Subcommittee on Science, Technology, and Space held 3 days of hearings on recombinant DNA research in November 1977; the subcommittee later examined the possible commercial applications of this technology. These inquiries reflect the subcommittee's concerns both about the protection of public health and the environment and about the implications of regulation for scientific research and development activities generally. While the former concern dictates caution in the conduct of recombinant DNA research, the latter concern dictates care in the design and implementation of restrictions on it. The following oversight report presents the subcommittee's conclusions and recommendations for legislative and executive action.
Initial concerns

Scientists involved in genetic and biomolecular research first suggested that there might be risks associated with recombinant DNA experimentation. In a series of conferences and public statements beginning in 1973, they stressed the need to obtain more factual evidence concerning these hypothetical risks and the need, in the meantime, to devise a strategy to protect laboratory workers, the public, and the environment. Most scientists willingly agreed that they should exercise great caution during this period of risk investigation and assessment.

Reflecting these concerns, the National Institutes of Health in July 1976 published guidelines governing all recombinant DNA research supported with NIH funds. The NIH guidelines prohibited certain experiments that were presumed to be dangerous and prescribed procedures for others that might create unintended hazards. Other Federal agencies subsequently adopted these rules, and the handful of private firms engaged in recombinant DNA experimentation voluntarily agreed to observe them. Officially, however, the guidelines did not cover privately funded activities; only Government-supported research projects were subject to review for compliance and penalties for violations.

As the scientific community developed what the majority of researchers considered responsible self-controls, public debate ensued over the relative benefits and risks of recombinant DNA research. In addition to fearing that pathogenic organisms might be created in the laboratory and released into the environment, many persons were deeply concerned about tampering with the natural genetic order. Much of this debate took place outside of Washington, D.C., in universities and before State legislative bodies and city councils. Several communities extended the NIH guidelines to privately supported research activities; but more restrictive regulations were considered and, in a few instances, were adopted. At this juncture many of the same scientists who raised the question of potential dangers expressed apprehension that excessive regulation and differing State and local standards would have a chilling and disruptive effect on scientific investigation.

During this period (1974–77) additional evidence relating to the concerns about recombinant DNA research began to accumulate. The results pointed to a high level of safety associated with the use of certain laboratory-developed experimental organisms, such as the K–12 strain of the bacterium *Escherichia coli*, although other presumed risks were still acknowledged. Some experiments indicated that many of the DNA recombinations initially believed by scientists to be “novel” were, in effect, only laboratory-controlled duplications of events that occur in nature. There were also reports of advances in the use of recombinant DNA technology to produce mammalian hormones.

For many scientists, although not all, this new evidence made it less necessary and desirable for the Federal Government to regulate conduct of the research. Revisions of the NIH guidelines to reflect recent scientific findings were proposed. By mid-1977 these developments, taken together, raised doubts about the wisdom of the type of legislation previously contemplated.
Legislative activity

James Watson, co-recipient of the Nobel prize for characterizing the structure of the DNA molecule, first called the attention of Congress to the likely development of new techniques in genetic research during a 1971 hearing before the House Committee on Science and Technology. Four years later the Health Subcommittee of the Senate Committee on Human Resources held hearings on genetic engineering. During the past 3 years, nine separate sets of hearings have been held by committees of the House and Senate.

The Carter administration sent draft legislation to Congress in early 1977. Several Senators and House Members introduced their own bills, and it seemed all but certain that Congress would complete action on recombinant DNA legislation prior to the July 4 recess. The Human Resources Committee reported S. 1217, introduced by Senator Edward Kennedy of Massachusetts, in July 1977. In early August, Senator Gaylord Nelson of Wisconsin introduced to S. 1217 an amendment in the nature of a substitute which followed the basic regulatory approach contained in the legislation developed by Representative Paul Rogers of Florida, chairman of the Health and Environment Subcommittee of the House Committee on Interstate and Foreign Commerce. In September, Senator Adlai Stevenson of Illinois, chairman of the Subcommittee on Science, Technology, and Space, suggested in a Senate speech that the recent scientific developments and the reassessments then being conducted by the National Institutes of Health and the Carter administration made it desirable to postpone final legislative action until 1978. In the meantime Senator Harrison Schmitt of New Mexico, ranking minority member, requested that the subcommittee hold hearings on the issue.

In these circumstances, the subcommittee conducted 3 days of hearings on November 2, 8, and 10, 1977. Twenty-seven witnesses (listed in the appendix) testified. Among the questions discussed at these hearings were the following:

What are the actual and potential benefits of recombinant DNA research and technology? How long will it take for the potential benefits to be realized?

What hazards must be taken into account in devising regulations for recombinant DNA research and technology? What has scientific investigation disclosed concerning the hypothetical risks that initially concerned many scientists?

What approach should underlie regulation of recombinant DNA research in the public and private sectors? Should there be common regulatory procedures covering both publicly funded and privately funded research? Do the NIH guidelines provide a basis for regulation of the private sector?

Do existing Federal statutes provide a basis for regulating recombinant DNA research and technology conducted with private funds?

Should there be uniform standards for research in all localities of the country? How can the concerns of State and local populations for public health and environmental protection be accommodated?
How can the Government insure the health and welfare of the public without intruding unnecessarily on the freedom of scientific inquiry?

When is the commercial application of recombinant DNA technology likely to begin? Do adequate Federal regulatory safeguards exist to protect human beings and the environment from the potential hazards associated with large-scale use of this technology?

In addition to the testimony at the November hearings, the subcommittee received extensive supplementary material from witnesses and others. Federal agencies perceived to have any role in supporting or regulating recombinant DNA research or technology were asked whether existing statutes could provide an adequate basis for Federal controls. A list of those who submitted written statements and responses to the subcommittee's inquiries are found in the appendix.
PART I—PRINCIPAL FINDINGS

Actual and Potential Benefits

The Technique and Its Scientific Significance

In recombinant DNA research, specific sections of a DNA molecule are extracted from an organism or constructed biochemically and then inserted into another DNA sequence. The so-called recombinant DNA molecule is then introduced into a host organism where it can survive and replicate in cell division. This technique of artificial genetic exchange may be performed with organisms that commonly exchange DNA or with genetic material from two very dissimilar organisms, such as a mammal and a bacterium.

The host organism used in the vast majority of experiments is a strain of the common bacterium *Escherichia coli*. In addition to its single large chromosome containing DNA, *E. coli* has one or more independently replicating smaller loops of DNA known as plasmids. The plasmids are relatively easily isolated from the bacteria and broken open by restriction enzymes. The foreign DNA is linked to the plasmid DNA and its circular form restored. The plasmid “vector” is then returned to the whole cell bacterium where it can resume replication, duplicating not only the native DNA sequence but also the foreign one. If, in addition, the foreign DNA molecule carries with it the mechanism which regulates its expression, it may produce the protein or other chemical for which it codes.

The development of this technique is widely regarded as a major advance in the biological sciences, both as a means of studying basic biological phenomena and as a technology with numerous beneficial applications. In his testimony to the subcommittee, Philip Handler, President of the National Academy of Sciences, described DNA recombination as a research tool of “extraordinary power” for understanding the structure and functioning of the genetic apparatus. He referred to a recent report, “The Risks and Benefits of Recombinant DNA Research Performed Under the NIH Guidelines” (November 1, 1977), by a panel convened by the National Research Council of the Academy, which cited work using preselected genes of various animals including fruit flies, frogs, and sea urchins. The report states that “the distribution of likely regulatory sequences along cellular chromosomes has been mapped, using cloned recombinant DNA segments, and has suggested an unexpected mobility of genes.” Similar experiments are being done with plants. These and other developments are contributing to an understanding of the general principles of chromosomal organization, genetic regulation, and inheritance as well as genetic abnormalities.

According to Stanford Professor Stanley Cohen, in a letter to the subcommittee, more than 250 scientific investigations involving recom-
binant DNA have been published in the last 4 years. The National Institutes of Health, which has supported a large proportion of this research, is presently funding approximately 375 projects.

APPLICATIONS OF RECOMBINANT DNA TECHNOLOGY

Laboratories supported by both public and private funds are already working on possible applications of the technique in medicine, industry, and agriculture. Officials of the Pharmaceutical Manufacturers Association reported that three member firms are engaged in recombinant DNA research and three others are financing experiments being conducted in universities. PMA President Joseph Stetler cautioned that "a substantial amount of basic research will be necessary before the feasibility of recombinant DNA technology in commercial development can be determined with any degree of accuracy." Researchers and knowledgeable observers have, nonetheless, become increasingly optimistic in recent months. Several witnesses predicted that at least a few commercial uses of recombinant DNA will be developed within 5 or 10 years.

Products from micro-organisms

The application most often mentioned involves the propagation of large quantities of microorganisms with recombinant DNA for the production of a useful product, followed by the extraction of the product and destruction of the cell material and other byproducts. This procedure may become a source of animal proteins such as antibodies, blood-clotting factors, human hormones, and antigens or of industrial enzymes for fermentation and other biochemical manufacturing processes. Although unproven, it is hoped that the technique will be more efficient than present laborious or costly methods of synthesis and extraction, provide a source for products in short supply, or produce substances with entirely new commercial uses.

There has been notable progress in the development of this process. In the spring of 1977, researchers at the University of California Medical School at San Francisco successfully introduced and cloned in E. coli bacteria the gene which codes for the production of insulin in rats, although the material lacked the mechanism which controls the production of insulin. More recently, a team of Harvard University and Joslin Diabetes Foundation scientists achieved the synthesis of rat proinsulin, the precursor protein. In the opinion of William Rutter, a member of the San Francisco research group, it will be possible to produce human insulin in bacteria inexpensively and in greater quantity than is now available. As an added benefit, the insulin obtained in this manner may not induce production of antibodies in diabetic patients.

Another accomplishment within the past year by scientists at UCSF, the City of Hope Medical Center, and the Salk Institute involved the incorporation into E. coli of the gene for the mammalian hormone somatostatin, accompanied by the genetic material necessary for expression. In this case, the gene was synthesized chemically since it has not been isolated from the exceedingly complex mammalian DNA sequence. A small amount of somatostatin was obtained from the bacterial culture. Somatostatin is secreted by the hypothalamus and acts
as an inhibitor to the production of glucagon and insulin and to the pituitary gland’s release of hormones regulating body growth.

Roy Curtiss of the University of Alabama noted in his testimony that modification of the microorganism so that gene expression occurs is only the first of several difficulties that will be encountered in producing hormones commercially.

Second will be to prevent the microorganisms from degrading proteins which are nonfunctional, and the presence of a hormone would seem to be in that category. Third will be to allow the microbial host to secrete the hormone into the culture medium to facilitate its recovery, free from bacterial contamination. Fourth, in addition to these essential modifications of the microbial host-vector system, it would be highly desirable to have the microorganism adapted for use in fermentation technology and thus grow on an inexpensive medium with maximum yields of hormone and minimum yields of microbial cell mass.

Nevertheless, Ronald Cape, president of Cetus Corp. of California, suggested that some nonmedical products could be available in a year or two if there are adequate markets for them.

Other applications

More speculative uses of recombinant DNA include the release of the modified host cell into the environment for some specific purpose such as the conversion of organic material in sewage treatment, the oxidation of petroleum spills, or improvement in the nitrogen-fixing capability of plants. In all of these examples the intention would be to establish the recombinant organisms in a natural environment as substitutes for organisms which perform the same functions but less efficiently. Alternatively, it has been suggested that a modified vector, probably a virus, could be used to infect plants or animals in order to increase the photosynthetic capability of plants, destroy insect pests, or produce some other desired genetic change. The most dramatic example would be the injection into human beings of a virus capable of correcting disease-causing genetic defects.

Service industry

If research and development with recombinant DNA progress as the subcommittee’s witnesses expect, it may become profitable for commercial firms to supply specialized products to academic and commercial laboratories. These include not only restriction enzymes but also selected or general DNA segments, vectors with precise specifications, and even organisms containing recombinant DNA. Such material is already routinely exchanged among research laboratories. More than likely, the volume of shipments would not be large, for the naked DNA would be inserted into a small number of vectors, the vectors incorporated into microorganisms, and the organisms propagated in quantity in the research or industrial laboratory.

Potential Hazards

General concerns

The ability to transfer genetic information across biological barriers previously considered to be blocked has raised three distinct concerns: first, that some new pathogenic microorganism might be created, escape from the laboratory, and prove dangerous to man or the
environment; second, that research may ultimately lead to genetic manipulation of human beings; and third, that interference with natural evolutionary processes may do incalculable ecological damage. In Philip Handler's opinion, only the first of these apprehensions is amenable to scientific evaluation; the latter concerns involve issues of basic social values that merit public discussion but are not yet capable of being resolved.

Public controversy and scientific assessments of the risks of recombinant DNA research have therefore focused primarily on its effects on public health and the environment. Researchers have studied the scientific literature and conducted new experiments to determine whether there is any evidence lending credence to speculations about new pathogenic forms of life. In the meantime, the NIH guidelines are intended to insure use of appropriate biological and physical containment methods. In cases where the presumption of risk is strong and cannot be offset by an important benefit, the experiments have been prohibited until more data are available.

Most speculations of risk cite the lack of knowledge about possible changes in function of the recombinant DNA molecule. It is suggested that the joining of a foreign gene with other genes of an organism or vector or the characteristics of the new gene itself might produce some unexpected adverse activity in the new cell environment. If so, the escape of the organism or the accidental transfer of the recombinant DNA molecule to another organism might cause disease in the laboratory worker or human beings, animals, or plants in the surrounding environment.

**EXPERIMENTS WITH "E. COLI" K–12 AS THE HOST ORGANISM**

The principal host cell employed in current DNA recombinant research is the K–12 strain of *E. coli*. Apprehensions about the use of K–12 arise in part from the fact that other taxonomically related strains of *E. coli* inhabit the human intestine. Several of these "wild" strains may, under certain circumstances, cause disease. Furthermore, because of the dissemination of human intestinal waste products in the environment, it has been suggested that widespread release of *E. coli* K–12 containing a recombinant molecule could have serious adverse effects if interactions occurred with the *E. coli* strains normally present in the human gut or with other organisms in the environment.

Frank Young of the University of Rochester pointed out in his testimony to the subcommittee that all strains of *E. coli* are not alike. He has identified more than 580 biotypes of *E. coli* exhibiting a wide spectrum of pathogenicity ranging from nonpathogenic forms to strains which produce various toxins. Young emphasized that it is necessary to examine the K–12 strain in detail in order to determine whether it poses any hazard.

Philip Handler listed the several questions about K–12 that the special panel of the National Research Council addressed in its November 1977 report. Could the use of this host cell lead to epidemics through some modifications produced by introducing new genomic material by DNA recombinant techniques? Could the recombinant DNA molecule transferred experimentally to the K–12 cell be transferred
in turn to another strain of *E. coli* or other organism if the K-12 cell were accidentally introduced into the intestinal tract? Could some DNA recombinant manipulation produce novel *E. coli* cells which would be pathogenic or ecologically disruptive? Could genes from higher organisms be transferred to any of the prokaryotic cells (cells without a typical nucleus, such as *E. coli* or other bacteria or algae) and be expressed in such a way as to cause harm? Is it possible to construct a host cell for recombinant DNA research which would be so fastidious in its growth requirements that it could not grow outside the laboratory?

**Creation of a novel pathogenic *E. coli***

The Academy panel’s conclusions, while not absolute, indicate a negligible risk of creating a novel pathogenic *E. coli* in experiments with the K-12 strain host cell and special variants developed specifically for recombinant DNA work. The K-12 strain lacks the genetic capability to synthesize an important substance involved in the pathogenicity of other strains of *E. coli*. The K-12 strain cannot establish itself as a resident organism in the human intestine and does not multiply in that environment. K-12 is therefore a “safe” research host cell without any modification to reduce further its survival capabilities.

The panel based these judgments in part on the conclusions of a meeting of microbiologists and epidemiologists at Falmouth, Mass., in June 1977. The conference reviewed a variety of experimental findings including the following:

*E. coli* K-12 cannot be converted into an epidemic pathogen by laboratory manipulations with DNA inserts.

Deliberate attempts to induce virulence in K-12 by inserting genes known to regulate virulence factors in other wild strains of *E. coli* failed to produce a fully pathogenic strain of K-12. These experiments used standard genetic methods rather than DNA recombinant techniques.

K-12 deliberately fed to human volunteers soon disappears from the human intestine; in one case limited colonization occurred but did not persist beyond 6 days. The human body defense mechanisms are very effective against K-12; the strain is easily destroyed by normal chemical activities in the intestine.

A deliberate attempt to produce a hybrid of K-12 and *Shigella flexneri*, an organism which can produce infection in the bowel, resulted in a hybrid that picked up genes from *Shigella* but failed to produce any disease and quickly disappeared from the intestines of volunteers who ingested it.

The special nontransmissible plasmids used in recombinant DNA work with K-12 cannot be spread to other host bacteria within the human intestine.

An attempt to produce a virulent K-12 by transfer of plasmids from naturally occurring *E. coli* strains was unsuccessful.

Taken together, these results suggest that K-12 cannot be made pathogenic by processes which convert other varieties of *E. coli*.

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1. The proceedings of the Falmouth conference are published in the *Journal of Infectious Diseases*, vol. 137, May 1978, pp. 613-714.
Transfer of recombinant DNA from E. coli K-12 to other organisms

A few scientists argue that while K-12 itself is unlikely to be harmful, its interaction with other E. coli strains could produce hazards. Jonathan King of the Massachusetts Institute of Technology observed in his testimony that hospitals have been experiencing increasing numbers of infections from E. coli strains other than K-12. This increase is attributed in large part to the acquisition of antibiotic resistant plasmids by E. coli bacteria in the intestine. King infers that the escape of a laboratory clone or contact between K-12 and other organisms in the environment could result in the transfer of recombinant DNA molecules to a wild strain of E. coli and might induce a new form of pathogenicity. He argued that the evidence summarized in the Academy report and examined at the Falmouth conference is insufficient to conclude that use of K-12 eliminates any potential danger from recombinant molecule exchange.

King and other investigators who disagreed with the majority opinion at the Falmouth conference point to the evidence that K-12 can persist in the human intestine for as long as 6 days. In further experiments with variants of K-12 enfeebled by a technique affecting plasmid transferability, transfer did not occur in the intestine but was accomplished in the laboratory; but these researchers suggest that while the probability of transfer of recombinant DNA plasmids from K-12 is low, it cannot be disregarded. Moreover, they claim that insufficient work has been done to insure that transfer by mechanisms other than direct transformation would not occur; nor have any experiments adequately addressed the possibility of gene transfer outside the intestine, in sewer systems, soil or via intermediate hosts.

As yet there is no evidence that transmission of recombinant DNA molecules would be harmful, but researchers are nonetheless attempting to determine the likelihood of such transfers. Oliver Smithies of the University of Wisconsin referred in his testimony to a then unpublished paper reporting that in a 2-year period of monitoring the feces of laboratory workers engaged in nonrecombinant DNA research, no K-12 bacteria or K-12 plasmids with multiple drug resistance markers were ever found. The workers in question were using plasmids capable of being transferred, whereas in recombinant DNA experiments transmission-deficient plasmids are used with a weakened variant of K-12. Thus, the paper concluded that if transmission-proficient plasmids used without any special physical precautions did not appear, there is little if any risk of gene transfer from K-12 plasmids in recombinant DNA work. This study is widely regarded as a significant demonstration of the safety of the K-12 host.

Development of further weakened E. coli hosts and vectors

Even though the available evidence shows “normal” K-12 to be a very defective organism, even more enfeebled variants have been developed to prevent colonization and transfer of recombinant DNA in the event of accidental release of the organism. Roy Curtiss of the University of Alabama described his success in producing additional mutational changes in K-12 which greatly limit the ability of the

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bacteria to grow in a nonlaboratory environment. The resulting mutant, named Chi 1776, met the criteria for EK2 containment developed by the NIH Recombinant Advisory Committee and was approved for experimental use by the Director.

Oliver Smithies, a member of the recent Academy panel, discounted any possibility of risk with the host organism constructed by Curtiss and his colleagues. Smithies said in his testimony:

** ** the negligible risk of Chi 1776 ** ** surviving in the feces or of the recombinant DNA plasmid being transferred to some other bacteria becomes less than one chance per 100,000 laboratory workers working for 10,000 years without special physical precautions. (With the application of) physical precautions, ** ** the risk is no longer worth considering.

Several essentially nontransferable plasmids have also been developed for use as vectors with K-12 Chi 1776.

Curtiss and others therefore disagree with the suggestion that preference be given or experimentation restricted to use of host cells that do not normally inhabit human beings. Not only are the genetic characteristics of *E. coli* K-12 well known but also substantial evidence of its safety is beginning to accumulate. A requirement to use another host organism would impede research and raise greater uncertainties about potential risks.

**USE OF OTHER HOST-VVECTOR SYSTEMS**

The data on mutant strains of K-12 do not support a conclusion that all recombinant DNA research is without risk. Curtiss argued in his testimony that his own findings should not be applied to any other host-vector system; even knowledge about other variants of K-12 is insufficient. He referred specifically to two host cells of potential interest, *Bacillus subtilis* 168 and *Pseudomonas putida* PpGi. Unlike *E. coli*, both of these bacteria are soil microbes and are nonpathogenic; however, there are few if any data on the factors that influence their survival in a natural environment or their ability to transmit recombinant DNA to other micro-organisms, let alone data on what is required to cripple these organisms in order to prevent their proliferation. Curtiss believes that such data should be collected on alternative host-vector systems before they are approved for recombinant experimentation. Stuart Newman of the State University of New York at Albany in a letter to the subcommittee suggested that once a new host is certified, investigators should closely monitor their experimental cultures to insure that contamination, type reversions, or other unexpected changes have not occurred.

At present, comparatively little effort is being devoted to non-K-12 systems with the exception of *Bacillus subtilis* and a few viral vectors. Yet many researchers with commercial applications in mind believe that *E. coli* K-12 may not be the ideal organism to receive certain kinds of genes and recommend development of a variety of host-vector systems. Ronald Cape took this position in his testimony to the subcommittee. Even in basic research, the failure of gene expression by a recombinant DNA molecule may be a function of the particular host cell environment; and the availability of other host cells would facilitate investigation of a greater variety of DNA functions. For these
reasons, the number of a host of organisms employed in DNA recombinant research and development is very likely to increase.

OTHER CONCERNS

The volume of recombinant material produced will also increase if commercial applications of the technique become feasible. The experience of the biomedical and chemical industries suggests that large-scale production of recombinant organisms will be required in order to obtain useful products in sufficient quantity for marketing. Some researchers insist that special procedures and facilities could prevent escape of these organisms from an industrial laboratory, but the NIH Recombinant Advisory Committee has assumed that probability of escape from containment barriers ordinarily increases with scale. The committee recommended and NIH included in its guidelines a production limit on recombinants known to make harmful products of 10 liters, which is generally adequate for experimental work.

The limit is arbitrary, however, for there are no calculations of the correlation between the volume of organisms and the probability that some of these organisms will enter the environment. Investigations of potential risks associated with recombinant DNA have yet to address this question.

The deliberate release of a recombinant molecule, which is contemplated for various future applications of the technology, is also cause for concern. Although available data indicate that the accidental escape of K-12 would pose minimal risks to health or the environment, its behavior in a variety of natural circumstances has not been examined. For example, no one knows the effects of introducing K-12 containing a recombinant molecule into an environment where sewage treatment is inadequate or where contact with large numbers of different species of bacteria is inevitable. Moreover, alternative host-vector systems are yet to be evaluated. Apprehensions about damage to complex ecosystems are reasonable, particularly if host cells common in the soil or water are used. For the time being, therefore, the NIH guidelines prohibit the deliberate release of recombinant DNA material.

The long-range-evolutionary effects of recombinant DNA work are thus ill defined and partly philosophical. Recently published research by Chang and Cohen at Stanford suggests that many of the DNA exchanges previously considered to be unique to laboratory experiments are duplications of natural capabilities of E. coli; but these data are limited and do not satisfy all participants in the debate. Robert Sinsheimer of the University of California at Santa Cruz has frequently expressed concern about disrupting the dynamic equilibria among competing species of organisms. In a statement submitted to the subcommittee he concluded:

The possibilities of long-range environmental hazards, of short- or long-term effects upon basic microbiological equilibria, which are essential to many ecological concerns, remain unaffected by the new observations.

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Current Federal Regulation of Research

Origin and Provisions of the NIH Guidelines

Research with recombinant DNA molecules has been subject to voluntary or involuntary restrictions almost from its inception approximately 5 years ago. Participants in the 1973 Gordon Conference on Nucleic Acids raised the possibility that some experiments could be hazardous and urged the National Academy of Sciences to create a study group to recommend guidelines or other appropriate action. The following year the NAS committee proposed that scientists voluntarily "defer" certain experiments that might, indirectly, encourage the spread of antibiotic resistance, toxin formation, and cancer-causing or other animal viruses. Other recommendations of the committee led to the creation of the NIH Recombinant DNA Molecule Program Advisory Committee in 1974 and to an international meeting of scientists and others at Asilomar, Calif., in February 1975.

The consensus at Asilomar was that most of the contemplated work with recombinant DNA should proceed but that precautionary measures should be used to minimize the spread of artificial recombinant DNA's in human populations or other nonlaboratory environments. From the publication of the Asilomar report in May 1975 until June 1976, the conference recommendations guided NIH-supported investigators and, apparently, were observed by scientists throughout the world. In the meantime, the NIH Recombinant Advisory Committee proceeded to draft a more detailed set of guidelines to govern NIH research projects. The Director of NIH issued these standards on June 23, 1976, and they were published in the Federal Register of July 7.

The National Science Foundation, Department of Agriculture, and other Federal agencies subsequently agreed to apply them to their own grantees or in-house research activities. Other nations followed suit. British guidelines were announced in August 1976 and Canadian guidelines early the following year. More recently, guidelines have also been published in France, the Federal Republic of Germany, and the Soviet Union and are in preparation in other countries. According to a report on a recent survey by a Federal interagency committee, some 175 research projects are being conducted in Europe, Canada, Australia, Japan, and the Soviet Union under various safety procedures, most of them modeled on the NIH or United Kingdom guidelines.

The NIH guidelines take several complementary approaches to preventing the spread of possibly harmful products of recombinant DNA research. First, certain experiments continue to be prohibited. Examples are the introduction of antibiotic resistance traits to pathogenic organisms and the formation of recombinant molecules containing genes for the production of dangerous toxins. Second, deliberate release into the environment of any organisms containing recombinant DNA is forbidden. Third, experiments producing more than 10 liters of culture containing recombinant DNA known to make harmful products are also banned. Fourth, permitted experiments must be conducted with procedures and equipment intended to prevent the escape of recombinant DNA material into the immediate or general
environment. These measures of "physical containment" are grouped into four categories, P1, P2, P3, and P4, each level more stringent than the one preceding to correspond to the presumed potential risks of various experiments. Fifth, researchers must use biologically weakened vectors and host organisms that are unlikely to survive in a non-laboratory environment or exchange DNA with other organisms. These materials are also graded, EK1, EK2, and EK3, to provide "biological containment" commensurate with the potential risk of harm. Before they can be used in recombinant experiments, EK2 and EK3 host-vector systems must undergo extensive testing, review by the Recombinant Advisory Committee, and certification by the Director of NIH. Thus, permitted experiments are assigned levels of physical and biological containment which are to a degree interchangeable; an increase in biological containment may permit a lowering of physical containment requirements.

EFFECTS OF THE GUIDELINES

According to testimony before the subcommittee, these measures, taken together, provide a high degree of protection of public health and the environment. Philip Handler stated the conclusion of the National Academy Panel on Risks and Benefits of Recombinant DNA Research, whose members included authorities in molecular biology, genetics, infectious diseases, and epidemiology. He quoted:

Currently available evidence leads us to conclude that the many benefits of recombinant DNA research and technology can be achieved with negligible risks to the biosphere when the work is carried out within the NIH guidelines.

Despite minor reservations about the permissiveness of the standards, Bruce Levin of the University of Massachusetts characterized their approach to the unknown risks of recombinant DNA as properly one of "extreme prudence." Paul Berg, Frank Young, Roy Curtiss and others generally agreed with this assessment.

In the past, physical containment procedures similar to those required by the NIH guidelines appear to have been effective in preventing infections from human pathogens used in research. In other public testimony, the Director of the National Cancer Institute's Office of Research Safety described the experience with high containment at the former biological warfare laboratory at Fort Detrick, Md. During a 10-year period ending in December 1969, only one laboratory-acquired infection occurred as a result of an accidental glove puncture. The environmental impact statement accompanying the guidelines included an analysis of laboratory-acquired infections data from the Center for Disease Control, the National Animal Disease Center, and the National Institutes of Health as well as Fort Detrick; it found no case where a disease was transmitted from an infected laboratory worker to another person. The EIS noted that only eight such cases have been documented for other American and foreign laboratories. In short, scientific research with pathogens under stringent containment appears to have an excellent safety record.

Roy Curtiss and others who have attempted to calculate the risks of survival and reproduction of a weakened test organism or vector should physical containment fail believe that these risks are exceed-
ingly small. Although the probability of survival is greater at lower levels of biological containment, the experiments permitted at these levels generally involve organisms known to exchange genetic information by natural processes.

On the other hand, neither the containment measures nor the assessments of their effectiveness are infallible. In the opinion of Jonathan King, even a small number of accidents might do irreparable harm if a deleterious combination of genes should establish itself in the environment. He believes that monitoring of laboratory workers' health and maintenance of medical records have been inadequate. In the absence of base-line health data, it is not possible to judge the effectiveness of physical containment methods which are, in any event, entirely dependent upon the training and behavior of laboratory personnel. Others have pointed out that the conduct of research with known pathogens may be quite different from the conduct of experiments for which no hazards have been demonstrated. Arthur Schwartz, a University of Michigan mathematician, questioned the calculations of potential risks in recombinant DNA research. He stated in his testimony to the subcommittee that in his estimation the methods used by Curtiss and others to estimate probabilities are flawed because they do not take account of multiple factors and successive events.

The majority of scientists, however, considers the present rules too stringent, particularly with regard to the use of K-12 bacterial hosts and plasmid vectors. Curtiss and others urged approval of the revisions of the guidelines recommended in September 1977 by the Recombinant Advisory Committee; these changes would generally reduce the physical and biological containment requirements for E. coli experiments. Nevertheless, Paul Berg observed that most scientists accept the present guidelines as "an interim solution to the anxieties that remain." No testimony at the subcommittee hearings suggested that the rules per se have greatly impeded progress in recombinant DNA research, although they have added to its cost and inconvenience and undoubtedly entailed some delays. Referring to the more than 300 NIH-funded research projects and the recent accomplishments in cloning the rat insulin gene and producing somatostatin, Marshall Shapo of the University of Virginia concluded that "research has indeed flowered. *** That seems to me *** to indicate that regulation and talk of regulation has not been either chilling or productive of inefficiency, given the uncertainty that originally existed."

That most researchers have accommodated themselves to regulation and that regulation has permitted dramatic advances in research do not justify the continuation of unnecessary restrictions. The subcommittee inquired whether the current work in risk assessment is likely to remove all reasonable doubt about the safety of recombinant DNA experiments and thus the need for regulation. The responses suggest that most scientists expect further research to justify a selective relaxation of the containment standards, but they view this as a gradual process. They do not reject the possibility of discovering some hazards. Roy Curtiss predicted that within 2 or 3 years scientists will have acquired "adequate information" on E. coli K-12 but cautioned that it will take longer to evaluate new host systems.

Jonathan King rejected the notion of a short-term risk assessment program. He said, "Evolution goes on; new niches occur in the environ-
ment, and the research proliferates. New and more ingenious kinds of experiments are proposed.” And Paul Berg agreed that a 2-year evaluation is not sufficient. In view of the likelihood that considerable uncertainty will remain, particularly about newly developed techniques and host-vector systems, there is broad support for continuing to prohibit certain recombinant DNA experiments and control others, provided that there is opportunity to relax or remove restrictions on research that is shown to pose no significant risk. Marshall Shapo suggested, “*** Where present foresight of some possible risks remains dim, regulation is justified to a level that corresponds with the uncertainty; though not a more stringent one.”

DEFICIENCIES OF THE GUIDELINES

Coverage

Although Federal sponsors of research with recombinant DNA other than NIH have adopted its guidelines, there appears to be great variation among their respective review procedures; initial evidence suggests a very superficial approach by some Federal agencies. The subcommittee is inquiring further about the activities of the National Science Foundation, the Department of Agriculture, the Veterans’ Administration, and the Department of Energy, and will report its findings at a later date. Thus far the principal concern of Government officials, public interest groups, private industry, and State and local officials has been that privately supported research activities in universities and industry are not subject to the NIH standards or external review except on a voluntary basis.

In issuing the 1976 regulations, Donald Fredrickson, Director of NIH, urged all Government agencies and “all who support or conduct such research throughout the United States” to adhere to the guidelines voluntarily. In November 1976, the Environmental Defense Fund and the Natural Resources Defense Council petitioned the Secretary of HEW to promulgate regulations governing all recombinant DNA activities in the United States under the authority granted by section 361—Control of Communicable Diseases—of the Public Health Service Act (42 U.S.C. 264). Members of the Pharmaceutical Manufacturers Association and other industrial firms which have agreed to observe the guidelines urge that their coverage be formalized.

The concern is not merely about compliance by unregulated sponsors and performers of research. As the president of the PMA and the president of Cetus Corp. observed to the subcommittee, the present guidelines are written for Federal grantees. Commercial firms have had ample opportunity to comment on the standards and the proposed revisions, and have consulted NIH officials on their interpretation, but they have no representation on the Recombinant Advisory Committee nor on the Advisory Committee to the Director of NIH which reviews changes in the guidelines. Private laboratories may be prevented from receiving recombinant DNA materials from an NIH grantee for lack of certification or may be handicapped in their research and development efforts by the 10-liter limit. At present, there is no formal mechanism for resolving issues that concern the private sector. As more private firms enter recombinant DNA research and as the research becomes more sophisticated, the private sector is likely to experience
greater difficulty in complying with the guidelines. Ronald Cape of Cetus Corp. stated, "We want to be treated both in the letter as well as the spirit like everybody else in terms of these guidelines."

Procedures

The effectiveness of the NIH guidelines does not depend upon reasonable standards alone. It also requires procedures to review and enforce compliance. It cannot be argued that the guidelines are merely advisory. The October 1977 environmental impact statement on the 1976 guidelines states that "Noncompliance with the guidelines will result in termination of funding of research grants and contracts." Yet NIH's lack of experience in regulation is indicated by the ambiguity of the guidelines' procedural provisions, by the guidelines' failure to establish clearly the responsibilities of institutions, institutional biohazards committees and investigators, and by the absence of any mention of procedures to investigate and correct violations. 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.

These conclusions result from the subcommittee's investigation of an acknowledged violation last year by researchers at the University of California at San Francisco Medical School, reported originally in the September 30, 1977, issue of Science magazine. The case involved the unauthorized use of an EK2 plasmid vector with E. coli x 1776 in a P3 experiment to clone the rat insulin gene. The vector in question, pBR322, was submitted to NIH for certification in December 1976, approximately 6 months after publication of the guidelines in the Federal Register. The experiment using pBR322 was conducted from mid-January to mid-March, 1977, at which time the organisms containing the recombinant DNA were destroyed. Subsequently, the experiment was successfully repeated with an authorized vector. The plasmid pBR322 was not certified by NIH until July 7, 1977.

Chapter IV of the guidelines—"Permissible Experiments: E. coli K-12 Host-Vector Systems" states, "For the time being, no EK2 or EK3 host-vector system will be considered bona fide until the Recombinant Advisory Committee has certified it." This requirement is intended to insure that material used in moderate- and high-risk experiments has a very low probability of surviving and exchanging DNA with other organisms in a natural environment. In fact, the language of the section is misleading; it is the Director of NIH who certifies EK2 and EK3 vectors after review and upon recommendation by the Recombinant Advisory Committee (RAC). Nevertheless, a November 26, 1976, NIH memorandum advised all institutional biohazards committees that only one EK2 host-vector system had been certified, and that when others were certified, "You will be notified and their availability will be announced in the Nucleic Acid Recombinant Scientific Memoranda." The memorandum also states that the institutional biohazard committees are responsible for informing researchers at their institutions of NIH policies and actions. In any event, on January 16, 1977, the Recombinant Advisory Committee only tentatively recommended approval of pBR322 subject to the receipt of additional data supporting its safety; these were submitted in early February. Further experimental data were requested by the committee
in late March in accord with newly adopted test criteria for EK2 vectors. The committee finally recommended certification of pBR322 on June 23.

In his testimony to the subcommittee, William Rutter, chairman of the UCSF Department of Biochemistry and Biophysics and a member of the insulin research team, attributed the premature use of pBR322 to information that the RAC had fully "approved" the vector in January and to a literal interpretation of the guidelines' reference to certification by the RAC. He also argued that he and his colleagues were convinced of the vector's safety by the supporting data given to NIH: "By one criterion of 'safety,' this plasmid is 10,000 to 1 million times better than EK2 plasmid vectors then approved." Herbert Boyer, a member of the UCSF department who developed pBR322 and applied for its certification, testified that he was aware that it had not been certified in January but did not immediately inform members of the insulin team and did not discover that they were using it until early March. Director Fredrickson agreed that there had been understandable confusion about NIH procedures in early 1977 but stated that NIH had subsequently improved its communications with grantees. Boyer and Rutter assured the subcommittee that the university had also adopted new procedures to prevent similar occurrences.

Although the use of pBR322 posed no hazard to the researchers or others, the subcommittee believes that the incident has serious implications for Government and institutional regulation of recombinant DNA research. Documents and testimony in the record of the subcommittee's hearing support the following additional findings concerning this violation:

Contrary to the implication of its November 1976 memo, NIH did not promptly notify applicants or prospective users of host-vector systems in writing of the actions by the RAC or the Director. Researchers at UCSF who decided to proceed with the pBR322 experiments relied on information from technicians in their laboratory who said they had heard, indirectly, that the vector had been approved. No one on the research team attempted to confirm its status with NIH officials or consulted the biohazards committee prior to the experiments.

Approximately 3 weeks after the experiments commenced, Boyer scheduled a meeting at which he informed members of the insulin team that pBR322 had not been certified; apparently, they did not reveal that they were using it. The researchers continued to grow and examine the host organisms in which they had inserted the plasmid in order to determine whether they contained the recombinant DNA.

At the meeting in early February, Boyer also announced that a log book would be kept to record use of the P3 laboratory. (Neither the guidelines nor the institutional biohazards committee required such a log book.) No official entries were made, however, until mid-March. At that time the use of pCR1, the first certified vector, was recorded retroactively to February 1. Later, the use of pMB9, certified in April, was also listed. There was no reference, however, to the use of pBR322 in the interim.
In the absence during this period of the principal investigator on the insulin project, Howard Goodman, Boyer was designated to NIH as the acting principal investigator. Goodman also asked Brian McCarthy, another member of the department, to be available to advise the investigators in his laboratory. Boyer and McCarthy also shared responsibility for supervising the newly constructed P3 facility. Both knew that pBR322 had not been certified but claim they were unaware of its use by two post-doctoral fellows conducting the experiment, Axel Ullrich and Jonathan Shine.

Shortly after the first of March, Goodman and Rutter discovered that pBR322 had not been certified. They attempted to ascertain from NIH whether certification was imminent. Finding that there would be a further delay, Rutter called the NIH Deputy Director for Science, Dewitt Stettin, between March 16 and March 19 to seek his advice about the continuing use of the vector. Rutter was advised to destroy the host organisms; at that point he and Goodman decided to terminate the experiment. The Deputy Director did not inform the NIH Office of Recombinant DNA Activities (ORDA) or other officials of the call.

In late May a member of the Rutter laboratory staff informed David Martin, chairman of the UCSF biohazards committee, of the pBR322 incident. After making a personal inquiry, Martin told a meeting of the committee on June 3 that researchers had used a vector on the advice of NIH officials who predicted its "imminent" certification. When certification was not forthcoming, the researchers had to destroy their work "to avoid non-compliance with the director's wishes, although consistent with the guidelines." The committee approved a letter of complaint to NIH that referred to the delay in certifying pBR322 but not to its use. It was not until September that the full committee learned of the violation.

Apart from Rutter's call to the Deputy Director in March, no one at UCSF reported the incident to NIH; officials of ORDA and the Office of the Director did not learn about it until late summer when the Science reporter inquired. Even then, no investigation was made; rather, ORDA requested a written report from the new chairman of the biohazards committee, James Cleaver, for the purpose of answering further public inquiries to NIH. Although the report, dated October 25, indicated that the experiment continued for several weeks after the investigators discovered that the vector was not certified and that neither the biosafety committee nor NIH was fully apprised of the incident, NIH took no further action until prompted by the subcommittee's investigation. On December 1, ORDA asked for a supplemental written report from the biohazards committee chairman.

The UCSF violation occurred shortly after NIH issued procedural instructions for implementing the guidelines and coincided with the formulation of test criteria for host-vector systems. It resulted in part from confusion about the NIH approval process. Witnesses stated that NIH has since improved its publication of certification actions and clarified the roles of the RAC and the Director. Accord-
ing to William Rutter, the system is now tighter and more business-like. Be that as it may, the researchers who conducted the experiments neglected to confirm the rumor of pBR322 approval and then delayed correcting their error in the hope that the obvious remedy would not be necessary. The acting principal investigator, the biohazards committee, and other permanent members of the department exercised so little supervision that they did not discover the use of the uncertified vector by their colleagues. Director Fredrickson left the subcommittee with no doubt that this lack of action was contrary to the intent of the NIH guidelines.

The guidelines themselves, however, are deficient. They require grantees to report accidental equipment failures and problems of operation and implementation of safety procedures but make no provision for reporting or investigating violations. Only an unusual set of circumstances, not monitoring by the institutional biohazards committee or NIH, brought the incident to light after the researchers had decided to keep it to themselves. It is not at all clear, as Fredrickson maintained, that the institutional committee is the proper body to investigate allegations of a violation. In the absence of any standard procedure, both the local committee and the Office of Recombinant DNA activities failed to conduct a thorough inquiry and relied instead on statements by the principals. Finally, the episode demonstrates the inadequacy of the guidelines' enforcement mechanisms; NIH has little recourse other than to withdraw the grant of the principal investigator, who seemingly bears less responsibility in this matter than other members of the department and the biohazards committee.

Appropriate legislation and reasonable regulations can formally correct these deficiencies but will not have universal acceptance. Not the least disturbing testimony in the affair was William Rutter's rationale for secrecy—the researchers' presumption of safety and fear of exacerbating public controversy. First, he said, "the Recombinant DNA Committee had voted to approve the plasmid as an EK2 vector. The DNA insert was placed in a region of the plasmid such that it was unlikely it could be read or expressed. The experiment had been carried out with no ill effect." Second, an "inflamed social and political climate *** existed with respect to recombinant DNA technology. *** The press, among others, had sometimes fanned the flames of controversy. *** Repressive and punitive legislation was being considered." This assumption of superior judgment threatens not only regulation but also productive scientific inquiry. If even a few scientists ignore the common ground rules of research, they undermine the basis of healthy scientific competition. If they are discovered, they undermine public confidence in their enterprise. It is clearly in the interest of the scientific community to cultivate a willingness to comply with the guidelines. No enforcement system can ever fully substitute for a spirit of good faith observance among investigators.

Regulation of commercial applications

As previously mentioned, the subcommittee heard several predictions that practical commercial applications of recombinant DNA technology will be feasible within a few years, much earlier than
was previously assumed. The success of the California investigators in cloning the rat insulin gene and in developing a synthetic gene for the production of the hormone somatostatin points to the possibility of producing a variety of hormones and industrial enzymes in large cultures of recombinant DNA organisms. Presumably, the organisms would be contained and eventually destroyed, as they are in the research laboratory; but their large volume would increase the likelihood of worker exposure and escape of the organisms from the facility.

More speculative uses actually contemplate the deliberate release of the modified host cell into the environment for some specific purpose such as the conversion of organic material in sewage treatment, the oxidation of petroleum spills, or improvement in the nitrogen-fixing capability of plants. Aside from the possible hazards of the organism itself, these uses may have adverse indirect effects. Plants with superior nitrogen-fixing characteristics might displace others or valuable resources be destroyed. Alternatively, there has been mention of using a modified vector; probably a virus, to infect plants or destroy insect pests. In these cases, environmental exposure, for example, from spraying, would be difficult to control. The use of a modified vector for correcting a genetic defect in man raises moral as well as safety concerns.

The NIH guidelines do not purport to deal with these possibilities and the apprehensions they raise. Indeed, if they were applied to the private sector, the 10-liter production limit on certain cultures, the ban on release, and the physical containment measures might singly or in combination preclude all of these applications. More importantly, uses involving the introduction of recombinant DNA molecules into a natural environment run directly counter to the concept of biological containment which is a principal safeguard in the guidelines. The utility of the modified organisms or vectors would depend entirely upon their ability to survive and/or exchange DNA with other organisms, whereas the hosts and vectors now prescribed for research are specifically designed to have no such capability.

It is impossible to predict what will be the perception of recombinant DNA hazards and the status of the guidelines when and if any of these applications becomes feasible. For the present, the risks in commercial exploitation of the technology appear to many observers to be more varied and more serious than any that may be associated with research experiments. Roy Curtiss doubted that commercial uses of genetically modified micro-organisms would pose "any threat to the public or the well-being of any other organisms in the environment," but said, "I think it is essential in these applications of recombinant technology that we obtain appropriate experimental evidence to validate this general belief." David Newburger of Washington University, St. Louis, Law School expressed concern that the issue had not been addressed in previous discussions of recombinant DNA regulation.
PART II—RECOMMENDATIONS

Recommendations for Regulation of Research

Legislative Authority

In response to the concern that some recombinant DNA research was unregulated, the Secretary of HEW convened an interagency committee in the fall of 1976 under the chairmanship of Director Fredrickson. The committee included representatives of the Federal agencies and departments sponsoring and conducting recombinant DNA research and those having regulatory authority that might be applicable in this area. Its first task was to consider whether the extension of the guidelines beyond NIH to the public and private sectors could be accomplished under existing statutory authority or whether new legislation was required. Having reviewed the relevant statutes, the Interagency Committee reported in March 1977 its conclusion that “no single legal authority or combination of authorities currently exists that would clearly reach all research and other uses of recombinant DNA techniques and meet all the requirements.” Dr. Gilbert Omenn, Assistant Director of the Office of Science and Technology Policy, reiterated this position in his testimony to the subcommittee on November 8; and it was generally supported by Marcia Cleveland, attorney for the Natural Resources Defense Council, in a December memorandum requested by the chairman of the subcommittee.

The Interagency Committee rejected use of the Occupational Safety and Health Act of 1970, the Toxic Substances Control Act, the Hazardous Materials Transportation Act, the authorities of the Food and Drug Administration and the Center for Disease Control and several more specialized statutes primarily on the grounds that they could not be extended to cover all performers or all aspects of research with recombinant DNA. For example, the Occupational Safety and Health Act defines “employer” to exclude States and their political subdivisions unless the OSHA standards are voluntarily adopted. Twenty-six States have not done so and thus their public universities would not be subject to Federal regulation. Section 5 of the Toxic Substances Act exempts from the requirement of registration with EPA those chemical substances used in small quantities for the purpose of scientific experimentation or analysis. The Hazardous Materials Transportation Act would not apply to the handling of recombinant DNA materials in the laboratory. The licensing authority of the Center for Disease Control under section 353 of the Public Health Service Act is limited to clinical laboratories. FDA’s authorities are generally interpreted to reach the manufacture only of commercial products.

The Interagency Committee found no such obvious deficiencies in section 361 of the Public Health Service Act, on which the Environ-
mental Defense Fund relied in its petition to the Secretary of HEW. This section authorizes the Surgeon General, with the approval of the 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 United States or from one State to another. He may provide for "inspection, fumigation, disinfection, sanitation *** and other measures" to carry out such regulations.

Section 368 provides for a fine of $1,000 or imprisonment for not more than 1 year, or both, of persons who violate the regulations under section 361. The Interagency Committee suggested that this authority could be broadly interpreted to support regulation of most recombinant DNA research activities, although it might not apply to research with materials that could pose a hazard only to nonhuman animals, plants, or the environment. On the other hand, unless a reasonable basis could be shown for concluding that the products of recombinant DNA research might actually cause human disease and be communicable, the Interagency Committee was concerned that the regulations might not withstand legal challenge.

Although the Carter administration endorsed the Interagency Committee report and proposed legislation that was introduced in the last session in both Houses, the failure of Congress to act in the following months led the executive to reconsider alternative ways of insuring universal compliance with the NIH research guidelines. In his testimony to the subcommittee on November 8, 1977, Office of Science and Technology Policy Director Frank Press proposed that the Department of Commerce undertake a program of "voluntary compliance and meaningful surveillance" involving businesses engaged in recombinant DNA research. Press said that the Department planned to consult with pharmaceutical and other firms on appropriate procedures for external monitoring of their recombinant DNA research activities. These discussions are still in progress.

Following its hearings, the chairman of the subcommittee wrote to Press and HEW Secretary Califano in part to ask their current views on the use of section 361 to regulate either research with or commercial applications of recombinant DNA. At the same time, OSTP requested HEW to reconsider use of this authority in the absence of new legislation. In his reply to the subcommittee, the Secretary stated, "Our office of the General Counsel *** believes it is preferable for a regulatory effort of the magnitude required to oversee all recombinant DNA activities, whether or not known to affect human health, to be based on the explicit support of the Congress as well as that of the administration, particularly in light of the active interest the Congress has shown in this area. The consensus needed for this type of program is not best established by applying a general provision of law to this specific situation."

In a separate letter to the subcommittee, Frank Press acknowledged Secretary Califano's preference for specific legislative authority. OSTP had, nevertheless, reviewed the administrative history of section 361 and concluded that its application to recombinant DNA research would be appropriate. Press pointed out that the Public Health Service and the Food and Drug Administration have used the act's unusually broad delegation of authority in a variety of ways to regu-
late drinking water, milk and animal products, shellfish and pet
turtles that might pose a danger to public health. Even noninfectious
materials have been regulated. These applications, according to Press,
show a clear "preference for prevention of the occurrence of any risk,
rather than control of the spread of infection." In the absence of con-
clusive evidence to the contrary, the possibility that recombinant DNA
research on nonhuman animal or plant materials could result in human
infection would justify comprehensive regulation of the research
under this authority. For these reasons, the Office of Science and
Technology Policy reserves the option of recommending that regula-
tions be issued under section 361 if legislation is long delayed.

Views of the subcommittee

The subcommittee believes that the Federal Government should
rely on full legal authority in regulating all recombinant DNA re-
search regardless of its locale or sources of financial support. A pro-
gram of voluntary compliance by and monitoring of industrial
research activities is insufficient. Whatever form such a program might
take, it would leave unclear the status of privately supported research
in universities. Moreover, because it would require the consent of all
participants, there is no assurance that it would achieve universal
coverage in the private sector. It would not afford those subject to it
an adequate voice in the drafting or subsequent revision of the guide-
lines. The lack of effective sanctions for violations would undermine
public confidence that the guidelines were being observed. Finally,
duplication in the Department of Commerce of expertise which
resides in the Department of Health, Education, and Welfare and
elsewhere would be wasteful and unnecessary.

The subcommittee agrees that the Occupational Safety and Health
Act, the Toxic Substances Control Act, the Food, Drug and Cosmetic
Act and other specialized public health and environmental protection
statutes do not provide adequate authority to regulate all research
with recombinant DNA, although, as Secretary Califano observed in
his letter to the subcommittee, the Food and Drug Administration
"could, under existing authority, require any firm seeking ap-
proval of a product which may be the end product of recombinant
DNA research to certify to the Agency that it has complied with the
NIH Guidelines on recombinant DNA." and could inspect firms mak-
ing such certification. Use of this authority, even though it would
apply only after the research had been conducted, would be an impor-
tant incentive for companies subject to the food and drug laws to com-
ply with the NIH standards. Furthermore, as the Interagency Com-
mmittee observed OSHA, FDA, and EPA will have important roles
to play when recombinant DNA techniques reach the stage of com-
mercial application. (See Applicability of Existing Statutes, p. 41.)

The subcommittee is not persuaded that the legal obstacles to use
of section 361 of the Public Health Service Act are insuperable. While
it is the case that no person is known to have been injured by ex-
posure to recombinant DNA material, the possibility of unintention-
ally transferring a pathogenic characteristic capable of causing
disease in laboratory workers or others in the surrounding environ-
ment is the principal concern that led to the Asilomar conference rec-
ommendations, the NIH guidelines, and the similar precautionary
measures adopted in numerous other countries. The further possibility that such a disease would be resistant to present methods of prevention and treatment enhances the reasonableness of these measures.

Section 361 does refer only to communicable diseases affecting human beings. Presumably, there are or will be recombinant DNA experiments that could pose a risk of injury to plants, animals, or the environment but not of human infection. If necessary, however, the protection of nonhuman animals and plants might be achieved in cooperation with the Secretary of Agriculture using his authority under the animal quarantine laws (21 U.S.C. 111, 114, 114(b), 123, and 134(a)) and the Federal Plant Pest Act (7 U.S.C. 150bb and 150dd), which are similar in purpose and structure to section 361. (See letter from the Secretary of Agriculture in appendix.)

In any event, according to recent court opinions, the National Environmental Policy Act (42 U.S.C. 4321 et seq.) imposes a duty on Federal agencies to protect the environment in all major actions whether or not an authorizing statute specifically provides for environmental protection.

Of greater concern to the subcommittee is whether an effective and appropriate regulatory system could be established under section 361. Its use to prohibit certain kinds of scientific experiments, prescribe standards for the conduct of others, certify research facilities, or register research projects would indeed be unprecedented. The act would not limit the power of State and local governments to impose standards at variance with the Federal standards. The criminal penalties in section 361 would be inappropriate except for the most serious willful violations of the regulations that result in harm. Nevertheless, the agency is the appropriate one and the delegation of authority broad. The Secretary or Surgeon General would not be encumbered by specific statutory requirements in revising or rescinding regulations as warranted by new scientific evidence. There is also merit in avoiding the necessity for Congress to legislate, perhaps repeatedly, in highly technical areas of scientific research that are conceivably but not demonstrably hazardous.

The subcommittee has not reached a final judgment on the legal issues relating to the use of section 361 of the Public Health Service Act to regulate recombinant DNA research. In view of the Secretary's apparent desire for specific new authority for this purpose, the subcommittee believes that legislation is the more likely and preferable course of action. However, the subcommittee recommends that the Secretary of HEW give serious consideration to promulgating standards and procedures under the authority of section 361 if Congress does not complete action on legislation or if the legislative committees with jurisdiction conclude that existing authority is adequate. The Secretary should prepare for this contingency. The testimony before the subcommittee left no doubt that the application of NIH standards to all recombinant DNA research should be accomplished as expeditiously as possible.

SCOPE, IMPLEMENTATION AND DURATION OF LEGISLATION

The consensus that regulation of all recombinant DNA research should be "based" on sections II (Containment) and III (Experimen-
nal Guidelines) of the NIH guidelines does not resolve a variety of controversial and technical legislative issues. How should recombinant DNA research activities be defined? Should regulation be temporary in the expectation that further research will demonstrate the safety of all recombinant DNA experimentation or that public concern will diminish? Should legislation simply extend the present NIH standards to non-NIH-funded research projects or require new regulations to be issued? Are the July 1976 guidelines or the changes recommended to the Director of NIH by the Recombinant Advisory Committee the appropriate basis of regulation? What provisions should be made for future changes in the standards to reflect new scientific evidence of greater or reduced risk? Should legislation exempt from the standards experiments that are proven to be safe or to duplicate DNA exchanges that occur naturally?

Several of these questions reflect the concern of the scientific community that needless restrictions may be instituted and thereafter perpetuated. For example, there have been various proposals to appoint a committee of experts to study the evidence relating to the hazards attributed to recombinant DNA research and to report its findings to Congress and the executive branch within a specified time. Proponents of a study commission appear to assume that further scientific investigation will show that most if not all recombinant DNA experiments pose negligible risks to health and the environment. On this assumption that regulation will be necessary only until the commission has completed its work, they favor short-term or “interim” legislation. Various witnesses before the subcommittee supported the inclusion in legislation of a sunset clause that would compel Congress to reconsider the need for regulation of recombinant DNA research after a few years.

The subcommittee also heard proposals to limit the scope of regulation. Philip Handler urged that only P3 and P4 facilities be required to be licensed and inspected. Halvorson would exempt P1-level experiments from all regulation. Others have recommended that the law direct the Secretary to identify “non-novel” experiments, producing DNA recombinants that are known to occur in nature and are therefore presumably safe; these would be exempt from regulation altogether. Alternatively, the definition of recombinant DNA research activities could exclude certain kinds of experiments.

A related issue concerns the pending revisions of the physical and biological containment standards required by the July 1976 guidelines. These changes were recommended by the NIH Recombinant Advisory Committee, published in the Federal Register on September 27, 1977, and are now being considered by the Director. In the subcommittee’s hearings, representatives of environmental organizations argued that no conclusive evidence exists to justify relaxation of the present standards. On the other hand, several scientists, while approving some prohibitions and restrictions on experiments, are convinced that these requirements are too stringent, at least with respect to uses of E. coli K-12 host-vector systems. They preferred that the proposed revisions of the guidelines be the basis of regulation under new legislation. A number of witnesses urged that any future administrator have authority to modify the standards in light of new scientific data, whether such
evidence reveals that the risks are greater or less than is now thought to be the case.

There have also been various suggestions for incorporating the guidelines in law. The simplest approach is said to be a provision that, upon enactment of legislation, the guidelines will be applicable to all sponsors and conductors of recombinant DNA research without further administrative action. A second alternative, which anticipates the need for procedural provisions appropriate to the private sector, is to extend the guidelines as interim rules and require the promulgation of final regulations within a specific period of time. Third, Congress could dispense with the interim extension of the guidelines and require that comprehensive regulations be issued.

**Views of the subcommittee**

The subcommittee believes that knowledge of the effects of recombinant DNA experimentation will be acquired over the course of years in the normal process of scientific investigation. Progress in assessing its safety will be accompanied by rapid development of the technique and use of a variety of host-vector systems, each requiring evaluation. From this perspective, the subcommittee prefers the creation of an advisory apparatus, including scientists and lay persons, operating on a continuing basis rather than a special commission directed to reach a final judgment within an arbitrary time period. When the prospective uses of recombinant DNA techniques are better known, it will be necessary to address the moral and public policy issues of human genetic engineering, perhaps by a Government-appointed group of experts and laypersons. Because these advanced applications are not yet subject to verification or regulation, however, the subcommittee believes that legislation should deal only with the health and environmental consequences of recombinant DNA research. On the other hand, it sees merit in a sunset provision to insure a reassessment of both the need for and effectiveness of Federal regulation. Since these judgments cannot be made for some time after the regulations become effective, the subcommittee recommends that the law expire no earlier than 3 years after its enactment.

The legislation’s definition of recombinant DNA should be the definition in the current NIH guidelines. The administering agency should have authority to remove restrictions on certain categories of experiments; but the criterion should be that the experiments pose no significant risk to public health or the environment, and the test procedures and criteria for assessing such risks should be published with the regulations. The concept of “non-novelty” is ambiguous and not invariably indicative of safety. The subcommittee recognizes a certain anomaly in restricting operations that occur in nature but believes that the basis for removing such restrictions should be consistent with the purpose of the legislation. To insure that important risk-assessment studies can be carried out, the subcommittee recommends that the administrator be authorized to waive the ban on presumably dangerous research for individual experiments to be conducted under specified conditions and supervision.

The scheduling of the subcommittee’s hearings shortly after publication of the proposed revision of the guidelines did not permit a
thorough examination of the recommended changes, but the subcommittee accepts the view that recent findings justify a careful revision of the physical and biological containment standards for certain experiments. There is also a clear need to correct existing procedural deficiencies and to devise ways of applying the standards to privately supported research activities, including appropriate methods of monitoring and enforcing compliance. Because the sanctions and administrative section of the current guidelines are predicated upon the NIH grant review process, legislation cannot merely "extend" the guidelines to the private sector.

For these reasons, the subcommittee favors a provision requiring promulgation of standards and requirements necessary to secure and maintain compliance as soon as practicable after passage of legislation. This approach would permit both substantive and procedural amendments to the guidelines. The subcommittee strongly supports the discretion of the administering agency to make further changes in the standards, provided that the supporting evidence is published and there is ample opportunity for public comment. In order to avoid prolonged delay in issuing the initial regulations, however, it may be necessary to modify the requirements of the Administrative Procedure Act.

WHO SHOULD REGULATE

The recombinant DNA debate has generated a variety of proposals for national and local regulatory agencies, commissions, and committees. At issue is the extent to which research scientists should be entrusted with responsibility for their own conduct, individually or through peer review, or be subjected to external scrutiny and control. Related issues are the proper balance between Federal and State or local responsibilities and the appropriate role of lay persons in the regulation of recombinant DNA research.

In legislative terms, these issues raise the following questions: First, which Federal agency should have authority to issue and enforce rules governing recombinant DNA research? Second, what apparatus should be established to provide expert assessment of the risks associated with such research and to recommend measures to protect public health and the environment against those risks? Third, what should be the responsibilities of institutions and investigators conducting recombinant DNA research? Fourth, should the Federal Government preempt the authority of States and localities in the interest of uniform regulation?

Federal agency

Several witnesses discussed the merits and drawbacks of leaving regulatory authority with the National Institutes of Health. Joseph Grady of the Upjohn Co.'s Department of Infectious Disease Research and William Rutter of the University of California at San Francisco argued that NIH has the greatest expertise for evaluating physical and biological containment of recombinant DNA material and should therefore be the monitoring agency; but their view was in the minority. The NIH Director himself stated that there is "an inherent conflict of interest" in the agency's both sponsoring the research and acting as its "policeman." He also said that NIH has little capability or
experience as a regulator, although it is well qualified to propose standards. Clifford Grobstein, Roy Curtiss, and Frank Young, among others, agreed with Director Fredrickson's recommendation that inspection and enforcement authority be transferred to another agency in HEW, perhaps the Center for Disease Control, with its extensive experience in controlling infectious agents and supervising laboratory practices. Grobstein saw merit in the creation of an independent regulatory commission, but only in the long run, when the implications of genetic manipulations in the areas to extend beyond considerations of health and safety to applications in the areas of energy, agriculture, pharmaceuticals, the environment, and possibly human genetic engineering.

Advisory system

Criticisms of the Recombinant DNA Research Advisory Committee, the authors of the 1976 guidelines and the proposed revisions, also focused on committee members' involvement in recombinant DNA work and their relatively narrow expertise, as well as the National Institutes' failure to encourage broad scientific and public participation in the standard-setting process. According to Jonathan King, among others, the advisory committee has been dominated by biochemists and molecular biologists skilled in the techniques of recombinant DNA and interested in their application but not expert in the assessment of their effects. He charged that scientists with relevant experience in public health, pollution, microbial ecology, and occupational health, for example, had "essentially been excluded from the proceedings." Furthermore, the advisory committee's reliance on unpublished data, communicated by letter and phone call, had contributed to "the abrogation of the normal process of scientific decisionmaking."

Roy Curtiss, a current member of the advisory committee, conceded that "in hindsight, it is clear that the guidelines could have been drafted with much greater public input." To allay the criticisms which would become increasingly deleterious to science and society, he called on the scientific community to "entrust certain decision-making authority with representatives of society * * *" by supporting the establishment of two independent advisory committees. One committee, with responsibility for formulating physical and biological containment standards and reviewing applications for approval of host-vector systems, would be composed of scientists in genetics, molecular and cell biology, infectious diseases, epidemiology, ecology, agricultural science, industrial microbiology and other fields that are or might become relevant. A second committee, representative of "all segments of society" and possibly including scientists not engaged in recombinant DNA work, would approve or disapprove but not amend the proposed regulations, suggest how the regulations are to be implemented, and make other recommendations based on a continuing evaluation of the social impact of recombinant DNA technology. Jonathan King endorsed this proposal, particularly its provision for a broadly representative committee to study longer range issues of genetic research and engineering policy.

Role of institutions engaged in research

The NIH guidelines assign primary responsibility for approving the research facilities and procedures and for monitoring compliance
to an institutional biosafety committee. These committees commonly include researchers engaged in recombinant DNA work, other knowledgeable scientists, members of professional school or liberal arts faculties, and, in some instances, public members, although the guidelines do not specify their composition or appointment procedures. In all cases, service is voluntary and in addition to members' other responsibilities.

Nearly all of the subcommittee's witnesses, including representatives of the private sector, supported a provision for onsite review committees, though for somewhat different reasons. Many scientists regard the biosafety committee as an essential instrument of self-regulation, others as a mechanism for employee participation and public scrutiny. Some observers question whether a part-time committee, most of whose members have close ties to the institution and researchers engaged in recombinant DNA work, can be expected to monitor the research carefully and enforce the regulations vigorously. Thus, there is moderate disagreement, not only about the committees' composition but also about their functions and accountability. Harlyn Halvorson, speaking for the American Society of Microbiology, recommended that each biosafety committee include public representatives but have a majority of members with "technical expertise in the activities conducted at the institution in question." King considered it "*** imperative that laboratory workers be fully involved in decisionmaking processes ***. Their representatives must sit on biohazard committees ***." Marshall Shapo observed, from his own experience on the University of Virginia biohazard committee, "*** It (is) important that we give opportunities for intramural collegial discussion, and we also *** provide for some kind of independent review outside of the institution, so that the people who are doing the review are not people who are in any substantial way beholden to those who are doing the research."

Role of State and local governments

In their testimony before the subcommittee, representatives of both the American Society for Microbiology and the Pharmaceutical Manufacturers Association predicated their support of legislation on its preemption of State and local laws imposing greater restrictions on recombinant DNA activities than those provided by the Federal standards. Harlyn Halvorson stated, "It is our fear that if this is not done, we will see a patchwork of conflicting laws regulating microorganisms which recognize no political or geographical boundary ***. Excessive and variable restrictions would increase the cost of recombinant DNA research and could lead, in many cases, to abandonment of such research." Joseph Stetler of the PMA agreed, "A proliferation of State or local laws and regulations would probably not increase safety, but it could seriously impede the development of the potential benefits of this new technology."

Public interest group representatives were equally insistent that States and localities be permitted to impose stricter standards. Marcia Cleveland of the Natural Resources Defense Council argued that leaving the way open for State and local regulation is essential as an avenue for public participation and political outlet for public opposition. "** When citizens are aroused about the hazards of recombinant
DNA, they can respond, and they can respond intelligently." Furthermore, there are many Federal regulatory programs which rely on States to promulgate regulations. "Somehow in each of these we managed to deal with diversity. I see no particular reason why recombinant DNA should pose a greater problem."

The controversy represented by these opposing points of view has seriously impeded congressional action on recombinant DNA legislation and therefore merits careful evaluation. Assuming that there is a strong Federal interest in regulating effectively all recombinant DNA activities in order to protect public health and the environment, the subcommittee has tried to assess whether stricter State and local regulation would seriously impede scientific research and development of beneficial uses of the technology, whether States and localities have demonstrated a strong desire to regulate recombinant DNA activities, whether they have special competence that would be useful, and whether there is a compelling legal or constitutional argument for permitting State and local governments to regulate as they see fit.

The subcommittee has found that while public controversy has flourished in several academic communities and a few States, it has generally not resulted in the passage of legislation more restrictive than the NIH guidelines. Academic and industrial scientists appear to be concerned primarily about proposals to prohibit all recombinant DNA research, prevent the construction of higher containment research facilities, or, on the other hand, restrict all experiments to high containment laboratories. Joseph Grady of Upjohn Co. cited unsuccessful efforts in Cambridge, Mass., to stop construction of a P3 laboratory, while Bruce Levin of the University of Massachusetts referred to a proposal, since rejected by the New Jersey Department of Health, to impose EK2, P3 requirements for all experiments. He commented, "I don't think that is justified ** *. I think that would be an inhibition on scientific freedom of inquiry."

According to other witnesses, the prospects of such actions by State or local governments have become increasingly remote. Paul Berg of Stanford predicted that "** the worst that can happen is that a community will say that we want everything to be done under the NIH guidelines." Cetus Corp. president, Ronald Cape, suggested that "** some of the pressure for State and local regulation has been motivated in part by a desire to goad Washington into action, particularly since it was felt that the apparent failure of the NIH guidelines to cover industry represented a real problem." And the president of the PMA agreed that there would "not ** be a lot of enthusiasm in local communities to proceed" once Congress acts to regulate all recombinant research.

Recently passed or proposed city ordinances and State legislation tend to confirm these impressions. In requiring all recombinant DNA experiments to be "undertaken only in strict conformity with the guidelines of the National Institutes of Health ** **," the Berkeley, Calif., City Council noted that "the guidelines are only applicable to NIH-funded research, while many non-NIH-funded private and public research projects continue to be unregulated." (Ornance No. 5070-NS, October 21, 1977.) Shortly after the subcommittee's hearings, the New Jersey Public Health Council unanimously adopted a
binding resolution that the conduct of artificial recombinant DNA research in the State be carried out under the NIH guidelines. According to the attorney general of New Jersey, the council “chose not to adopt the positions of the public advocate and its own hearing officer regarding any modifications of the NIH guidelines.”

An exception is a resolution of the New York Council (No. 1013, August 25, 1977), calling on the Congress “to preserve local autonomy” in the regulation of recombinant DNA research, although the Governor of New York, in vetoing a bill passed by the State legislature, stated that such regulation “should be national in application and not imposed in random fashion from State to State.” (Statement of Gov. Hugh Carey, August 12, 1977.)

On the other hand, there are areas of public health where the States have traditionally had regulatory responsibilities and developed some competence. Marc Lappé referred to the California Health Department’s supervision of clinical laboratories. In a letter submitted to the subcommittee, the director of the laboratory division of the Connecticut State Department of Health reported that his agency had registered and inspected facilities engaged in recombinant DNA research in accord with the State’s public health statutes and regulations. David Newburger, professor of law at Washington University in St. Louis, generalized:

Under our Federal system of government, the States have a right to protect the health and safety of their citizens, just as the Federal Government exercises some rights in that area on a nationwide basis. Unless there is some compelling national reason for us to distinguish this kind of research from all other research, I cannot see any reason to preempt the area.

**Views of the subcommittee**

The subcommittee believes that legislation or administrative action to regulate recombinant DNA research should correct the deficiencies of the present system but retain its successful features as well as maintain continuity. In view of the fact that existing statutory authorities are, on the whole, adequate to regulate commercial applications of the technology, no new Federal agency is needed. (See below.) Instead, legislation should assign authority to the Secretary of Health, Education, and Welfare, who will draw upon the expertise of NIH in formulating standards but should delegate monitoring and enforcement responsibilities to the Center for Disease Control or another suitable agency in the Department. The subcommittee agrees that NIH may appear to be compromised by its commitment to supporting recombinant DNA research; nor is it well equipped by previous regulatory experience to perform the latter functions. The subcommittee is concerned that HEW give adequate attention to recombinant DNA research directed toward agricultural, energy, and other nonhealth applications, but believes that no other Federal agency has comparable expertise in the broad range of work with recombinant DNA.

The present membership of the Recombinant DNA Molecule Program Advisory Committee should form the core of an expanded advisory committee to the Secretary, including members with expertise in regulatory procedures, safety and health regulation, and laboratory work. Lay opinion should also be represented. In view of the rapid development of recombinant DNA research, however, the legisla-
tion should not specify the committee's composition in detail. The subcommittee carefully considered Roy Curtiss' proposal to establish two independent advisory committees, but concluded that the technical and social policy aspects of even the physical and biological containment standards or host-vector approval cannot be readily distinguished. Moreover, communication among scientists and nonscientists who advise the Secretary should be encouraged rather than inhibited. The enlarged advisory committee should continue to exercise the functions assigned to the NIH Recombinant Advisory Committee, of recommending changes in the regulations and evaluating host-vector systems submitted for certification.

The subcommittee recommends that the chief administrative officer of any institution, company, or laboratory conducting recombinant DNA research be required to appoint a committee whose members should include scientists not engaged in recombinant DNA work, representatives of laboratory workers, and public members not affiliated with the institution. Again, however, the responsible official should have some discretion in the appointments.

The subcommittee doubts that part-time members of institutional committees will have sufficient time and motivation to monitor experiments regularly and to investigate thoroughly allegations of violations of the regulations. The committee's primary responsibilities should be to approve research facilities and procedures for individual projects, oversee the training of researchers and laboratory workers, and serve as a channel of communications between researchers and the Department of HEW. This role, though more limited than that implied by the current guidelines and proposed changes, is nonetheless essential to insure compliance with the recombinant DNA research standards.

The subcommittee finds that States and localities have generally recognized that compliance with the physical and biological containment standards of the NIH guidelines provides adequate assurance of safety in the conduct of recombinant DNA research. Actions by States and communities to prohibit some or all experiments or to impose higher containment standards than are required by the Federal Government could impede scientific inquiry and the development of beneficial uses of recombinant DNA technology. Congress may preempt State and local regulations that impose such a burden on interstate commerce. On the other hand, the subcommittee recognizes the responsible nature of most State and local government actions to date and the value of informed citizen participation in developing policies governing scientific activities. In addition, observance by researchers of Federal standards is likely to vary among localities and laboratories. Many communities have demonstrated an interest in attempting to insure compliance with the NIH guidelines and have experience in related areas.

For these reasons, the subcommittee recommends a partial Federal preemption of State and local regulation of recombinant DNA research. Under this provision, a State could not by regulation or legislation directly or effectively prohibit experimentation or require physical or biological containment measures exceeding those required by the Federal Government, unless the Secretary of HEW elects to waive
Federal preemption upon the presentation of convincing reasons in support of stricter standards. A State or political subdivision would be permitted to take other actions to assure its citizens that the Federal standards were being observed. These actions include registering and inspecting facilities, requiring public representation on the institutional biosafety committee, investigating alleged violations of applicable regulations, and seeking an injunction to stop a violation. A State would also have standing in Federal court to obtain injunctive relief, pending an investigation and appropriate action by the Secretary, in the unlikely emergency that an activity being conducted in compliance with the regulations were found by the court to pose an imminent threat to the health of laboratory workers or the general public. Finally, a State, community, private organization or citizen should have an opportunity to comment to the Secretary on an application to conduct recombinant DNA research.

PROCEDURES

A large majority of NIH research grants are made to institutions rather than individuals, but it is the principal investigator who bears primary responsibility for compliance with the NIH recombinant DNA research guidelines and can be held accountable for disregarding them. Among other duties, he or she must submit with the grant application to NIH a Memorandum of Understanding and Agreement (MUA), certified by the institutional biosafety committee, and describing the proposed experiment and the procedures and facilities that will be used to achieve the required levels of physical and biological containment. The NIH Office of Recombinant DNA Activities must review and approve or disapprove the proposed MUA before the work can begin. In the event of a violation of these procedures or standards, NIH's only recourse is to deny the use of grant funds for recombinant DNA experiments or halt further expenditures of grant funds if the experiment is in progress. The latter may be an embarrassment to the institution but is a relatively severe sanction for the principal investigator and his colleagues on the project. NIH has taken this action in only one instance, upon discovering that no MUA had been approved, as required, for a project begun before the guidelines were issued.

Witnesses before the subcommittee acknowledged the need to devise new procedures applicable to privately supported research activities. What impressed the subcommittee, however, was the degree of consensus on elements of a regulatory system appropriate to both the academic and industrial sectors. Stetler of the PMA, Halvorson of the ASM, Joseph Keyes of the American Association of Medical Colleges, and OSTP Director Frank Press all advised against licensure of individual researchers as "onerous and burdensome" but recommended a system of Federal licensing of facilities to conduct recombinant DNA work. They said that revocation or suspension of such a license would be an effective deterrent to misconduct. Stetler also proposed the registration of individual research projects with the Federal agency, although primarily for informational purposes. Grady of Upjohn suggested that researchers file the equivalent of an MUA,
which would automatically become effective after 30 days. Press cautioned that:

The notion that all paths of investigation must be identified and approved in advance flies in the face of the scientific method, in which the results of one step in the process guide the next decision point. A cumbersome review of experimental protocols and the many contingent experiments may prove counter-productive.

Similarly, witnesses generally opposed provisions for seizure of research materials, high fines, or criminal penalties for violations. Several pointed out that civil or criminal fines would impose a greater hardship on academic than on industrial research scientists.

A number of witnesses called for a scale of penalties, each appropriate to a particular offense. When asked what action should be taken in the event of a violation of the containment standards, Oliver Smithies of the University of Wisconsin said that it would be appropriate to revoke the license for conduct of a prohibited experiment or use of an untested organism. A less serious offense might merit closing of the laboratory for a period of time equal to the duration of the violation. With reference to the behavior of individual researchers, David Newburger suggested that:

... the Federal Government through the self-regulatory committees and in consultation with them should ultimately have the power to control the conduct of individuals in the laboratories ... for example, by having the power to bar a person from working in a laboratory ...

In addition to requiring the submission of information on recombinant DNA activities, the Federal Government should have authority to inspect laboratories, according to spokesmen for the pharmaceutical manufacturers and some academic scientists. Levin suggested a sampling of facilities at all four containment levels, while Frank Young of the University of Rochester preferred that inspections be limited to the higher containment laboratories. Jonathan King noted the present difficulty of identifying the biological material used in recombinant DNA work and said that NIH should invest in developing procedures for such monitoring. He also regarded it as essential to monitor laboratory workers' health. In the absence of such records and suitable comparative data, he argued it would be impossible to say what are the health effects of recombinant DNA materials.

Whatever certification, registration, and inspection system is established presents the further problem of public disclosure of normally confidential information. The problem characterizes all business regulation, but it is unusually troublesome when the subject of regulation is basic scientific research with an exceedingly promising technology. Joseph Keyes described the two concerns of the academic research scientist—first, that he may be deprived of the opportunity to exploit his ideas by premature disclosure of a research application or information submitted in compliance with regulatory requirements, and second, that the opportunity to patent an invention and license its development may be lost by premature publication. In the United States, a patent must be applied for within 1 year of publication; in other countries there is no grace period. As a result of the recent Supreme Court decision in 

Parker v. Bergy, 46 U.S.L.W. 3788 (U.S., June 26, 1975), the patentability of purified or genetically manipulated living organisms
is in doubt; but if further judicial interpretation or legislation eventually upholds such patent rights, HEW policy would permit grantee institutions to acquire patents and award licenses for recombinant DNA discoveries. As for the private sector, Cetus Corporation President Ronald Cape predicted that the insecurity of patent rights would deter commercial firms from investing in the development of recombinant DNA applications. "(We) will be without a mechanism for useful exploitation of a technology which was invented in this country. It will certainly be exploited elsewhere."

In the absence of statutory protection of the confidentiality of research plans, the Freedom of Information Act (5 U.S.C. 552) would govern their disclosure by the regulatory agency. Subsection (b)(4) of the FOIA provides an exception from mandatory disclosure for "matters that are *** trade secrets and commercial or financial information obtained from a person and privileged or confidential"; but academic and industrial scientists regard the so-called trade secret exemption as inadequate on several counts. In Washington Research Project, Inc. v. Department of Health, Education, and Welfare (504 F. 2d 238 (D.C. Cir. 1974)), the court of appeals affirmed a lower court decision ordering release of research grant applications including experimental protocols on the grounds that there were no trade secrets in a "noncommercial scientist's design."

The court further said that "it defies commonsense to pretend that the scientist is engaged in trade or commerce." While that argument would not arise in the case of industrial recombinant DNA research, the interpretations of subsection (b)(4) give little guidance as to the trade secret content of a research design. The leading case, National Parks and Conservation Association v. Morton (498 F. Supp. 965 (D.D.C. 1974)), applies two tests, of which the relevant one is whether release of the information by the Government agency might cause substantial harm to a competitive position. The Federal criminal statute (18 U.S.C. 1905) barring a Government official's release of proprietary information appears to give little protection because it only applies "unless otherwise provided by law," as in the FOIA.

On the other side of the disclosure controversy are those who insist on public access to all information relevant to the protection of public health and the environment. Marcia Cleveland observed:

Over the past 10 years... this country has come to recognize the importance of citizens having access to the information which... forms the basis of government activities that affect our lives. That is what the Freedom of Information Act is about... In the field of recombinant DNA, I don't think that citizens can effectively participate in any sort of regulatory or advisory activity unless they have access to information in the hands of the government... and industry.

Cleveland suggested that, if need be, the patent laws should be amended to eliminate the penalty for prior publication. On the other hand, Marc Lappé opposed the granting of any patents for recombinant DNA research discoveries.

Views of the subcommittee

The subcommittee agrees with the admonition of Philip Handler, president of the National Academy of Sciences, to establish only the "minimal arrangements that would suffice to maximize compliance" with the standards governing recombinant DNA research. It has no
desire to create a large Federal bureaucracy of licensing officials and inspectors or to impose on scientists requirements that effectively curtail productive research. On the other hand, accomplishment, prestige, profit, and expectation of benefits for society are positive incentives to proceed as rapidly as possible with the use of recombinant DNA, as with any other promising research technique. Some scientists are already convinced that it poses no significant health or environmental hazard; some may be inclined to substitute their own judgment of safety for that of a regulator. The incidents at the University of California at San Francisco underscore the need for greater accountability.

To support the primary role of the institution in guaranteeing the safe conduct of recombinant DNA research, the subcommittee recommends that the Department of HEW certify individual universities, corporations, private laboratories, or their autonomous divisions to conduct the research. Approval should be conditional upon a showing that the chief administrative officer of the institution has appointed a qualified biosafety review committee thoroughly familiar with the Federal requirements to approve projects and facilities and to provide for the training of investigators and laboratory personnel in proper physical and biological containment methods. The application should describe the facilities and physical containment levels at which the research is planned to be conducted. Further, the institution must agree to monitor the health of laboratory workers and to keep such records and make such reports as the agency prescribes, including reports of any violations of the regulations. The certificate should be valid for the duration of the act or not more than 3 years. If the institutional committee fails to carry out its responsibilities, however, the Secretary should suspend its authority to approve recombinant DNA projects or, where appropriate, specific categories of experiments.

The subcommittee believes that the Department will not have sufficient information to achieve compliance unless privately supported as well as federally funded projects are registered with it in advance. The registration should describe the proposed experiments, the physical and biological containment levels required, the facilities, materials, and procedures that will be used, and other data that the Secretary may prescribe. These projects should not be subject to the rigorous review given Federal research grant applications; indeed it would be appropriate for a project to commence unless the Department raised objections within a brief period of time, such as 14 days. To the extent feasible, qualified institutional or local biosafety officers should be appointed to advise investigators and monitor experiments; but the Secretary should have authority to inspect research facilities and to order the destruction of hazardous or potentially hazardous material prepared in violation of the standards. The Secretary should consider supporting biosafety training programs for investigators and technicians, perhaps conducted on a regional basis.

The suspension of an institutional committee is a severe sanction to be reserved for rare cases of serious dereliction on the part of the institutional officials or their agents. Even the withdrawal of a Federal grant may not be an appropriate response to misconduct by an individual or a small group of researchers. Civil penalties may be ap-
propriate in cases of knowing violations, but the subcommittee also recommends that the Secretary have authority to suspend research being conducted in violation of the regulations and persons from participating in recombinant DNA research for a specified period of time. With regard to both institutional and individual suspensions, the Secretary should be able to issue an administrative order rather than be obliged to seek a court injunction. The judicial route would incur delay and might require a showing of harm or potential harm. Nevertheless, due process must be assured; the more severe the penalty, the more rigorous should be the procedural safeguards.

The subcommittee believes that realization of the benefits of recombinant DNA technology requires some protection of the confidentiality of research ideas and procedures, but it recognizes the public's right of access to information necessary to judge compliance with the Federal standards and their effectiveness in protecting public health and the environment. Unfortunately, the subcommittee has found no ideal balance between these competing values. Two major study commissions have recognized, however, that the disclosure of academic research protocols, submitted in application for Federal funds, is a generic problem, not limited to research with recombinant DNA. Indeed, enactment of legislation to regulate such research would not significantly increase the likelihood of such disclosures. Consequently, the legislation should not establish for recombinant DNA researchers a right of confidentiality which is not accorded to other scientists. Rather, for the time being, HEW should continue its present policy of refusing to disclose a grant application prior to funding and, after consultation with the grantee, of maintaining the confidentiality of potentially patentable information contained in a funded research protocol. In the long run, this policy may entail a heavy administrative burden and possibly further litigation. The appropriate committees of Congress should therefore address the general problem of protecting intellectual property rights, as the President's Biomedical Research Panel and the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research have recommended.

Regulation of the use of recombinant DNA techniques would expose the private sector to disclosure of proprietary information at the beginning of research and development, whereas present Government regulation of products and processes is limited for the most part to the manufacturing and testing stages. The subcommittee believes that some measure of protection against this risk of disclosure should be provided, especially in view of the fact that recombinant DNA techniques may be only a part of a larger research project. Nevertheless, the concern of the pharmaceutical manufacturers and others is also a general one; they argue that regulatory agency and court interpretations of subsection (b) (4) of the FOIA and 18 U.S.C. 1905 fail to protect much trade secret information, particularly against disclosure to competitors.

The subcommittee doubts that the solution lies in attempting to define in recombinant DNA legislation categories of information, some of which would remain confidential and others be subject to disclosure. Instead, the legislation should establish a notification
and consultation procedure similar to that followed by NIH in deciding whether to release research protocols submitted by grant recipients.

**Recommendations for Regulation of Commercial Applications**

As discussed previously, the possible commercial applications of recombinant DNA research are numerous, including the production of pharmaceuticals, pesticides, enzymes, plant growth stimulators, environmental decontaminants, and other materials of value to industry, medicine, agriculture, and the consumer. While some applications of the research may be decades away, others could be available within a few years.

Both the production of large cultures of recombinant DNA organisms to manufacture useful substances and the release of modified hosts or vectors into the environment are contemplated. Congress has the responsibility to insure that any hazards associated with these uses of recombinant DNA techniques for commercial purposes are fully understood and appropriate safeguards are established to prevent any undue risk to human health or the environment. The following section examines a number of policy issues relevant to the applications of recombinant DNA technology. Documents relating to the applicability of current statutes to the regulation of these applications are included in the appendix.

**Locus of Regulatory Responsibility**

Twelve existing statutes have been identified by the American Law Division of the Congressional Research Service as possible authorities under which to regulate commercial uses of recombinant DNA. (See appendix.) Since a large number of statutes are involved, it has been argued that the most direct way to deal with the problem is to consolidate all of the regulatory authority within a single agency and a single authority. In fact, some legislation (for example, S. 1217) would effectively preempt all Federal statutes except the Occupational Safety and Health Act (29 U.S.C. 631, et. seq. (OSHA)), and lodge responsibility for the regulation of all recombinant DNA activities with the Secretary of Health, Education, and Welfare or an independent commission. Thus, whether or not a recombinant DNA application is pesticidal (now subject to the jurisdiction of the Environmental Protection Agency), for industrial purposes (also largely in EPA's jurisdiction), pharmaceutical (Food and Drug Administration’s jurisdiction), or involves the transportation of hazardous materials (Department of Transportation's jurisdiction), sole regulatory responsibility would be vested in a single agency.

While a consolidation of authority appears to be in the interest of administrative efficiency, it would duplicate expertise and responsibilities now existing within other agencies of Government. For example, if an agency or commission were given jurisdiction over a proposed use of recombinant DNA to control insects on agricultural crops, this grant of authority would duplicate the function and expertise of EPA under the Federal Insecticide, Fungicide, and Rodenticide Act—7 U.S.C. 135, et seq. (FIFRA). Similar duplica-
tion would occur with respect to transportation, waste disposal, and other problems that may be associated with recombinant DNA applications and for which expertise and regulatory responsibility have already been established. The types of regulatory problems presented by recombinant DNA may differ, however, from those of conventional materials regulated under existing laws and require specialized training or additional personnel familiar with the scientific aspects of recombinant DNA. Nonetheless, with the exception of regulation of research activities for which HEW currently has primary responsibility, consolidation of all authority in the Department of HEW or an independent commission would require creating a new administrative structure and assembling the expertise to deal with the large number of potential applications of recombinant DNA technology.

APPLICABILITY OF EXISTING STATUTES

Given the speculative nature of the eventual uses of recombinant DNA research, it is difficult to identify precisely the different kinds of public health and environmental problems that may arise. Nonetheless, some observations are appropriate. There are a number of substances which may require control as recombinant DNA technology becomes commercially feasible. While many of these materials may present little or no hazard in and of themselves, the ability to control their production, movement, and use in recombinant activities may be important control mechanisms. Included are the recombinant DNA molecules, the enzymes necessary to split DNA molecules and to recombine them, DNA segments to be inserted in host DNA molecules and the organisms serving as hosts for insertion of recombinant DNA. The authority should also exist to control substances produced by recombinants.

With the exceptions noted below, all of the materials associated with recombinant DNA applications are apparently subject to one, and possibly several, statutes designed to protect health and the environment. If the material produced, either an organism or a product of an organism, is to be used as a pesticide, the terms of FIFRA apply. Pharmaceutical products and manufacturing processes are subject to the Federal Food, Drug, and Cosmetic Act—21 U.S.C. 301, et seq. (FDCA). To the extent that the substances necessary to produce pesticide products or products subject to the FDCA are not covered by those statutes, they are covered by the Toxic Substances Control Act—15 U.S.C. 2601, et seq. (TOSCA). Similarly, Federal laws relating to water pollution, waste disposal, air pollution, occupational safety and health, and communicable disease all appear applicable to recombinant DNA materials and organisms if they are related to those types of hazards. The extent to which these statutes provide adequate regulatory authority merits closer examination.

There is substantial question regarding the control of organisms containing recombinant DNA under TOSCA. This is particularly important when examining requirements for premanufacturing review of organisms which are not pesticidal or subject to the FDCA. For example, attempts may be made to improve the efficiency of sewage
treatment microflora, confer nitrogen-fixing capability on food plants, or accelerate the production of methane or hydrogen by micro-organisms from hydrocarbon sources such as garbage and waste oil.

TOSCA may be capable of embracing organisms containing recombinant DNA by virtue of the coverage by that act of DNA molecules. Section 5(2) defines a chemical substance subject to the act as "any organic or inorganic substance of a particular molecular identity." The definition also includes "any element or uncombined radical." It is thus clear that DNA molecules or segments of DNA molecules are fully subject to the provisions of TOSCA, including the premanufacuring notice provisions of section 5.

The authority contained in TOSCA enables the Administrator of EPA to extend controls to any "commercial use" of those molecules, presumably including their use in organisms. For example, EPA would prohibit or limit the commercial "use" of a recombinant DNA molecule in an organism that would present unreasonable risks to health or the environment. While this may provide some authority over the organisms themselves, EPA concludes that TOSCA is not meant to control organisms directly. EPA would thus not impose restriction on organisms, only on molecules that might be inserted into them. EPA does not question the coverage by TOSCA of DNA molecules or segments of DNA. Nonetheless, in the absence of specific authority addressing the recombinant DNA question, EPA has committed itself to utilizing the authority under TOSCA to the fullest extent necessary to prevent undue risk to health and the environment. (See Appendix.) Clarifying the authority to reach organisms utilized in recombinant DNA activities would also insure that those persons purchasing DNA recombinants from a producer for the purpose of further cloning would also be regulated to insure no undue risk to health or the environment.

Section 361 of the Public Health Service Act (42 U.S.C. 264) provides the Secretary of Health, Education, and Welfare with authority to prevent communicable disease. In relevant part, section 361 authorizes the 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 state or possession into any other state or possession **." Because of the broad discretion given the Secretary, it has been argued that section 361 provides sufficient authority to control the commercial applications of recombinant DNA. In fact, the Environmental Defense Fund and the Natural Resources Defense Council petitioned the Secretary of HEW on November 11, 1976, asking him to impose control over all recombinant DNA activities under section 361 of the Public Health Service Act. An important issue in the use of section 361 of the Public Health Service Act, or any other statute whose primary purpose is to protect public health, is the extent to which environmental concerns may also be addressed. While environmental concerns often manifest themselves as public health problems, there are other ecological insults, such as the destruction of wildlife habitats or the despoilation of wilderness, whose "public health" link is tenuous. The National Environmental Policy Act (42 U.S.C.
4321, et. seq. (NEPA)). requires in part that all agencies shall insure "* * * that presently unquantified environmental amenities and values be given appropriate consideration in decisionmaking along with economic and technical considerations. * * *" (sec. 102(2) (B)). It has been argued that NEPA requires agencies to protect the environment in actions taken, whether or not the authorizing statute specifically provides for environmental protection. Thus, once an agency has established jurisdiction over a substance for whatever purpose, then it is automatically obligated in its actions to protect the environment.

The extent to which NEPA imposes an additional substantive duty upon each Federal official to protect the environment has not been extensively litigated. Nonetheless, in three important cases (Calvert Cliffs v. AEC (2 ERC 1779), Zabel v. Tabb (1 ER 449), and EDF v. Matthews (8 ERC 1879)) the courts have upheld the authority and responsibility of agencies to protect the environment, notwithstanding an authorizing statute which does not explicitly provide for environmental protection.

While the authority of section 361 is broad and arguably could reach many, if not all, of the commercial applications of recombinant DNA research, it is highly unlikely that the Secretary of HEW will use the authority in this manner. In the absence of definitive judicial rulings, using section 361 of the Public Health Service Act to safeguard the environment could result in litigation.

PREVENTION OF HAZARDS

With the passage of TOSCA in October 1976, Congress established the principle that chemical hazards should be controlled before their hazards become manifest. The act's mechanisms for premarket review, which were in part patterned after similar provisions in pesticide and drug law, provided the first comprehensive means of enabling regulators to review hazards and take action before a substance reaches the channels of commerce. Experience in recent years with such chemical disasters as PCB, kepone, PBB, vinyl chloride, and others demonstrated that the Nation could no longer afford to act against chemicals after the damage was done. In his environmental message of April 1977 President Carter reiterated this policy and stated emphatically that the administration embraces preventive control. The reasoning that resulted in the preventive control measures in TOSCA and other statutes applies as well to commercial products developed with recombinant DNA techniques.

Apart from FIFRA and the FDCA, the only statute explicitly providing for premanufacturing review is TOSCA. The premanufacturing review coverage of TOSCA is broad, excluding only pesticides, tobacco and tobacco products, nuclear material, firearms, materials subject to FDCA, and mixtures of chemical substances. While other statutory authorities, like section 361 of the PHS Act, may also be interpreted to provide this type of authority, the explicit terms of TOSCA provide for premanufacture review of new chemical substances and significant new uses of existing ones. However, the limitations of TOSCA described above relative to the coverage of recombinant DNA
organisms also apply to the premanufacturing review provisions of the act. Nonetheless, since the commercial manufacture of new molecules, including the manufacture of new DNA molecules, requires premanufacturing review under TOSCA, some further discussion of its provisions is appropriate.

Under section 5 of TOSCA, manufacturers of new chemical substances (in this case, new DNA molecules) are required to give notice to EPA 90 days prior to the first manufacture of those substances. Significant new uses of existing substances are also covered by the same provision. The premanufacturing review period may be extended to 180 days if the Administrator finds good cause. The premanufacturing notice must include: (a) the identity of the substance, (b) the proposed uses, (c) the amounts to be produced, (d) a description of byproducts, (e) employees exposed, and (f) the manner or method of disposal. The results of any tests which have been conducted on the substance must also accompany the submission.

During the premanufacturing review period, the Administrator of EPA is authorized to halt or limit the manufacture of the new substance or significant new use of an existing substance if the Administrator finds an unreasonable risk of injury to health or the environment. In addition, mechanisms exist to halt or limit the manufacture of the substance if the information available to the Administrator is insufficient to permit a reasoned evaluation of the health and environmental effects, and the Administrator makes a determination that an unreasonable risk exists or that there will be significant human or environmental exposure.

While TOSCA provides for premanufacturing review, manufacturers are free to proceed if the Administrator fails to take action during the premanufacturing review. There is substantial question as to whether this type of "catch me if you can" procedure is sufficient to guard against potential dangers of recombinant DNA exposure. Premanufacturing review and certification by the Administrator that no undue risk to health or the environment exists, as is now the case with pesticides and drugs, appears to be warranted.

FIFRA requires premanufacturing approval of pesticides by EPA. In order to obtain approval, a manufacturer must demonstrate to the Administrator that the pesticide will perform its intended function without unreasonable adverse effects on the environment, including humans. If a manufacturer is unable to demonstrate an absence of unreasonable adverse effect, it is the intent of this statute that registrations not be granted. While the EPA has been criticized for failing adequately to screen pesticidal products prior to registration, it is clear that this procedure, if exercised correctly, can serve as a basis for eliminating undue risk to health or the environment associated with the pesticidal uses of recombinant DNA techniques prior to any manufacture, sale, or movement in commerce. A similar procedure exists under the FDCA with respect to food additives, color additives, new drugs, new animal drugs, devices, and pesticide residues. A major shortcoming of the FDCA is that the regulatory authority extends only to the protection of human and animal health, not to the protection of the environment.

In summary, with respect to (a) substances subject to FDCA, (b) pesticides, and (c) substances subject to section 5 of TOSCA, it is:
clear that Congress intended that materials not be approved for use until risks are identified and judgments made on the extent to which those risks can be tolerated. Very few, if any, of the commercial uses of recombinant DNA technology should escape the premanufacturing review provisions of these three statutes.

A necessary adjunct to any mechanism for premanufacturing review is the authority to take regulatory action where there is cause for concern but no irrefutable evidence of injury. While this principle is embraced in most statutes controlling hazardous materials, it is particularly important when controlling risks associated with recombinant DNA applications since we know far less about their effects on health and the environment.

After a recombinant DNA molecule or organism has been approved for use and manufacture has begun, generally a greater degree of risk must be evident in order to take action, in part because the economic effects of regulation are greater. While in theory an absence of assurance of safety of a pesticide or drug should result in withdrawal of its approval, action is rarely taken unless positive indicators of risk are developed from test data or other evidence. Nonetheless, it is clear that evidence of actual injury, as opposed to risk, need not be demonstrated. Recent cases in environmental law support this conclusion.

The major exception appears to be in standards established for the protection of worker health under OSHA. The authority of the Secretary of Labor under that act is limited to recognized hazards to the working environment. In _American Mining and Refining Company v. The Occupational Safety and Health Review Commission_ (501 F. 2d 504 (1974)) the court ruled that the regulatory authority under that act covers only airborne contaminants known to be dangerous. Whether OSHA’s authority extends to unquantifiable and speculative dangers is thus questionable. (See Appendix.)

Under TOSCA, the Administrator of EPA is required to exercise his authority to the extent that risks may not be prevented or reduced to a sufficient extent by actions under Federal laws not administered by EPA (section 9(a)). Since actual injury need not be shown in order to take action under TOSCA, EPA has the authority and responsibility to protect worker health if the authority of OSHA is insufficient.

Control of Manufacture

The previous discussion has focused largely on the authority of existing statutes to control the products of recombinant DNA research following their manufacture. An equally important consideration is whether existing statutes are sufficient to control hazards that may arise in the process of production and expose those inside or outside the facility to risks. While certain statutes, such as the Clean Air Act and the Federal Water Pollution Control Act, provide control over waterborne effluents and airborne emissions, the authority of these statutes does not extend to specifying the manner of production in order to avoid the effluent or emission. Likewise, OSHA gives the Secretary of Labor authority to establish environmental standards within the workplace but does not give the Secretary authority to specify the manner of production of any substance.
Of the three principal statutes which might be used to control the commercial products of recombinant DNA technology (FIFRA, TOSCA, and FDCA), only the FDCA may contain sufficient authority to insure that products subject to that act are manufactured in a safe manner. Section 701(a) gives the Secretary of HEW authority to issue general rules for the efficient enforcement of the act. This broad grant of authority may be sufficient to reach the manufacture of recombinant DNA.

FIFRA, while providing ample authority to protect against hazards associated with the products of manufacture, contains no authority which would enable the Administrator of EPA to impose requirements with respect to the manner of manufacture. Likewise, TOSCA, while providing broad authority to deal with recombinant DNA molecules and other chemical substances, contains only limited authority to specify the manner of manufacture. Section 6(b) of TOSCA enables the Administrator to order that quality control procedures be invoked in the event a chemical substance or mixture is manufactured or processed in a manner which unintentionally causes it to present unreasonable risks to health or the environment. In addition, in imposing quality control procedures, the Administrator is required to undertake a potentially time-consuming and laborious adjudicatory procedure in order to impose requirements. While other statutes, such as section 361 of the Public Health Service Act and perhaps the plant and animal quarantine laws, may be construed to provide this kind of authority, an explicit statutory declaration of the authority would be desirable.

Many of the problems associated with manufacture are similar to those associated with conducting research with recombinant DNA molecules. The scale is larger and, arguably, the opportunity for environmental damage is greater in manufacturing situations than in research because of differences in personnel training, volume of materials used, and methods of production. Nonetheless, the types of controls necessary to protect workers in the environment and commercial manufacture are similar to those that may be imposed in the laboratory.

Hazards to health and the environment that may occur after commercial manufacture present different problems that must be addressed separately. While tests to determine health and environmental effects may be similar, the control mechanisms developed to prevent hazards in transportation, use, and disposal of the material will be very different in character than those applied inside the laboratory or manufacturing plant. The latter controls will be characterized largely by biological and physical containment requirements similar to those in the NIH guidelines and future regulations governing experimentation.

**TESTING REQUIREMENTS**

It is implicit in any premanufacturing review system that decisions to approve the manufacture of recombinant DNA or derived products will be made intelligently with as full knowledge as possible of the risks. This means that test data relating to health and environmental effects must be available in the premanufacturing review.
process so that these decisions are made properly. It is also implicit in any system for premanufacturing review that the responsibility for developing tests with respect to health and environmental effects should lie with those who will benefit economically from the commercialization.

Moreover, authority should exist to order testing after premanufacturing review in order to insure that health and environmental data is current. There have been important improvements recently in the design of test mechanisms for health and environmental effects of chemical substances and other materials. The development of rapid screening systems, including the so-called Ames test, for mutagenesis and possible carcinogenic activity is but one indication of progress in hazards testing technology. The availability of testing authority should help insure that the latest in testing technology is used fully.

Each agency of Government with regulatory responsibility applicable to recombinant DNA technology and related products also has research authority or access to it. In addition, TOSCA contains authority for the EPA Administrator to require testing by manufacturers and processors of chemical substances, which could include recombinant DNA and other derived products. The testing authority of TOSCA is broad and requires the Administrator to order testing when there is insufficient information or when a substance will be produced in substantial quantities. Congress intended that the provision be broadly interpreted: the conference report accompanying TOSCA indicates that testing may be required whenever "there is a basis for concern." (Senate Report 94–1302, 94th Congress, second session, page 61.) This authority appears to be sufficient, although the task is complicated by the fact that it may be very difficult to design tests to determine potential health or ecological impacts of a unique new organism.

**RECORDKEEPING AND REPORTING REQUIREMENTS**

Section 8(a) of TOSCA provides comprehensive authority for the Administrator of the EPA to require recordkeeping and the submission of reports concerning a broad range of activities associated with the commercialization of chemical substances. Information that may be required includes the identity of the substance, categories of use or proposed categories of use, the amount produced, any byproducts resulting, existing data concerning environmental and health effects, human exposure, and the manner or method of disposal. The authority contained in section 8(a) is limited, however, by an exemption for small business from the general reporting requirements. As a substantial number of producers of commercial recombinant DNA could well fall within most definitions of "small business," the limitation of section 8(a) could be detrimental.

Section 8 (c), (d), and (e) requires producers and distributors to maintain records of adverse reactions, to maintain lists of health and safety studies conducted, known, or reasonably ascertainable with subsequent submission upon request by EPA, and notice to the Administrator of substantial risks associated with substances. The small business reporting exemption does not apply to section 8 (c), (d), and (e).
Other statutes providing for the regulation of recombinant DNA also have separate recordkeeping and reporting requirements. While certain statutory authorities, such as section 361 of the Public Health Service Act, do not explicitly provide for reporting and recordkeeping, these requirements are presumably within the discretion of the Secretary. To the extent that other statutes provide for recordkeeping and reporting, the Administrator of EPA is admonished in section 8(a) of TOSCA not to impose requirements which are "unnecessary or duplicative." As Jonathan King pointed out in the subcommittee hearings, however, there are presently no techniques for tracking inadvertent contaminations for adverse health or ecological effects.

Views of the subcommittee

In examining the anticipated uses of recombinant DNA technology, the subcommittee recognizes the limits of present knowledge. Neither the course of research and development nor the progress of risk assessment can be predicted with accuracy. It may be, as Roy Curtiss suggested, that commercial uses of genetically modified micro-organisms will pose no threat to public health or the environment. On the other hand, the risks of large-scale production and release of recombinant DNA organisms may be greater than those attributed to experimentation in research laboratories.

Congress and the executive branch should anticipate these potential hazards before they materialize. With that in mind, the subcommittee has studied existing statutes to determine whether they are capable of insuring the safe manufacture, processing, use, transportation, and disposal of recombinant DNA products. There should be adequate provisions for premanufacturing or premarketing approval, quality controls in manufacture, testing of effects, recordkeeping and reporting, and appropriate packaging and handling. With the exceptions noted above, the subcommittee has found surprisingly few obvious gaps in these authorities; effective regulation, however, depends upon their proper administration.

The subcommittee believes that Federal regulation should focus on the nature of the prospective uses of recombinant DNA techniques rather than on the technology per se. It therefore makes little sense to create a new agency or bureaucracy to regulate all activities involving recombinant DNA when existing agencies have appropriate authority and expertise in controlling a variety of chemical hazards, insuring drug safety, regulating waste disposal and transportation of hazardous materials, and performing similar functions. Thus, authority over pesticidal uses of recombinant DNA technology should remain with the Environmental Protection Agency. Regulation of pharmaceutical and other applications subject to the Federal Food, Drug, and Cosmetic Act should remain with the Food and Drug Administration. The same reasoning applies to transportation and plant and animal protection. Legislation relating to research should not preempt existing authorities that are applicable to commercial uses of recombinant DNA. There is a danger, however, of conflicting regulation by different agencies. In the case of university and industrial research activities, this danger is minimized by the limitations mentioned above in the Occupational Safety and Health Act,
the Food, Drug and Cosmetic Act, and the Toxic Substances Control Act. With respect to commercial activities beyond the research stage, however, the likelihood of overlapping regulation is much greater. The subcommittee urges close coordination among the relevant executive agencies; memoranda of understanding or Executive orders may be appropriate methods of sorting out their responsibilities. The executive branch should begin at once to make these determinations. To the extent that reorganization of the executive branch consolidates jurisdiction over matters of health, safety, and environmental protection, authority over commercial applications of recombinant DNA should also be consolidated.

The subcommittee further recognizes that certain agencies may need to acquire expertise in recombinant DNA techniques and additional personnel and other resources. For example, the Environmental Protection Agency will likely assume much of the burden for screening and controlling recombinant DNA molecules and their uses. Depending upon how rapidly the technology is developed, EPA should be given additional funds and manpower as necessary to administer the program.

Finally, existing statutory authorities should be used to the maximum extent feasible. There is broad discretion in several statutes, including section 361 of the Public Health Service Act and the plant and animal quarantine laws, to protect public health and, to an uncertain degree, the environment. Careful consideration should be given to using those authorities to remedy weaknesses in other Federal laws more directly related to recombinant DNA applications. It is particularly important that recombinant DNA organisms intended to be released into the environment be subject to premanufacturing review and certification that they pose no significant risk. If authority to accomplish this is questionable or extensive litigation likely, Congress should consider amendments to the relevant statutes. The executive branch should make these determinations as soon as possible and propose appropriate legislation to Congress.
MINORITY VIEWS OF SENATOR HARRISON SCHMITT

I cannot agree with the general thrust toward the excessive regulation of a form of basic scientific research that is inherent in the majority's recommendations. The suggested risk cited for recombinant DNA research is purely theoretical and hypothetical. This suggestion is not supported by our knowledge of recombinant processes that have occurred in nature since life began billions of years ago or by other scientific considerations.

Many of the conclusions and recommendations made by the majority are unwarranted and not supported by the weight of the testimony presented during the 3 days of hearings held by the Science, Technology, and Space Subcommittee. Because of the debilitating effect that over-regulation of basic research would have on all science and technology in the United States, the following dissenting views are offered for the benefit of committee members and others.

GENERAL CONSIDERATIONS

At the outset, it is important to emphasize that the potential risk surrounding research with recombinant DNA molecules was brought to the public's attention by the specific group of research scientists involved in such research. This was done at a very early stage in our understanding of recombinant processes. The end result was the creation of the present National Institutes of Health (NIH) guidelines governing publicly funded DNA research. This is an aspect of the recombinant DNA controversy that should not be ignored, for it demonstrates both a high level of professional responsibility and the fact that the system can work without unnecessarily restrictive regulations. (See attachment A.)

Moreover, it is significant that some of the scientists who first called attention to the conjectural hazards, after more research and after consultation with scientists in related disciplines, have since reassessed the situation and changed their perception of the risk. (See attachment B.) The NIH is presently considering proposed revisions to the guidelines that would have the effect of further relaxing the standards to take into account this new understanding. These factors demonstrate the preliminary nature of our knowledge in this relatively new field of scientific inquiry. Any actions taken by the Congress or the executive branch should be considered as an interim measure until further information is obtained from which we can make an accurate assessment of the hazards, if any, associated with such research.

The use of recombinant techniques to modify fundamental genetic material offers great promise for all mankind through improved understanding of biological processes, and varied applications in such fields as medicine, production of enzymes for industry, and agriculture. It is now one of our foremost weapons in the search for an inexpensive
prevention or cure of cancer as an alternative to increasingly expensive treatment. The testimony of several witnesses indicated that the first real benefits from practical applications of recombinant DNA research are not far off and may be only the beginning of a vast new capability to benefit mankind. Major breakthroughs have already been achieved with the structural genes that specify insulin (used in treatment of diabetes) and the protein somatostatin, which has been described by Dr. Philip Handler, President of the National Academy of Sciences, as a "scientific triumph of the first order" because of its significance for the understanding of the structure and function of the genetic apparatus.

Nevertheless, as with any new field of scientific research, it is impossible at this stage to say with absolute certainty that there are no future hazards attendant to such research. To date, however, there have been no illnesses or other harm associated with recombinant DNA research. Hearing testimony made it clear that there have been recombinant processes occurring in nature since life began, and nature has built-in defenses against aberrant DNA strains. (See attachment C.) However, we cannot ignore the theoretical risks and the necessity to take all reasonable steps to protect the health and safety of the public and the environment until further evidence is accumulated. The continued emphasis of the NIH guidelines in public and commercial activities is clearly justified at this time.

There is a need for Congress to play an active role in the discussion and formulation of Federal science policies with respect to the conduct of recombinant DNA research. The Science, Technology, and Space Subcommittee has acted, and should continue to act, to fulfill its responsibility for science and technology policy oversight. The hearings held by the subcommittee on this issue were conducted pursuant to its broad jurisdiction over "science, engineering, and technology research and development policy." Chairman Stevenson is to be commended for his efforts to ensure that legislation was not passed prematurely and for holding the hearings on recombinant DNA and related science policy issues suggested by the minority. The testimony presented at last fall's hearings provides valuable insight into the hypothetical nature of the risks and the potential benefits associated with recombinant DNA research and its applications.

The potential risks and benefits of regulation of scientific research were also explored during the subcommittee hearings. However, there is a need for further study and evaluation of the implications of regulation for all research in basic science and technology. The recombinant DNA controversy is particularly significant since policy decisions made with respect to the conduct of recombinant DNA research and technology could significantly impact other aspects of scientific research and development. For that reason, it is essential that we move cautiously and fully explore all of the implications that could result from its statutory regulation.

REGULATION

My objections to the majority report cover both the scope and impact of its regulatory recommendations. In recommending a broad
regulatory structure, the majority report ignores the broad science-policy aspects of the issue. We must address several broad science-policy questions before recommending the regulation of recombinant DNA research. For example:

—What is the impact of various regulation alternatives of science and technological development and innovation?
—What is the appropriate role of the scientific community, of the public, of the Congress, etc., in the regulation of basic scientific research?
—What are the appropriate mechanisms and forms for efficiently resolving conflicts and formulating science policies?
—To what extent should the public participate directly in the formulation of science policies, and what should be the role of the State and local governments in the formulation of such policies?
—To what degree is there a constitutional guarantee of freedom of scientific inquiry, and under what conditions may it be abridged?
—What will be the consequences of regulation on the activities of other nations and on our competitive economic position relative to them?

These and other questions relating to the social, legal, political, and ethical implications of regulating scientific research must be addressed. To that end, I have introduced a bill, S. 2267, The National Science Policy Commission Act, designed to provide a mechanism for a comprehensive, 2-year reassessment, clarification and analysis of Federal science policies regarding potentially hazardous research activities. Under the bill, a national commission would be established to study and report to the Congress with respect to its findings, conclusions, and recommendations regarding Federal science policies.

Although it may be that there are alternatives to a commission of the sort as envisioned by S. 2267, the need for some mechanism to assist the Congress in the development of broad science policies is clear. It is essential that there be broad and varied participation by representatives of all sectors of the economy in the policy formulation process. I am hopeful that the subcommittee will continue to explore these issues in the following months.

If the Congress should take the unfortunate action to regulate recombinant DNA research, such regulation at least should be flexible and interim in nature. The majority report recommends that legislation extend for at least 3 years to allow sufficient time to assess the effect of Federal standards. Research with recombinant DNA molecules is a unique field in which major scientific breakthroughs have been achieved in a relatively short period of time. Our knowledge of recombinant processes has increased many fold in the past several years. It would not be unrealistic to expect a continued growth in our understanding of the risks and benefits associated with such research as our laboratory experience grows. Unnecessarily restrictive Federal standards could seriously impinge upon our Nation’s research efforts and unfavorably alter the course of scientific progress and development. Legislation, if passed, should expire no later than 2 years from the date of enactment. Subsequent review and analysis based upon an improved understanding of the nature of the risks and the effect of Federal standards would determine if there was truly a need for any legislation.
PREEMPTION

One element of science and technology policy, and a central element of proposed recombinant DNA legislation, concerns the degree of public participation in the policymaking process. At issue is the extent to which Federal legislation should preempt State or local government action with respect to regulated activities. The majority report recommends a "partial" Federal preemption of State and local regulation which would in effect prohibit State or local governments from enacting stricter standards that the Federal Government unless "convincing reasons" are shown.

At the subcommittee hearings, the scientific community testified strongly in support of the need for Federal preemption in order to achieve uniform standards. On the other hand, it must be recognized that any form of Federal preemption represents an encroachment on the rights of State and local governments and restricts the traditional right of the public to act to protect the public health and safety. A delicate balancing process is necessary to assure that States have the right to regulate research activities conducted within their borders while at the same time avoiding an unnecessary patchwork of conflicting local regulations. It is encouraging to note that the scientific community and local governments appear to be working out satisfactory arrangements on their own once they began to communicate with each other rather than confront each other.

National decisions made with respect to recombinant DNA research activities will have implications for other areas of science and technology. For example, a similar controversy surrounds the subject of nuclear waste management and the rights of States to prohibit permanent disposal of radioactive wastes within their borders.

In any case, the step to preempt State and local action is a serious one which should not be taken without a full understanding of its implications. I am not satisfied that we possess the necessary information at the present time. There is a need for further study of the appropriate roles of the public, and State and local governments, and the effects of preemption. Whatever is ultimately decided, there must be adequate provision for public and congressional participation in science policymaking.

SECTION 361 OF THE PUBLIC HEALTH SERVICE ACT

I am extremely disturbed by the language in the majority report which suggests that extension of the NIH guidelines to the private sector could be accomplished by regulatory action under the authority of section 361 of the Public Health Service Act (PHSA, 42 U.S.C. 264). The majority report recommends that the Secretary of Health, Education, and Welfare (HEW) reconsider using the authority of the PHSA if Congress does not act on legislation. Further, the report recommends that the Federal Government rely upon the "full legal authority" in extending the guidelines, and states that the subcommittee is "not persuaded that the legal obstacles to use of section 361 of the Public Health Service Act are insuperable." While the majority concedes that it has not reached a final judgment on the legal issues relat-
ing to the use of section 361 to regulate recombinant DNA research, they nonetheless recommend that the Secretary of HEW “give the most serious consideration” to promulgating standards under section 361 if the legislative committees conclude the existing authority is adequate. The majority report also suggests that the Secretary prepare for the use of section 361.

The effect of these statements, in my view, is to give unjustified and ill-advised support to the use of section 361 to regulate recombinant DNA research in lieu of legislation. At this time, I am opposed to any language in the report that might suggest that the subcommittee considers section 361 to be appropriate for regulation of recombinant DNA research.

The majority’s recommendations regarding section 361 are somewhat surprising inasmuch as the applicability of that statutory authority to recombinant DNA research was not a subject of the hearings held by the subcommittee. The only reference to that section during the entire course of the hearings on recombinant DNA research was made by Dr. Gilbert Omenn of the Office of Science and Technology Policy. Dr. Omenn expressed the opinion that regulation by invoking a law designed to protect against contagion would amount to overkill. There is no support in the hearing record for application of section 361 of the PHSA to recombinant DNA research.

The majority apparently has been persuaded by subsequently acquired evidence that application of section 361 would be appropriate. I am not so convinced. In fact, information presently available indicates many problems associated with use of this section to control recombinant DNA research.

As the majority report acknowledges, section 361 refers only to “communicable diseases” affecting human beings. Its application to plants, animals, or the general environment is questionable at best. Clearly, section 361 was not intended by Congress to apply to basic scientific research activities such as with recombinant DNA. Support for this conclusion can be found in the report of the Federal Interagency Committee on Recombinant DNA Research and a response from the Congressional Research Service (CRS), both of which agree that “no single legal authority or combination of authorities currently exist that would clearly reach all research and other uses of recombinant DNA techniques and meet all the requirements.” (See attachment D.)

Moreover, there is some question as to the application of section 361 to activities of a purely intrastate character. The most recent court decision construing section 361 ruled that the scope of this section extends to intrastate activity where necessary to prevent the interstate spread of disease. (State of Louisiana v. Matheus, 427 F. Supp. 174 (1977)). With reference to DNA research, there is no evidence to support the position that intrastate regulation is necessary to prevent the interstate spread of communicable disease. Any hazards arising from recombinant DNA research are at this time purely speculative and highly unlikely.

The Department of HEW has stated on several occasions that it prefers legislation, and that the use of section 361 to regulate recombinant DNA activities would be both inappropriate and inade-
quate. (See attachment E.) Because of my concerns over the possible application of section 361, I wrote to the Secretary of HEW on May 4, 1978, asking for his views on the scope and nature of authority included under section 361. (See attachment F.) The Secretary's formal response has yet to be received.

In response to a similar inquiry, the Director of OSTP acknowledged that use of section 361 to regulate recombinant DNA research could create problems because (1) it acknowledges a significant risk of transmission of communicable disease, (2) it creates precedent for broad intrusions into the research environment, and (3) it does not apply to hazards to the environment that have no effect on human health. (See attachment G.)

At the very least, application of section 361 to recombinant DNA research would be subject to legal challenge. Section 361 has been employed in the past exclusively to regulate known human disease organisms, as well as known carriers of these organisms. There is no legal precedent supporting the application of section 361 to purely hypothetical risks. Given the complexity of the issue, use of section 361 is likely to generate litigation which would further cloud the status of legislative and administrative efforts.

I am also concerned about the scope of regulatory authority granted to the Secretary of HEW under section 361. On its face, it would grant to the Secretary unbridled discretion to promulgate and enforce such regulations as he deems necessary, and to take other measures necessary to carry out the regulations. There are no apparent restrictions in the law on the power of the Secretary nor are there procedural requirements that he must follow in implementing and enforcing these standards. It is my fear that by encouraging action by the Secretary of HEW to regulate a form of basic scientific research under an unusually broad grant of authority without a specific and clear mandate, we could unwittingly be initiating a dangerous regulatory precedent for all basic science and technology. It is especially unsettling that this broad discretion would be given to the Department of HEW, the largest and most bureaucratic regulatory entity in the world. Under these circumstances, I cannot agree with the conclusion implicit in the majority's recommendation that it would be preferable to avoid legislation if the Secretary can be persuaded to act under section 361.

There are numerous other deficiencies with the recommended use of section 361. Violations of section 361 would be punishable under section 368(a) of the PHSA by a fine of not more than $1,000 or by imprisonment for not more than 1 year. This is extraordinary punishment for violations of rules governing hypothetical and unproven risks. There is no sunset provision or other similar provision limiting the duration of any regulations or other action taken by the Secretary pursuant to section 361. There is no Federal preemptive authority under this section. The authority of the Secretary in relationship with other Federal laws would not be specified. It would not contain Administrative Procedure Act or National Environmental Policy Act waivers for initial promulgation of the NIH guidelines as regulations. Section 361 would not authorize the Secretary of HEW to waive regulatory requirements for activities that pose no significant risk to health or the environment. In view of all these deficiencies, the
majority’s recommendations concerning section 361 are without significant merit.

Recent events, however, suggest that increased attention will be focused on the use of section 361 in lieu of legislation. Based on presently available information, it would be unwise for this subcommittee to condone or support the use of such inadequate statutory authority, especially in such a delicate matter as the regulation of basic scientific research. If there is shown to be a need for statutory authority to ensure compliance with the NIH guidelines by the private sector, it should be accomplished by specific legislation expressing the clear intent of the Congress rather than unilateral action by the executive branch.

**SUMMARY**

I am greatly disturbed with the substance and implications of the majority’s recommendations which results in unwarranted and excessive regulation of a field of scientific research where the risks are purely theoretical, inconsistent with other knowledge, and unproven. The consensus of the testimony presented at the subcommittee hearings does not support such action.

The testimony presented at the hearings supports the position that if there is determined to be a need for immediate legislation it should be directed solely toward extending the NIH guidelines to nonfederally funded research on recombinant DNA. I generally agree with that conclusion, although I am nevertheless concerned that we might initiate unnecessary and unreasonable restrictions on the conduct of basic scientific research. Even here the guidelines are already being applied voluntarily in the private sector. Certainly there should be only those minimal requirements necessary to ensure compliance with the guidelines.

Based on my experience in the scientific community and the general level of professional responsibility demonstrated by the scientists themselves, I cannot concur with the majority’s conclusion that a system of voluntary compliance would be inadequate. I do believe that scientists must continue to insist on ethical compliance with the NIH guidelines and general principles of good research procedures.

There is a need to further examine alternatives to a harsh and unwieldy system of regulations for enforcing the guidelines. One example which appears promising is the use of patent withdrawal to enforce compliance with the guidelines. In his testimony before the subcommittee, David Newburger, assistant professor of law at Washington University, indicated that conditioning the grant of patents for discoveries resulting from research on recombinant DNA technology on a showing of compliance with the NIH guidelines would provide a substantial incentive for investigators to abide by the guidelines. Such a system would avoid the need for excessive regulatory and licensing requirements. The investigator would ultimately be held accountable for his adherence to the guidelines and a system of monitoring could be incorporated.

Uncertainties still exist with respect to the possible scope of such a system and whether it would reach all recombinant DNA research. Nevertheless, this is at least one option which deserves further examination before we set up a major regulatory structure.
ATTACHMENT A

THE DNA RESEARCH SCARE

(By Bernard D. Davis*)

Four years ago a group of molecular biologists publicly expressed grave concern over the potential dangers of research with recombinant DNA, a novel technique that allowed a small amount of DNA, the material of which genes are made, from any organism, to be incorporated into a bacterium. At their urging the National Institutes of Health issued an elaborate set of guidelines, forbidding the formation of certain kinds of recombinants and placing various restrictions on others. And last spring Congress was framing legislation carrying additional restrictions and harsh penalties.

But the NIH is now considering substantial relaxation of the guidelines, congressional committees are considering much milder legislation, and the need for any legislation is increasingly questioned. It is important to know why the dangers seem so much smaller today.

First, people for several years have been making recombinants in many laboratories, without a single resulting illness. It is clear that the predicted dangers remain entirely hypothetical.

Second, the recombinant technique is increasingly recognized as a tool of great versatility, comparable to the use of radioactively labeled molecules in studying the chemical processes in living systems. For example, recombinants make it possible to isolate human genes. Moreover, they also make it possible to study the action and the regulation of these genes in the thousandfold simpler background of a bacterial cell. And gene regulation—the selective turning on of some genes and turning off of others—is a crucial problem in modern biomedical science.

It is the key to the normal development of a fertilized egg into a human being, and also to the abnormal development of a cancer (a line of cells that have escaped from normal growth regulation). Other uses of recombinants, of more immediate medical and industrial importance, will include the manufacture of innumerable useful human products, such as insulin, other hormones, antibodies and antiviral agents. With such benefits in sight we will be paying an extravagant price if we perpetuate restrictions that are not justified by the hazards. Moreover, if this price involved only money, like the tens of millions of dollars wasted on lunar quarantine, it would be bad enough. But it also involves a greater, hidden cost: hindrance of research on diseases that are meanwhile taking human lives.

A DIFFERENT SCIENCE

Third, though the development of these novel recombinant organisms was created by specialists in molecular biology, the assessment of the possible hazard is a problem in quite a different area of science: infectious disease. Unfortunately, few professionals in this field were included in the early discussions, though they might have kept the scenarios within realistic bounds. The NIH finally assembled a world-

*Dr. Davis is Adele Lehman, professor of bacterial physiology at Harvard Medical School.
wide group of such experts last summer, and they agreed that the proposed recombinants could not be as dangerous as many known disease producing organisms, which are cultured in thousands of medical laboratories every day.

Fourth, the bacteria being used in this work are special, weakened strains, carefully developed to require nutrients that are not encountered in natural environments. Moreover, in the absence of these required compounds the cells not only fail to grow, they are rapidly suicidal: If they accidentally infected a laboratory worker they would all die within a few hours. Hence recombinants made with such strains could not conceivably spread. Moreover, experiments in the past year have shown that the chance of escape of the recombinant genes from these dying bacteria into healthy ones is infinitesimal.

"Recombinant DNA is increasingly recognized as a tool of great versatility. . . . We will be paying an extravagant price if we perpetuate restrictions that aren't justified by the hazards."

Fifth, the present guidelines consider incorporation of the DNA of a virus into bacteria especially dangerous. But to cause disease, that DNA would have to be released from the host bacterium as naked DNA, which would then have to infect a human cell. This probability is also exceedingly low, for we know that the naked DNA of a virus is less infectious than the same DNA inside the viral coat, by as much as a million-fold. Recognizing these facts, European biologists are recommending great relaxation of the guidelines for virus-bacterial recombinants—much greater than that contemplated in this country. Hence excessive restrictions may cause this country to fall behind rapidly in this important area of medical research.

My sixth point concerns the class of recombinants containing human DNA. These have particularly broad promise for medical research; but they have been classified as particularly dangerous, because of fear that they might pick up and spread the genes of human viruses. But this fear is based on the additional assumption that these recombinants would be an entirely novel class of organisms, never encountered before in nature. With further discussion this assumption has become exceedingly unlikely. We know that bacteria can take up DNA (though infrequently); and since bacteria have been growing in the colons of our ancestors for millions of years, it is virtually certain that they have often taken up human DNA, released from dying cells of the surrounding intestinal wall. Accordingly, mankind must have long been exposed to recombinants of this kind.

Finally, the initial discussions not only neglected relevant principles of infectious disease, they also failed to take into account well-established evolutionary principles, which are essential for understanding the spread of any novel organisms.

Specifically, bacteria in great variety compete for survival and multiplication on various parts of our body, on plants and in the soil. The successful strains are those that are best adapted to a given location, and to be well-adapted they must have a well-balanced set of genes.

**NATURAL SELECTION**

This adaptation, and this balance, have been evolved over billions of years, by natural selection; it is a process that moves in small steps and that perpetuates only the tiniest fraction of all the genetic novelty
that appears. Hence splicing DNA from a distant source into a bacterium is not at all likely to produce a well-balanced, competitive set of genes, any more than inserting a random radio part would be likely to improve a watch.

With these developments, the initially very cautious attitude of the scientific community has shifted dramatically. The bluntest critique has come from James Watson (who triggered the development of molecular biology by his discovery, with Francis Crick, of the structure of DNA). Though he was one of those who first voiced caution, he now urges that we abandon the whole expensive bureaucracy of guidelines and release the wasted time and money for solving real health problems. It seems almost certain that Watson will prove right. But meanwhile it also seems clear that public anxiety, generated initially by scientists, cannot be reversed until the true nature of recombinant DNA research is widely understood.

The recombinant DNA story illustrates a broader problem: how to handle public policy issues that have a large technical content. If we wish to maximize beneficial research, without jeopardizing either public welfare or public confidence, we must find ways to work out more clearly the role of the community of experts in ascertaining the facts as objectively as possible, and the subsequent role of the broader public in making value judgments and policy decisions. For while the public has a right to know, it also has a right to be protected from false alarms. A useful model may be that of the medical profession, which often has to consider alternative diagnoses in a case but also exercises discretion in avoiding premature discussion of unproved possibilities that would unduly alarm the patient. Perhaps the scientific profession and the public are groping for a similar code.

ATTACHMENT B

THE NOBELIST VS. THE FILM STAR

RESTRICTIONS ON DNA RESEARCH ATTACKED

(By J. D. Watson*)

Until the last year, I never thought much about my allegiances. My parents were for Roosevelt and against the spoilage of our land by senseless land speculators or industrial giants who put steel mills where there had been sand dunes and the prairie warbler had nested. People who went on bird trips or camped in the national forests and wanted to save Mineral King were the right sort, while those who owned big yachts or stripped the rolling fields of Ohio for coal were the bad guys whom we must get laws to stop. So it was natural to make out a modest check whenever Robert Redford or some equally fine fellow asked you to help him defend the environment and fight the polluters who would give us more cancer.

Now, however, I must confess that I didn’t respond to Robert Redford’s latest appeal. It is not that I am against him as a folk hero, but, though he must be unaware, he and I are, for practical purposes, real enemies. For some of the money he raises for the Environmental

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*Watson, director of the Cold Spring Harbor Laboratory in New York state, won a 1962 Nobel Prize in medicine for his work on the structure of DNA.
Defense Fund is being used to try to stop the experiments we do with "recombinant DNA."

This test-tube-made genetic material now provides an incredibly powerful means to find out what human genes are like. And in so doing it will give us important new ways to think, say, about our immune systems, or how our blood cells are made or the nature of the genes that go out of control when cancer arises.

This being so, I most certainly am a Friend of DNA and want work with recombinant DNA to go as fast possible. In the old days, this impulse would generally be viewed as good for the earth. Now, however, there exist highly vocal groups who think I'm a danger to the world. The Friends of the Earth, the Sierra Club and the Natural Resources Defense Council, as well as the Environmental Defense Fund, all say that our experiments pose a realistic threat to our way of life and must be constrained by their new breed of environmental lawyers.

All this initially surprised me, since I had always regarded environmentalists as among our most intelligent public groups and thought that the original rub for work with recombinant DNA which had come out of the 1975 Asilomar Conference should more than reassure them. Particularly since I found those guidelines a terrible overkill and probably not at all necessary.

My fellow DNA workers wanted, however, to act more than clean and certainly to give the impression of being responsible citizens. So they suggested that we largely work with specifically enfeebled organisms that would not live well outside our test tubes. And when, after Asilomar, the matter was taken up by the National Institutes of Health, they in turn wanted to look like the perfect guardian of our health, and so the guidelines which we now have to live with became more than tough. In fact, they effectively blocked most of the better experiments that directly relate to cancer.

As a result, the DNA community is now very unhappy working under harsh rules we do not believe necessary and which waste vast sums of sorely needed research funds. We now want to relax greatly the guidelines we imposed upon ourselves.

Unfortunately, we find this task to be much more complicated than their original drafting. Our main problem is that in our original statements about recombinant DNA, we kept referring to "potential dangers." Instead we should have said "conjectural dangers," since there was, and still is, not a trace of evidence that any of the experiments pose a threat to those who do them, much less to the general public.

In being so linguistically sloppy, we gave a long awaited opening to two groups which were out to embarrass us. The first consists of disgruntled long-out-of-productive-science biochemists, who use any opportunity to say bad things about how the effects of modern science are carried out. The other is a tiny, though noisy, group of Boston-based academic leftists who fantasize that the rich will finally sub-
jugate the masses by giving them bad genes manufactured by recombinant DNA methodologies. This is a mad idea which I suspect they are too intelligent really to believe. It must be a tactical move in their zany campaign to convince the Boston poor to rise up against the elitist imperialism of MIT and Harvard.

We never expected, however, that we would be branded as polluters by the environmental movement. For until recombinant DNA came along, we always thought we were on their side.

After all, who wants to see our planet not fit for our children to inherit? When they went to court to block DDT or keep the skies of Monument Valley blue, we could only applaud. So why now are we on opposite sides? Can we have on blinders, and can our self interest as scientists not allow us to see how indifferent we are to the harm we may do? Might, in fact, the professional environmentalists present arguments that we just can't face up to?

I feel strongly this is not the case. Compared to almost any other object which starts with the letter D, DNA is very safe indeed. Far better to worry about daggers, or dynamite, or dogs, or dieldrin, or dioxin or drunken drivers than to draw up Rube Goldberg schemes on how our laboratory-made DNA will lead to the extinction of the human race.

The strains of viruses and cells we work with in the laboratory generally are not pathogenic for man, and all we know about infectious diseases makes it unlikely that the addition of a little foreign DNA will create any danger for those who work with recombinant DNA-bearing bacteria. Even if no special guidelines existed, and we only employed the standard microbiological practices of routine sterilization, we should have no reason to be concerned for our health. Equally important, we should not worry that our experiments will profoundly alter evolution by creating bizarre life forms unlike any seen before. DNA is frequently carried from one species to another by viruses, and the global evolutionary impact of our experiments must be negligible compared to naturally occurring DNA transfers.

If this is so, how can we explain the enthusiasm with which so many professional environmentalists wish to shut us down?

The answer, I fear, is that such groups thrive on bad news, and, the more the public worries about the environment, the more likely we are to keep providing them with the funds that they need to keep their organizations growing. So if they do not watch themselves, they will always opt for the worst possible scenario.

For the short term this may give them more recruits, but I worry about the long-term effect. No one will benefit if we perceive the credibility of our environmental movements to be no better than that of the most troglodytic of our industrial firms.

If what they say about DNA is nonsense, do we have any compelling reason to listen to them when they come out against pesticides that give us shiny apples or tell us that the waters of the Mississippi are likely to give us cancer? I would like someone to set me right on such matters, but whom to trust now is not that clear.
ATTACHMENT C

Research With Recombinant DNA—National Academy of Sciences

Epidemiological and Evolutionary Aspects of Research on Recombinant DNA

(By Bernard D. Davis)

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Underlying Principles

Natural Selection

Evolutionary change arises ultimately from hereditary variation, but its direction is dominated by natural selection. It is dramatic for George Wald to state that research with recombinants is dangerous because "a living organism is forever"—but a more balanced statement would also note that only an infinitesimal fraction of the products of evolutionary experimentation survive, the rest being ruthlessly culled out by natural selection. In particular, within a species the process of sexual reproduction produces a virtually infinite variety of recombinants, among which the standard pattern of selection is a stabilizing (normalizing) one: excessive deviation from the norm make an organism less effective in the Darwinian competition. It is only when the environment is altered that certain deviants from the norm turn out to be better adapted to the new environment, and selection then becomes directional.

It should also be emphasized that all natural selection is for a balanced genome. A gene that increases or decreases a trait is selected for, not in a vacuum, but only if it is coadapted to the rest of the organism’s total set of genes.

ATTACHMENT D


Suggested Elements for Legislation

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IV. Subcommittee Review of Existing Legislation

At the November 23 meeting of the Interagency Committee, the Federal regulatory agencies also reported on their regulatory functions. Following that review, a special Subcommittee was formed to analyze the relevant statutory authorities for the possible regulation of recombinant DNA research. All regulatory agencies were represented on the Subcommittee, assisted by attorneys from their offices of general counsel. (See Appendix II for the membership of the Subcommittee.) The Subcommittee held meetings on December 13, 1976, and on January 11 and February 8, 1977.
The Subcommittee was charged to determine whether existing legislative authority would permit the regulation of all recombinant DNA research in the United States (whether or not Federally funded) and would include at least the following regulatory requirements:

1. review of such research by an institutional biohazards committee before it is undertaken,
2. compliance with physical and biological containment standards and prohibitions in the NIH Guidelines,
3. registration of such research with a national registry at the time the research is undertaken (subject to appropriate safeguards to protect proprietary interests), and
4. enforcement of the above requirements through monitoring, inspection, and sanctions.

It was the conclusion of the Subcommittee that present law could permit imposition of some of the above requirements on much recombinant DNA laboratory research, but that no single legal authority or combination of authorities currently exists that would clearly reach all research and other uses of recombinant DNA techniques and meet all the requirements. The complete Subcommittee analysis is included in Appendix III. The Subcommittee, in reaching this conclusion, reviewed the following laws that were deemed most deserving of detailed consideration:

1. the Occupational Safety and Health Act of 1970 (Public Law 91–596),
2. the Toxic Substances Control Act (Public Law 94–469),
3. the Hazardous Materials Transportation Act (Public Law 93–633),
4. Section 361 of the Public Health Service Act (42 U.S.C. Sec. 264).

The Occupational Safety and Health Act gives the Occupational Safety and Health Administration (OSHA) broad powers to require employers to provide a safe workplace for their employees. The term “employer” in the Act, however, is defined in such a way as to exclude States and their political subdivisions unless the OSHA standards are voluntarily adopted. Twenty-four States have adopted the standards, but twenty-six states are not subject to them. Further, the OSHA standards do not cover self-employed persons. For these reasons it was determined that OSHA at present could not regulate all recombinant DNA research.

The Environmental Protection Agency, under the Toxic Substances Control Act, is directed to control chemicals that may present an “unreasonable risk of injury to the health or the environment.” The Subcommittee determined that the materials used in recombinant DNA research would appear to be covered in most cases by the Act's definition of “chemical substance.” Section 5 of the Act, however, explicitly exempts registration of chemical substances used in small quantities for the purposes of scientific experimentation or analysis. This represents a most serious deficiency, as the registration of activities was thought to be an essential element of any regulatory effort. Also, in order to meet the specifications of the Act, recombinant DNA
research would have to be found to present "an unreasonable risk of injury to health or the environment."

The Hazardous Materials Transportation Act (HMTA) and Section 361 of the Public Health Service (PHS) Act give the Department of Transportation (DOT) and the Center for Disease Control (CDC), respectively, authority to regulate the shipment of hazardous materials in interstate commerce. Both the DOT and the CDC, in implementing these acts with respect to biological products, have essentially aimed at imposing labeling, packaging, and shipping requirements, and were found to be wanting for regulation of all recombinant DNA research.

The Environmental Defense Fund, in November 1976, petitioned the DHEW to regulate recombinant DNA research under Section 361 of the PHS Act. (The petition is included in Appendix IV.) The Subcommittee carefully reviewed this section, which is directed to organisms that are communicable and cause human disease. Thus, under this section, there would have to be a reasonable basis for concluding that the products of all recombinant DNA research may cause human disease and are communicable. Further, Section 361 does not apply to plants, animals, or the general environment. It was the conclusion of the Subcommittee that Section 361 lacked the requisite authority to meet all of the requirements set for the regulation of this research.

The Subcommittee also considered the authority of the CDC to license and control the operation of clinical laboratories under Section 353 of the PHS Act, but this provision was not considered to be applicable to research laboratories.

Other authorities of EPA under the Clean Air Act, the Federal Water Pollution Control Act, and the Resource Conservation and Recovery Act of 1976 were considered briefly and thought only to apply, if at all, to isolated aspects of recombinant DNA research. The authorities of the Food and Drug Administration (FDA) were also reviewed, but it was concluded that recombinant DNA research has not yet reached the stage of commercial application that comes under the FDA's jurisdiction. The regulatory powers of the U.S. Department of Agriculture (USDA) were also reviewed and found applicable solely to nonhuman animals and plants.

In summary, the group concluded that no single legal authority, or combination of authorities, currently exists which would clearly reach all recombinant DNA research in a manner deemed necessary by the Committee. Although there is existing authority that might be broadly interpreted to cover most of the research at issue, it was generally agreed that regulatory actions taken on the basis of any such interpretation would probably be subject to legal challenge.

After completing an analysis of existing legislation, the Subcommittee on February 8, 1977, considered elements which might be included in legislation to regulate recombinant DNA research. The Subcommittee referred the analysis of existing legislation and elements for new legislation to the full Committee at a meeting held on February 25, 1977. The full Committee adopted the report of the Subcommittee on existing legislation and agreed that new legislation was required.
To: Hon. Harrison H. Schmitt.
From: American Law Division.
Subject: Questions concerning the applicability of section 361 of the Public Health Service Act to recombinant DNA research.

The following memorandum has been prepared in response to your several questions regarding HEW’s regulatory authority under Section 361 of the Public Health Service Act (42 U.S.C. § 264). Specifically, you have requested our opinion as to the regulatory scope of Section 361 and its applicability to public and private recombinant DNA research.

Initially, we must agree, based on our own extensive research, with the Federal Interagency Committee on Recombinant DNA Research that “no single legal authority or combination of authorities currently exist that would clearly reach all research and other uses of recombinant DNA techniques and meet all the requirements.” In a paper we prepared last December, we came to the same conclusion:

In brief, comprehensive regulation of the products resulting from recombinant DNA research techniques does not appear feasible under current laws. At best, regulation will be piecemeal and dependent on the uses for which those products are intended. Regulation will be dispersed throughout several federal agencies, where the research activities involved come under the respective department or agency mandate and it will be limited by the purposes enumerated in the appropriate authorizing legislation.

Several of your questions deal with Section 361 (42 U.S.C. § 264). While it can certainly be argued that section 361 does authorize the Secretary of HEW to promulgate regulations to protect the public from the introduction or spread of any suspect communicable disease, thus authorizing the regulation of recombinant DNA research, it is a highly disputed interpretation of the section. The section, on its face, refers to the prevention of the spread, etc, of communicable diseases. Admittedly the language of Section 361(a) is rather broad. However, specific statutory limitations in subsections (b), (c) and (d) to “diseases as may be specified” and to the control of interstate and foreign travel of infected persons, suggest that control of private intrastate research to assure protection of the public and environment from unknown dangers and unspecified diseases may well be outside the scope of the section. It can hardly be argued that Congress intended, when the original quarantine law was enacted, or superceded, that this regulatory authority extended to research which is just now becoming feasible. While there is no doubt that Congress intended the appropriate federal authorities to have broad and flexible powers (i.e. “the use of conventional public-health enforcement methods”) to prevent the spread of dangerous and destructive disease, it surely did not mean that scientific research was to be pervasively regulated.

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1 Originally enacted in 1879 (Act of Mar. 3, 1879), superseded in 1893 (27 Stat. 449), and in 1944 (58 Stat. 703.).

2 This language is from the House report accompanying the 1944 amendments.
There are few decisions of the courts in which these public health provisions have been construed. But those cases that have considered the scope of section 361 do not provide convincing authority for the belief that the Secretary's powers under that section are as broad as they must be to accomplish pervasive regulation of recombinant DNA research. The most recent case to construe section 361 was decided last year by the federal district court in the eastern district of Louisiana, *Louisiana v. Mathews*, 427 F.Supp. 174 (1977). The Secretary of HEW had banned the interstate and intrastate sale of all small turtles because of the danger that the turtles were or *might be* infected with two known communicable diseases. In that case, the court reasoned because the chances of contamination or re-contamination of turtles were so high (54 percent or greater), that "a total ban is permissible as necessary to prevent the spread of communicable disease." The alternative, the court noted, was to adopt a "patently unreasonable" and "onerous testing scheme." While an intrastate ban was deemed necessary, and the court sanctioned regulation to prevent the possibility of spread, etc. of disease, it is significant that well-known and widespread communicable disease already specified in the federal regulations were involved. Thus, the Secretary's regulatory authority will, in some cases, extend to intrastate regulation of potential disease, but the case does not support the conclusion that this is true in all circumstances, particularly those involving unspecified and as yet non-existent "diseases." We found no case supportive of the position that hypothetical dangers and diseases are within the scope of section 361.

On the other hand, presented with a case involving grave danger and the possible spread of recombinant DNA generated disease, the courts may choose to give section 361 and even more expansive interpretation that was applied in *Louisiana v. Mathews*. It should be considered however, that the courts have not yet dealt with this and litigation would inevitably result from extension of section 361 to recombinant DNA research. We have reviewed the letter of January 6, 1978 from Peter Barton Hutt to Gilbera S. Omenn and we recognize that his argument is persuasive. But we cannot, with assurance conclude that the Secretary's regulatory authority under section 361 is as broad as Mr. Hutt suggests. In the event that new legislation to provide authority for DNA regulation is deemed inadvisable at this time, we do agree that the Public Health Service Act may currently be the most effective means to regulate the conduct of recombinant DNA research.

Additionally you have asked for legal precedent supportive of the use of section 361 to regulate nonbacterial or nonviral research. The Drinking Water Standards, set out at 42 C.F.R. § 72.20, define pollution to mean the presence of "any foreign substance" including "organic, inorganic, radiological, or biological" products that may "constitute a hazard or impair the usefulness of the water." Currently however, these standards are the only ones promulgated under the Public Health Service Act which extend beyond bacterial, fungal, or viral, rickettsial and chlamydial etiologic agents. See. 42 C.F.R. § 72.25 (a) (c). We are aware of no court case that has dealt with the further extension of these regulations to agents other than vireable organisms and their toxins.
As to the Secretary's preemptive authority under section 361, "the purpose of Congress is the ultimate touchstone," Retail Clerks v. Schermerhorn, 375 U.S. 96, 103 (1963). An early Supreme Court case which upheld a state's quarantine laws (alleged to be in conflict with federal law), stated that "quarantine laws belong to that class of state legislation which is valid until displaced by Congress, and that such legislation has been expressly recognized by the laws of the United States almost from the beginning of government." Compagnie Francaise v. Louisianan Board of Health, 186 U.S. 380, 389 (1902); Louisiana v. Texas, 176 U.S. 1, 21 (1899). In enacting the federal quarantine laws (subsequently superseded by section 361), the Congress apparently did not express a specific intent to preempt state laws on the subject. The Supreme Court has stated that "we start with the assumption that the historic police powers of the States were not to be superseded by the Federal Act unless that was the clear and manifest purpose of Congress." Rice v. Santa Fe Elevator Corp., 331 U.S. 218, 230 (1947); Jones v. Rath Packing Co., 430 U.S. 519, 525 (1977). The most recent Supreme Court decision concerning federal preemptive capacity set out the general principles:

Often Congress does not clearly state in its legislation whether it intends to pre-empt state laws; and in such instances, the courts normally sustain local regulation on the same subject matter unless it conflicts with federal law or would frustrate the federal scheme, or unless the courts discern from the totality of the circumstances that Congress sought to occupy the field to the exclusion of the States. Malone v. White Motor Co., No. 76-1184 (April 3, 1978), slip opinion at 6.

Absent expressed congressional intent, it is probable that Section 361 does not give the Secretary of HEW authority to preempt state laws. Additional legislation is needed to accomplish that purpose.

In response to your additional questions regarding the Secretary's authority to license and inspect facilities, to extend guidelines to non-federally funded research, etc., we can not provide clear cut answers. Needless to say, all the powers you mention in your letter would significantly expand HEW's role in public health regulation from what it has been. Under Section 361(a) the Secretary has the power "to make and enforce such regulations as in his judgment are necessary" to fulfill the section's purpose. But again, for the reasons we have discussed throughout this paper, we can not say that all DNA activity will be subject to the Secretary's control. For the research that is, little question exists that the Secretary has the power to inspect and license facilities if it is in fact necessary and the constitutional and statutory rights of involved individuals are respected. As for intrastate regulation absent federal funding, there must be a clear relationship of the intrastate activity to some aspect of interstate commerce to justify federal regulation. If that nexus is established then the intrastate activity is subject to federal regulation as is necessary to accomplish the statutory purpose. See, Louisiana v. Mathews. Again, however, non-federally funded, wholly intrastate activity bearing no relationship to interstate commerce is not within the regulatory ambit of section 361.
Violations of section 361 are presently punishable under section 368 (a) of the Act which provides that any person who violates section 361, etc., "shall be punished by a fine of not more than $1,000 or by imprisonment for not more than one year, or both." Presently, injunctive relief for violations of section 361 is not specifically authorized under the Public Health Service Act.

Because of the constraints of time we are not able to provide a detailed comparison of the Secretary's authority under Senate Amendment 1713 and H.R. 11192 with the potential scope of his authority under section 361. It is obvious though, that under the pending legislation the Secretary's authority is subject to less dispute and clearly is more encompassing than it would be under section 361. The procedures for inspections are set out by Congress in the pending legislation. Should section 361 be used for regulation then HEW must develop its own procedures. Preemption will be accomplished under the pending legislation whereas preemptive capacity under section 361 is unlikely to exist. Injunctive authority is also clearly provided for in the pending legislation. Furthermore, the provision in the pending legislation for a study of DNA research and its applications could be useful in providing guidelines for future regulation of such a new and unprecedented area.

We hope that this information will be helpful. If you need additional information or analysis please feel free to call on us.

DONNA C. PARRATT,
Legislative Attorney.

The Library of Congress,
Congressional Research Service,

From: American Law Division.
Subject: Appraisal of correspondence concerning scope of authority
Under the Public Health Service Act.

As you requested as a follow up to our memorandum of May 12 regarding the use of section 361 of the Public Health Service Act to regulate recombinant DNA research, we have more carefully reviewed Mr. Peter Barton Hutt's letter of January 6 to Dr. Gilbert S. Omenn. We expressed the belief in our previous memorandum that although Mr. Hutt's arguments appear to have some force, we could not reach the very broad and general conclusions he did based on our interpretations of existing statutory and case law. You have asked us to elaborate on that position by addressing several particular conclusions expressed by Mr. Hutt in his letter.

First, you have asked us to analyze Mr. Hutt's position about the application of Section 361 to intrastate commerce. Mr. Hutt states on page three that this issue has been "definitively resolved by [State of Louisiana v. Mathews] upholding the legality of an FDA regulation banning all small pet turtles from both intrastate and interstate commerce under the sole authority of Section 361." In the last paragraph on page four, he further states that the court in Louisiana "ruled that section 361 permits FDA to control intrastate as well as interstate activity."
However, *Louisiana* did not hold that section 361 permits FDA to control intrastate activity in *all* circumstances. The court clearly explained that the intrastate ban was justified only because it was necessary to prevent the interstate spread of disease. As the court explained, the FDA regulation was due to the "particular facts and circumstances underlying the ban on turtles" which are not present in all cases.¹

With reference to DNA research, there is no evidence to support the position that intrastate regulation is necessary to prevent the interstate spread of communicable disease. Any hazards arising from recombinant DNA research are at this point in time purely speculative. Mr. J. D. Watson, an eminent authority on DNA, recently wrote:

[I]n our original statements about recombinant DNA, we kept referring to "potential dangers." Instead, we should have said "conjectural dangers," since there was, and still is, not a trace of evidence that any of the experiments pose a threat to those who do them, much less to the general public.

The strains of viruses and cells we work with in the laboratory generally are not pathogenic for men, and all we know about infectious diseases makes it unlikely that the addition of a little foreign DNA will create any danger for those who work with recombinant DNA-bearing bacteria. Even if no special guidelines existed, and we only employed standard microbiological practices of routine sterilization, we should have no reason to be concerned for our health.²

Therefore, while we agree with Mr. Hutt that intrastate commerce certainly may be regulated to prevent the spread of communicable disease, we cannot agree that all DNA research poses such a substantial threat of disease that all intrastate DNA activity can be reached under the Public Health Service Act. Mr. Hutt's position is based on an assumption that the "very nature of the controversy itself is sufficient . . . to establish the potential for harm that is required under Section 361. If that potential were agreed not to exist, the entire issue of regulatory control over this research would never have been raised in the first place." Needless to say, his position is not universally held.

Other considerations as well suggest that section 361 might not be interpreted to apply, across the board, to all recombinant DNA research. We briefly commend in our previous memorandum that the legislative intent behind the Public Health Service Act can hardly be said to comprehend recombinant DNA research even though the regulatory authority intended under the Act is broad. Because of the unique nature of recombinant DNA research, arguments can be made that absent express legislative intent the Public Health Service Act should not be utilized to regulate DNA work. It has been argued that recombinant DNA research, especially when conducted in an academic setting, involves First Amendment freedoms of speech. This has been urged by several constitutional law scholars as well as concerned and involved scientists. The nation's highest court has expressed in sev-

¹ See, e.g. 42 C.F.R. 72.21; 72.22.
eral cases a strong commitment to the principles of academic and intellectual inquiry and a presumption against governmental interference. In testimony last May before the House Subcommittee on Science, Research and Technology, Professor Thomas I. Emerson of Yale Law School expressed his belief that at least some aspects of recombinant DNA work must be characterized as deserving of First Amendment protections:

The first question . . . is whether the conduct involved in DNA research constitutes "expression" or "action." It seems to me that the development or exposition of theoretical ideas about DNA and other genetic materials and processes is clearly expression. Such conduct involves the search for truth in its primal form. The fact that the researcher works physically with complicated equipment does not deprive the conduct of its character as expression. In similar fashion a telescope is used to study the stars, an accelerator to study nuclear particles, a public address system to carry on a public meeting, and a xerox machine to make copies for distribution.

The more difficult question is the classification of experimentation. Experimentation is a vital feature on the development of new information, ideas, and theories. This is particularly so in the physical sciences. One must conclude that it is often an integral part of scientific research, that is, a part of the system of freedom of expression. Analogous conduct is the marching in a demonstration, the publication of a newspaper, and the organization of a political party. Although all such conduct involves more than sheer thinking or verbalization, nevertheless it is an essential feature of a system of free expression.

On the other hand, at some point experimentation clearly moves into the realm of action. Just as political assassination has an element of expression but is basically action, so an experiment to rest a theory of nuclear energy which might blow up a city, or contaminate the atmosphere of the whole world, is also predominantly action. The line has to be drawn on the basis of all the facts in a particular case and—in light of the proper function of a system of freedom of expression in a democratic society.

On the basis of present information available to me it is difficult to state more specifically what forms of experimentation should be classified as expression, and what as action. It does seem clear, however, that experiments which pose a serious threat to the physical health or safety of a community, must be classified as action. Such conduct is analogous to the use of violence against persons or property in a demonstration, or the throwing of rocks through the windows of the White House. The physical element of the conduct is the paramount concern, and the conduct therefore falls into the realm of action rather than the expression of ideas.

On this analysis, the broad search for information about DNA, the formulation of hypotheses, the exposition and discussion of theories and methods would constitute expression,
and be fully protected under the First Amendment. Thus the government could not prohibit, regulate or discourage in any way DNA research on the ground that mankind ought not to be pursuing ideas about ways to develop new forms of life. On the other hand experiments that presented a substantial and serious danger to the physical health and safety of the surrounding population could be subject to regulation without infringing the guarantees of the First Amendment. Only the requirements of due process, equal protection and other constitutional provisions would be applicable to such regulation. [Emphasis added.]

We are thus confronted with the additional problem that the proposed regulation may result in stifling the freedom of scientific inquiry. Using the framework developed by a noted constitutional law scholar at Harvard, Laurence H. Tribe, government regulation of DNA research might be described as being “aimed at noncommunicative impact but nonetheless having adverse effects on communicative opportunity.”

Government action in a case of this sort requires the balancing of competing interests. According to Mr. Tribe, “regulatory choices aimed at harm not caused by ideas or information as such are acceptable so long as they do not unduly constrict the flow of information and ideas.”

Presented with this difficulty should DNA research be characterized as having constitutional implications, the courts may be unwilling to uphold the use of section 361 for a purpose not clearly intended when the law was enacted.

Although there is little legal authority related to this problem, a recent case involving the Federal Communication Commission’s regulatory authority over cable television suggests that agency jurisdiction, even when its mandate is broad, is not without limits. Home Box Office, Inc., v. FCC., 567 F.2d 9 (C.A.D.C. 1977). In that case, the court was faced with F.C.C. regulation of cable television under the Communications Act of 1934. No provision in that Act authorized such regulation. The court cited Supreme Court precedent sanctioning the regulation of cable television “but only where the ends to be achieved were ‘long established’ in the field of broadcast television or were ‘congressionally approved’” Id., at 13 (citations omitted). This concern was of particular importance because of the First Amendment implications involved in regulation of the media. In an even more recent case, the Eighth Circuit also struck down F.C.C. regulation of cable television. Midwest Video Corp. v. F.C.C., 571 F.2d 1025 (8th Cir., 1978). The court expressed grave concern with governmental intrusion in areas affecting the exercise of Constitutional rights:

Though we find it unnecessary to resolve the serious constitutional issues raised, we do hold that where, as here, potential incursions into sensitive constitutional rights are involved, careful scrutiny is required in delineating the scope of authority Congress intended the agency to exercise. Id., at 1052 [Emphasis added.]


4 Id., at 581-582.
In Home Box Office, the court emphasized that the F.C.C.'s authority goes "no farther than to allow the Commission to regulate to achieve 'long established' goals or to protect its 'ultimate purposes.'" Id., at 28. In striking down some of the regulations, the court relied in part on a Supreme Court case involving a Civil Service Regulation barring resident aliens from employment in the federal competitive civil service. Hampton v. Mow Sun Wong, 426 U.S. 88 (1976).

In Mow Sun Wong, the Supreme Court emphasized that it was dealing with "a federal rule having nationwide impact." Id., at 100. The Court also acknowledged that federal power over aliens (like the interstate commerce power) is plenary. Id., at 101. But, the Court was concerned that at stake were liberty rights of these lawfully admitted individuals and that the decision to bar them from federal employment had been made at an agency level, rather than by Congress. Because constitutional interests were involved, despite the fact that the federal power is so plenary, the Court held that the Civil Service Commission regulation was unconstitutional. "The decision to impose that deprivation of an important liberty," the Court wrote, "must be made at a comparable level of government or, if it is to be permitted to be made by the Civil Service Commission, that it be justified by reasons which are properly the concern of that agency." Id., at 116. The Court found that "the Commission performs a limited and specific function"—"promotion of an efficient federal service." Id., at 114.

A comparison might be drawn between these cases and the suggested use of the Public Health Service Act to regulate recombinant DNA research. The purpose, as stated, of the Public Health Service Act is to prevent the spread of communicable disease. If constitutional rights are present, as many have argued, and the dangers from the research at this point are remote and purely speculative, then it may be argued that Congress should, if it finds it necessary, enact specific legislation with the clear purpose of protecting the environment from strains of viruses and cells that many scientists claim "generally are not pathogenic to man." See, infra, p. 2.

We are not raising these points to say that section 361 can not or even should not be used to regulate DNA work, but, we are saying that given the complexity of the problem, use of section 361 is sure to generate time-consuming and costly litigation, the outcome of which is unpredictable. The nature of the proposed regulatory scheme is such that we cannot conclude that the scope of section 361 is, without doubt, sufficiently broad to support pervasive regulation of all DNA research.

You have also asked for clarification of Mr. Hutt's statement on page seven concerning judicial review of administrative action. He states that HEW has "broad discretion ... to determine when the scientific evidence warrants reliance on Section 361 to prevent the possibility of communicable disease. Absent evidence that the HEW decision is wholly irrational, it is highly likely that the courts would uphold this exercise of discretion." [Emphasis added.] The applicable standard for judicial review of administrative agency action is found in the Administration Procedure Act, 5 U.S.C. 706. The scope of review is not whether agency action is "wholly irrational," but rather whether the agency action is: "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law: contrary to constitu-
tional right, power, privilege, or immunity; in excess of statutory jurisdiction, authority, or limitations, or short of statutory right; or without observance of procedure required by law." See, e.g., *Louisiana v. Mathews* for an example of application of this standard. Clearly these standards are much different from a test to determine whether agency action is "wholly irrational."

Finally, you have asked for legal precedent which supports the following statement from page eight of Mr. Hutt's letter: "All that is needed to support regulations under this provision is either apprehension or uncertainty about the possibility of potential harm, the lack of adequate information showing that the harm cannot occur, and the possibility that the harm would be serious (e.g., irreversible) if did occur." That standard is not found in the statute or in the regulations promulgated under it. Nor has any court, to our knowledge, applied such broad language. Certainly more is needed than merely "the lack of adequate information showing that the harm cannot occur" to justify intrusive government regulation.

Again, we hope this is responsive to the questions you have asked. If we can be of further assistance, please feel free to call on us.

**Donna C. Parratt,**
**Legislative Attorney.**

**ATTACHMENT E**

**The Under Secretary of Health, Education, and Welfare,**

**Hon. Harrison A. Williams, Jr.,**
Chairman, Committee on Human Resources,
U.S. Senate, Washington, D.C.

**Dear Pete:** I understand the Human Resources Committee will discuss possible action regarding DNA legislation in a markup session on Thursday, May 4.

I am enclosing a letter from the Secretary to Senator Stevenson and Dr. Fredrickson's testimony before the House Science and Technology Committee which express our strong support for passage of legislation similar to H.R. 11192. We do not believe Section 361 represents appropriate authority to achieve uniform regulation of DNA activities. In view of imminent House passage of H.R. 11192, we would urge the Human Resources Committee to consider passage of comparable legislation.

Sincerely yours,

**Hale Champion,**
Under Secretary.

**The Secretary of Health, Education, and Welfare,**

**Hon. Adlai E. Stevenson,**
Chairman, Subcommittee on Science, Technology, and Space Committee on Commerce, Science, and Transportation, U.S. Senate,
Washington, D.C.

**Dear Adlai:** This is in response to your letter of November 30, 1977, regarding our current and proposed authorities related to the control
of recombinant DNA research and related activities. Responses to questions directed to the Food and Drug Administration are also included in this letter.

1. Section 361 of the Public Health Service Act

Section 361 authorizes the Secretary of HEW to take action to prevent the introduction, transmission, and spread of communicable diseases from foreign countries and from State to State. The Interagency Committee on Recombinant DNA Research examined existing laws, including section 361, to determine if they provided adequate authority to regulate all recombinant DNA activities. The Committee concluded that new and specific legislation was needed.

The Committee’s report (a copy of which is enclosed) released March 15, 1977, contains the following conclusion concerning section 361:

“Section 361 could perhaps be interpreted more broadly to serve as legal support for more comprehensive regulation. However, in order to do so there would presumably have to be a reasonable basis for concluding that the products of all recombinant DNA research cause or may cause human disease. Such a conclusion would undoubtedly be tenuous at best, and it is unlikely that resulting requirements could be effectively imposed and enforced.”

On November 11, 1976, the Environmental Defense Fund and the Natural Resources Defense Council filed a petition with the Secretary of HEW asking him to impose regulations on all recombinant DNA activities, citing section 361 as authority (see Appendix IV of the Interagency Report). As explained in their petition (see pp. 57–59), they argued that the definition of communicable disease under section 361 can be read to include all recombinant DNA activities.

The Department has used section 361 to regulate a number of products which affect human health, including shellfish, pet turtles, primates, milk, drinking water, and human blood. Our Office of the General Counsel, however, believes it is preferable for a regulatory effort of the magnitude required to oversee all recombinant DNA activities, whether or not known to affect human health, to be based on the explicit support of the Congress as well as that of the Administration, particularly in light of the active interest the Congress has shown in this area. The consensus needed for this type of program is not best established by applying a general provision of law to this specific situation.

2. Other HEW Authorities

The Food and Drug Administration (FDA) is responsible for assuring that human drugs, biologics, medical devices, foods, cosmetics, and animal drugs, are safe, effective, and are produced in conformity with good manufacturing practices. For all new drugs, new animal drugs, biologics, food additives and color additives, and medical devices, the sponsor or manufacturer has the burden of demonstrating the safety and efficacy of product proposed for marketing. The Federal Food, Drug, and Cosmetic Act requires manufacturers of such products to submit safety and efficacy data supporting their petitions to FDA for review and approval before the product is introduced into interstate commerce.

The FDA has responsibility to safeguard the public from all potential hazards that may result from the development of products that are
subject to the Agency’s jurisdiction. This authority would extend to research on regulated products where recombinant DNA is involved. The Agency could, under existing authority, require any firm seeking approval of a product which may be the end product of recombinant DNA research to certify to the Agency that it has complied with the National Institutes of Health (NIH) Guidelines on recombinant DNA. For example, certification could be required for biologics, requests for certification could be required in petitions, such as new drug applications, license applications for biologics, requests for certification of antibiotics, and notices of claimed investigational exemption of a new drug. In addition, FDA under its investigational authorities may inspect firms making such certification to assure that they do, in fact, comply with the NIH guidelines. The Agency does have a number of regulatory sanctions it could bring to bear on any firm not in compliance with the Guidelines. These range from a denial of the petition to court actions.

3. Preemption of Federal Statutes

The Interagency Committee recommended in its report that HEW be the locus for the regulation of recombinant DNA activities. This is a sound suggestion, since a lead agency is essential to avoid duplication and to ensure uniform implementation of any DNA legislation. The Administration’s bill provides that the proposed authority would “not affect the authority of any Federal agency to regulate under any other Act activities involving recombinant DNA.” However, because the primary basis for controlling recombinant DNA activities is based on the potential threat to public health, other agencies should consult with HEW when those regulatory activities involve DNA.

The Department continues to support legislation to promote regulation of recombinant DNA activities as submitted to the Congress by this Department. We appreciate the contribution you and your Subcommittee have made to rational decisionmaking in this sensitive policy area. If we may assist in any way in your continuing work in this area please call on us.

Sincerely,

JOSEPH A. CALIFANO, JR.

ROUND ANOTHER HELIX IN THE LEGISLATIVE HELTER-SKELTER

The latest twist in Congress’ current attempts to draw up a recombinant DNA bill is a move which means that there may be no bill at all. According to his staff aides, Senator Edward Kennedy has now decided that no bill is necessary, a sentiment which is the polar opposite of his position last year but identical to that of the year before.

No one is predicting where Kennedy, or at least his staff aides, will be next week; but on present showing there may perhaps—but not definitely—be no Senate action this session and therefore no legislation at all.

The prospect is welcomed by scientists who oppose government regulation of research in principle, but is causing concern to those who hoped through legislation to preempt state and local authorities from

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1 Science magazine vol. 200, May 19, 1978.
writing rules more restrictive than the existing National Institutes of Health guidelines.

Meanwhile at a meeting last month the NIH committee that wrote the guidelines approved several important changes, including a proposal to delegate authority for initial approval of recombinant DNA experiments from the NIH to institutional committees. Experiments would still be reviewed by NIH, but could begin as soon as local approval was obtained, cutting bureaucratic delay by some 3 to 4 months.

The NIH committee also proposed reducing experiments with viruses to much lower containment levels.

If Congress fails to pass a bill, the Administration will then have to choose between continuing the present approach of voluntary adherence to the NIH guidelines, and invoking existing legal authority to give the guidelines the force of legislation. Each choice has its own advantages and difficulties.

It is far too early, however, to rule out the possibility of a Senate bill. The latest move by Kennedy’s staff aides is not as inconsistent as it may seem. Although it is ascribed by aides to a change in Kennedy’s perception of the hazards over the last 10 months, Kennedy has always seemed to be less interested in the possible risks of the research than in the principle of allowing the public and local authorities a voice in decisions about research. The bill pending in the House, which also has strong general support from certain senators, would preempt that role. Probably not having the votes to defeat preemption in the Senate, Kennedy’s staff may hope to obtain the same end by inaction.

Those who favor preemption, such as the NIH and the American Society of Microbiologists, may therefore press for a Senate bill to be passed. Other interested parties, such as Senator Adlai Stevenson, may also favor a Senate bill if the Administration declines to use existing powers.

Where matters now stand is that, at a meeting of staff aides of the Senate human resources committee on 1 May, it was decided that Kennedy would write to HEW Secretary Joseph Califano to the effect that legislation seemed unnecessary if the Administration were prepared to use already existing powers.

Califano’s response is hard to predict because the thought of no legislation at all is too new for people to have decided what they would like to do instead. Nor is the Administration all of one mind.

The NIH favors strong preemption, believing that a law without preemption would be the worst of both worlds. For this, among other reasons, the agency is lukewarm toward invoking existing authorities, such as Section 361 of the Public Health Service Act, which gives the Secretary of HEW sweeping powers to control communicable diseases but not to preempt state governments.

Other parts of the Administration, however, such as the White House staff, are not so hot for preemption and could live with Section 361. As the result of an internal compromise, NIH director Donald Frederickson recently testified in support of a weaker form of preemption than that stipulated in the House bill.

“It is our judgment that many aspects we desire could be achieved under Section 361,” says Gilbert Omenn, a staff member of the President’s science adviser’s office. But he also notes that voluntary compliance has worked well.
Kennedy's letter to Califano will probably ask, among other things, if Section 361 is an appropriate vehicle for regulating recombinant DNA. "Our response will be that simple legislation is required, and that 361 is not an appropriate statute," says an NIH official. In the NIH view, the section does not explicitly offer preemption (although some legal opinion holds that it would do so in practice), use of the statute might imply that recombinant DNA could give rise to communicable disease, and in any case Congress should carefully frame a special new law if it wishes to take the step of regulating biological research.

The problem of how to govern recombinant DNA research is as far from certain solution as ever. But the present range of likely outcomes is generally much less restrictive than those prevailing last year.—N.W.

ATTACHMENT F

U.S. Senate,
Committee on Commerce, Science, and Transportation,

Dear Mr. Secretary: As you are undoubtedly aware, Congress is currently considering legislation which would regulate recombinant DNA research and its applications. The use of recombinant techniques to modify the fundamental genetic material offers great promise for all of mankind through improved understanding of biological processes, and varied applications in such fields as medicine, production of enzymes for industry, and agriculture.

Nevertheless, as with any new field of scientific research, it is impossible at this stage to say with absolute certainty that there is no hazard attendant to such research. To date, there have been no illnesses or other harm associated with recombinant DNA research. There have been recombinant processes occurring in nature since life began, and nature has built-in defenses against aberrant DNA strains. However, we cannot ignore the theoretical risks and the necessity to protect the health and safety of the public and the environment until further evidence is accumulated.

The implications for all of science and technology from the regulation of scientific research dictate that we move cautiously and fully explore all of the alternatives and ramifications before embarking on a course of regulation. The Senate Science, Technology, and Space Subcommittee, of which I am the ranking member, held three days of hearings during November, 1977, to consider the major policy issues associated with recombinant DNA research. The general thrust of the testimony from the more than 20 witnesses was that if there is determined to be a need for legislation it should be directed toward extending the National Institutes of Health (NIH) guidelines to non-Federal funded research on recombinant DNA. I generally agree with that conclusion, although I am concerned that we might initiate unnecessary and unreasonable restrictions on the conduct of basic scientific research.

Both the House and the Senate have bills pending which would extend the NIH guidelines to the private sector and assign responsibility
to the Secretary of HEW to promulgate administrative and enforce-
ment regulations. Despite attempts to accommodate all interested
parties, the proposed legislation has been criticized by both environ-
mental groups and members of the scientific community. As the debate
continues over the most appropriate means of extending the NIH
guidelines, one must consider all options which might be effective.

In that regard, considerable attention has been focused recently on
the application of Section 361 of the Public Health Service Act (42
U.S.C. § 264) to recombinant DNA research in lieu of legislation.
Under this Section the Secretary of HEW is authorized to “make and
enforce such regulations as in his judgment are necessary to prevent
the introduction, transmission, or spread of communicable diseases…”.
It has been suggested that Section 361 provides adequate statutory
authority to extend the NIH guidelines to the private sector and to
promulgate such regulations as are deemed necessary to ensure com-
pliance with the guidelines. However, uncertainty remains as to the
scope of coverage of Section 361 and its applicability to situations
where DNA research represents a potential threat to plants, animals,
and the environment. Until we fully understand the implications of
relying on Section 361, it would be imprudent to recommend its ap-
lication to recombinant DNA research.

In order to assist the Congress in its deliberations over this most
difficult issue, I would appreciate your response to the following:

—What is your analysis of the provisions of the two principal bills
(H.R. 11192 and Senator Kennedy’s Amendment No. 1713 to
S. 1217) pending before Congress which would regulate recom-
binant DNA research?

—If Senate Amendment No. 1713 as presently drafted were enacted
into law, what specific steps would you take to implement the
requirements of that legislation?

—the Federal Interagency Committee on Recombinant DNA Re-
search concluded that “no single legal authority or combination
of authorities currently exist that would clearly reach all research
and other uses of recombinant DNA techniques and meet all the
requirements.” Do you agree with that conclusion?

—Do you feel Section 361 contains adequate statutory authority to
implement enforcement of the NIH guidelines to the private
sector?

—What problems, if any, do you see arising from the use of Section
361 to regulate recombinant DNA research?

—If directed to regulate recombinant DNA research pursuant to
Section 361, what specific regulatory action would you take to
ensure private sector compliance with the guidelines?

—What legal precedent supports the application of Section 361 to
recombinant DNA research or other forms of nonbacterial or
nonviral research?

—What legal precedent would indicate that Section 361 is not
appropriate for regulation of recombinant DNA research?

—What action, if any, do you plan to take if it becomes clear that
Congress will not pass legislation this session extending the NIH
guidelines to the private sector?

—Although the authority of the Secretary to regulate recombinant
DNA activities is outlined in both the House and Senate bills,
I am unclear as to the specific regulatory authority of the Secretary under Section 361. Please provide a comprehensive analysis of the Secretary’s total authority under Section 361 to regulate recombinant DNA research and related activities, including but not limited to the following items:

a. extension of the NIH guidelines to non-Federally funded research;
b. authority to license facilities;
c. authority to inspect facilities;
d. authority to promulgate regulations for administration and enforcement of the guidelines;
e. sanctioning authority with respect to civil penalties, injunctive authority, and criminal penalties;
f. role of local biohazard committees.

— Please compare the authority of the Secretary regarding recombinant DNA research and related activities under Section 361 with the authority of the Secretary under Senate Amendment 1713 and H.R. 11192.

— Does the Secretary have authority under Section 361 to preempt State and local actions concerning recombinant DNA research and related activities?

To assure that the Senate is informed on these very important issues prior to consideration of the pending legislation, I would request that you respond to this letter by May 13, 1978. Thank you for your continued cooperation.

Very truly yours,

HARRISON H. SCHMITT,
U.S. Senator.

ATTACHMENT G

EXECUTIVE OFFICE OF THE PRESIDENT,
OFFICE OF SCIENCE AND TECHNOLOGY POLICY,

Hon. HARRISON H. SCHMITT,
U.S. Senate,
Washington, D.C.

Dear Jack: Thank you for your letter of May 8, with questions about current legislation which would regulate recombinant DNA research and its applications.

Many of the issues you have raised, of course, we have discussed in previous correspondence and during the hearings on November 8 and February 10. As Gil Omenn testified to the House Science and Technology Subcommittee on April 11, we do support the passage of H.R. 11192. A copy of that testimony is attached.

Responses to your specific questions follow:

1. Analysis of the key provisions of the H.R. 11192 and S1713. The Administration prefers H.R. 11192 for the reasons stated in the Omenn testimony of April 11. The key provisions are the authority to waive regulation of much work which is judged to bear minimal risk; the authority to carry out potentially “high-risk” experiments in order to assess actual risks; and the mechanism for uniform national standards and regulations, with a means for local appeal to the Secretary of
DHEW. S1713 does not meet these needs as well as H.R. 11192 seems to do.

2. Do we agree with the conclusion of the Federal Interagency Committee on Recombinant DNA Research (March, 1977) that no present authority is sufficient to deal with recombinant DNA techniques in every regard? Yes. As we discussed in detail before your Subcommittee on November 8, only Section 361 of the Public Health Act has the potential to meet this broad mandate. However, 361 does not meet every aspect of the situation, as will be explained in the next few questions.

3. Could Section 361 be used to cover the private sector? Yes.

4. What problems might arise from use of Section 361 to regulate recombinant DNA research? One concern often raised is the notion that invoking Section 361 would seem to some to acknowledge a significant risk of transmission of communicable disease. Present evidence makes such risks strictly conjectural. Section 361, of course, was not written to regulate research. Its use in this regard may provide precedent for broad intrusions into the research environment, with Congressional debate. Section 361 does not deal with hazards to the environment that can be shown to have no primary or secondary effect on human health.

5. What are the authorities of the Secretary under Section 361? For a comprehensive analysis, you should inquire of the General Counsel at DHEW. Probably you have done so already. Our own review suggests that Section 361, together with Section 368, provides broad statutory authority for the development of detailed regulations for essentially all of the functions you name.

6. Compare the authority of the Secretary under Section 361 with that under the currently proposed legislation. In the absence of detailed analysis from DHEW on Section 361, such a comparison is not feasible. Certainly, authorities would be far more explicit under the specific bills than under Section 361.

7. Does the Secretary have authority under Section 361 to preempt State and local actions concerning recombinant DNA research and related activities? The Secretary apparently would not have the authority to preclude State or local actions more stringent than the national standards or regulations.

I hope that these responses are helpful to you in the current deliberations.

Yours sincerely,

Frank Press, Director.
APPENDIX

LIST OF WITNESSES

(In order of appearance)

Philip Handler, President, National Academy of Sciences
Paul Berg, Wilson Professor of Biochemistry, Department of Biochemistry, Stanford University Medical Center
Jonathan Alan King, Associate Professor of Molecular Genetics, Department of Biology, Massachusetts Institute of Technology
Roy Curtiss, III, Senior Professor of Microbiology, Department of Microbiology, University of Alabama
Bruce R. Levin, Associate Professor of Zoology, Department of Zoology, University of Massachusetts
Clifford Grobstein, Professor of Biological Sciences and Public Policy, University of California at San Diego
Daniel Callahan, Director, The Hastings Center Institute of Society, Ethics and the Life Sciences
Marshall S. Shapo, Professor of Law, University of Virginia
Marc Lappé, Chief, Office of Health, Law and Values, Department of Health, California
Frank Press, Director, Office of Science and Technology Policy, Executive Office of the President
Donald S. Fredrickson, Director, National Institutes of Health, Department of Health, Education, and Welfare
Margaret Mead, Emeritus Curator, American Museum of Natural History
William Rutter, Chairman, Department of Biochemistry and Biophysics, University of California, San Francisco
Herbert Boyer, Professor of Biochemistry, Department of Biochemistry and Biophysics, University of California, San Francisco
Harlyn Halvorson, Director, Rosenstiel Medical Sciences Research Center, Brandeis University
Oliver Smithies, Leon J. Cole Professor of Genetics, University of Wisconsin
Joseph A. Keyes, Director, Division of Institutional Studies, American Association of Medical Colleges
Frank Young, Chairman and Professor, Department of Biology, University of Rochester Medical Center
Marcia Cleveland, Attorney, Natural Resources Defense Council
Scott Thacher, graduate student in Biochemistry, Harvard University
Susan Wright, Lecturer in the History of Technology, Department of Humanities, College of Engineering, University of Michigan
Robert Corman, Attorney, Assistant Deputy Public Advocate, Department of the Public Advocate, State of New Jersey
Arthur Schwartz, Department of Mathematics, University of Michigan
Joseph Stetler, President, Pharmaceutical Manufacturers Association
Joseph Grady, Research Head, Department of Infectious Disease Research, Upjohn Company
Ronald E. Cape, President, Cetus Corporation
David Newburger, Assistant Professor of Law, Washington University School of Law

LIST OF ADDITIONAL STATEMENTS AND COMMUNICATIONS IN THE HEARING RECORD

Statements:
Council of Scientific Society Presidents, Resolution, August 4, 1977
Nelkin, Dorothy, Program on Science, Technology and Society, Cornell University, November 2, 1977

(81)
Newman, Stuart A., Professor, Department of Biological Sciences, State University of New York at Albany, November 29, 1977
Sinsheimer, Robert, Chancellor, University of California at Santa Cruz, December 5, 1977

Communications from:
Burris, Robert H., Professor of Agricultural Biochemistry, and Waclaw Szybalski, Professor of Oncology, University of Wisconsin, December 2, 1977
Cohen, Stanley N., Professor of Medicine and Genetics, Stanford University Medical Center, October 27, 1977
Hess, Eugene L., Executive Director, Federation of American Societies for Experimental Biology, November 29, 1977
Lennette, Edwin H., President, Tissue Culture Association, November 30, 1977
Magee, P. T., Chairman, Department of Microbiology and Public Health, Michigan State University, December 5, 1977
Shapiro, James A., Department of Microbiology, University of Chicago, November 10, 1977
Szybalski, Waclaw, Professor of Oncology, University of Wisconsin, January 4, 1978
Goldstein, Richard, Department of Microbiology, Harvard University School of Medicine, to Donald Fredrickson, Director, National Institutes of Health, August 30, 1977
Gorbach, Sherwood, Professor of Medicine and Microbiology, Tufts University School of Medicine, to Donald Fredrickson, July 14, 1977
Redys, John, Director, Laboratory Division, Department of Health, State of Connecticut, to Pamela Lippe, Friends of the Earth, November 7, 1977
Sullivan, Clare D., graduate student, Harvard School of Public Health, to Donald Fredrickson, December 29, 1977

EXECUTIVE OFFICE OF THE PRESIDENT,
OFFICE OF SCIENCE AND TECHNOLOGY POLICY,

HON. ADLAI E. STEVENSON,
U.S. Senate,
Washington, D.C.

DEAR SENATOR STEVENSON: Thank you for your letter of November 29 and for the opportunity to testify before your Subcommittee on November 8 about recombinant DNA research and applications.

You have raised searching questions about the appropriateness and usefulness of Section 361 of the Public Health Service Act as a basis for the issuance of regulations covering recombinant DNA activities. You are aware, I know, that the Department of HEW's Office of General Counsel, which must rule on the applicability of Section 361, took the position a year ago that there are flaws in the use of Section 361. Most of the analysis of existing authorities, therefore, was directed at the Toxic Substances Control Act and the Occupational Safety and Health Act, as reported in the Interagency Report of March 15, 1977. The language of Section 361, dealing with "quarantine" and with such communicable diseases as smallpox, cholera, yellow fever, and plague has certainly put off many policymakers and scientists. Dr. Omenn's comments, to which you refer, do indeed reflect a concern that use of Section 361 might imply that the strictly speculative hazards associated with DNA research may be real.

Since our November testimony, Dr. Omenn has looked into the background of the uses of Section 361, with the assistance of Mr. Peter Hutt, formerly Assistant General Counsel of HEW and Chief Counsel for the FDA. A copy of Mr. Hutt's detailed report is attached. It is clear that Section 361 has been utilized for a remarkable variety of relatively benign and even non-infectious threats to the public health. Its applicability to the private sector and to intrastate activities has been established in Federal courts. Its applicability to effects on plants, animals, or other components of the general environment seems adequate, so long as there is any possibility of further transmission of effects to humans. Most important, Section 361 has been applied to practices and facilities such as shellfish beds, pet turtle production, importation of nonhuman primates,
production of milk, and standards for water in a way that clearly establishes the preference for prevention of the occurrence of any risk, rather than control of the spread of infection. It is our understanding that the NIH Guidelines on Recombinant DNA Activities are directed at exactly the same objective: to assure that risks of infection being released be eliminated by stringent control over practices and facilities.

Thus, we have raised to an interagency group, including representatives of the Office of the General Counsel of DHHS, the potential applicability of Section 361 in the event that the Congress decides that legislation specific to DNA research cannot be agreed upon and that use of Section 361 is necessary. This single authority, with DHHS the clear lead agency, might well be adequate. We do agree with HEW, of course, that Section 361 was not written for the purpose of regulation of research or even of research applications and that extensive justification and detailed regulations would be required. Such regulations would be required under proposed legislation, as well. We understand that HEW prefers specific Congressional authorization and that Congressman Rogers is reviewing the Administration’s proposals along with other alternatives.

Now let me turn to the other two issues you raised.

**Issue No. 2**

The Department of Commerce activities are progressing satisfactorily. Staff from their Office of General Counsel and from the Office of Environmental Affairs, under Assistant Secretary Baruch, and staff from my Office have met several times with representatives of the Pharmaceutical Manufacturers Association and certain industrial firms. Meetings with labor officials and with representatives of environmental groups are being scheduled. The activity I mentioned above about use of Section 361 and the discussion of new legislation in the Congress has complicated the context of their inquiries, but they are going ahead. Surveillance mechanisms under discussion include registration, biohazards/biosafety committees with public members, and sanctions for violations of guidelines.

**Issue No. 3**

The preemptions provided in S. 1217 (now withdrawn by Senator Kennedy) and in Amendment 754 by Senator Nelson were introduced, I presume, to clarify responsibility for establishing regulations under any new legislation pertaining to DNA activities. Since the Secretary of HEW would be charged with the implementation of the Act, the Secretary could instruct FDA to require evidence of compliance with DNA regulations in order to approve new drug applications. The NIH Guidelines, as revised, will meet the needs of the Department of Agriculture, we are advised. OSHA reserves the possibility of entering into this matter later, if evidence of significant hazard to employees should arise. NIH guidelines and any regulations developed under new legislation or under Section 361 seem adequate for the workplace at present.

Therefore, we see no present need for changes in other statutes. Nor is there any apparent need to preempt existing statutes.

In closing, let me add that the recombinant DNA work seems to be progressing well and safely, with additional information during the past year that has permitted more sober and realistic discussion of the potential risks. These risks now seem sufficiently low and the NIH Guidelines sufficiently stringent that the public should be much reassured. Furthermore, I believe that the NIH has very effectively engendered public discussion, and I see little indication for a public commission to enhance or possibly reignite the debate of the past few years on this subject.

We are eager to work with you and with other Committees of the Congress in following the development of this research and its applications.

Yours sincerely,

**Frank Press, Director.**

**COVINGTON & BURLING,**

**Washington, D.C., January 6, 1978.**

GILBERT S. OMMEN, Ph. D., M.D.,
Assistant Director for Human Resources and Social and Economic Services,
Office of Science and Technology Policy, Washington, D.C.

DEAR GIL: As you requested, I have reviewed the background of Section 361 of the Public Health Service Act (42 U.S.C. 264), its interpretation and application by the Food and Drug Administration and the Public Health Service over
the past several years, and its interpretation by the courts. Enclosed is a copy of each of the documents to which reference is made in this letter, to facilitate your own evaluation.

I

The original Federal communicable disease law was passed by Congress in 1893 (27 Stat. 449). As you will see, Section 3 authorized the Supervising Surgeon-General of the Marine Hospital Service, Department of the Treasury, to issue regulations to prevent the introduction of contagious and infectious diseases into one state from another. Unfortunately, I have not had the opportunity to research and review the legislative history of this Act, and therefore cannot provide information on the specific congressional intent. It appears from the wording of the statute itself, however, that the Department of Treasury was given very broad and all-encompassing authority to prevent the spread of disease.

II

In 1944 Congress consolidated and revised all of the laws relating to the public health service in the Public Health Service Act (58 Stat. 682). (A copy of relevant portions of the House Report on that bill, as reproduced in 1944 U.S. Code and Congressional Service 1211, is enclosed. Section 361, which was later codified in the United States Code as 42 U.S.C. 264, is discussed on pages 1214 and 1224–1235.)

As you know, Section 361, as enacted in 1944, provides broadly that: "(a) The Surgeon General, with the approval of the Secretary, is authorized 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 State or possession into any other State or possession. For purposes of carrying out and enforcing such regulations, the Surgeon General may provide for such inspection, fumigation, disinfection, sanitation, pest extermination, destruction of animals or articles found to be so infected or contaminated as to be sources of dangerous infection to human beings, and other measures, as in his judgment may be necessary."

In addition, Section 368(a) provides that "Any person who violates any regulation prescribed under sections 361 . . . shall be punished by a fine of not more than $1,000 or by imprisonment for not more than one year, or both."

The wording of Section 361 is uniquely broad. By its terms, this provision authorizes HEW to promulgate any regulations necessary to prevent communicable disease, and to provide for inspection and any other enforcement measures that may be necessary. The legislative history does not detract from the broad statutory language. The House Report states that the "confusing limitations" in the 1893 Act were intentionally eliminated and that the new law was intended to "expressly sanction the use of conventional public-health enforcement methods" as well as to "authorize destruction of contaminated articles or infected animals which are dangerous to man, in those cases where no other disposition is safely possible."

Thus, there is no tenable argument that Section 361 was intended narrowly to be limited only to quarantine of human beings or humans and animals (since the law encompasses all "articles," a term commonly used in regulatory statutes to encompass all substances or objects of any kind), nor is there any argument that inspection is not permitted (since it is specifically mentioned) or that a wide range of other enforcement mechanisms is not authorized (since the law permits any "other measures" for carrying out and enforcing any regulations as in the judgment of HEW may be necessary).

III

Questions have been raised about the application of Section 361 to intrastate (as contrasted with interstate) commerce. Questions have also been raised as to whether Section 361 can be interpreted to authorize the prohibition (as contrasted with the regulation or control) of specified activity. Both of these issues have now been definitively resolved in a 1977 court decision upholding the legality of an FDA regulation banning all small pet turtles from both intrastate and interstate commerce under the sole authority of Section 361.

In the Federal Register of April 7, 1972 (37 F.R. 7005), FDA proposed a prohibition of the importation of small pet turtles, and a requirement of bacterio-
logical testing and certification for interstate shipment of such turtles, in order to prevent the spread of salmonella. This regulation was made final in the Federal Register of November 18, 1972 (37 F.R. 24670).

On the basis of additional information showing that the certification program was not effective, FDA issued two additional alternative proposals in the Federal Register of May 28, 1974 (39 F.R. 18463) that would either prohibit the sale and other distribution of small pet turtles or would improve the certification scheme and impose additional requirements on the sale and shipment of these turtles. In discussing the first of his two alternative proposals in the preamble, the Commissioner stated that:

"Under the Public Health Service Act, the Commissioner has the authority to extend a prohibition on distribution of all turtles and turtle eggs, whether or not they have passed through interstate commerce, if in his judgment such a complete ban would be necessary for effective control over the interstate spread of turtle-associated diseases." (39 F.R. at 18464.)

On the basis of the comments received, the Commissioner issued a final regulation in the Federal Register on May 23, 1975 (40 F.R. 22543), banning all such turtles from intrastate and interstate commerce. In paragraph 13 of the preamble, on page 22545, the Commissioner specifically rejected a suggestion that the turtles should be banned from interstate shipment but should be permitted for intrastate shipment.

Subsequently, the State of Louisiana brought suit to enjoin enforcement of this regulation on a variety of legal grounds. In State of Louisiana v. Mattheis, 427 F. Supp. 174 (E.D. La. 1977), the Court upheld the legality of the regulation against all challenges. Specifically, the Court ruled that FDA could properly ban all small turtles rather than only those turtles shown to be infected and thus to be health hazards, on the ground that "Congress has granted broad, flexible powers to Federal health authorities who must use their judgment in attempting to protect the public against the spread of communicable disease." The Court rejected, as unproven, a contention that less drastic means of regulation would be sufficient to protect the public. It ruled that Section 361 permits FDA to control intrastate as well as interstate activity. Finally, it rejected a contention that the regulation is discriminatory because there are no other comparable regulations. For another court decision broadly upholding the discretion of HEW to enforce Section 361 see United States v. Shinnick, 219 F. Supp. 759 (E.D. N.Y. 1963).

IV

Section 361 has been applied by the Public Health Service and FDA in the past in a wide variety of ways. In general, the Public Health Service was responsible for implementation of Section 361 until the late 1970s when responsibility for implementation of its foreign aspects were delegated to CDC and for implementation of its domestic aspects relating to the law enforcement functions of FDA were delegated to FDA. (Copies of the current regulations issued under Section 361 by the Public Health Service in 42 C.F.R. Parts 71 and 72, and by FDA in 21 C.F.R. Parts 1240 and 1250, are enclosed. Do not be misled by the citation, as legal authority for these regulations, of Section 215 of the Public Health Service Act; that provision merely authorizes HEW to issue regulations to implement the Public Health Service Act.)

As you will see, these regulations cover a wide variety of subjects. They deal in detail with the sanitation of interstate convergences. The Drinking Water Standards in 42 C.F.R. 72.201–207 relate not just to bacteriological quality, but also to physical and chemical characteristics which surely would not fall within any narrow definition of the concept of a “communicable disease.” The Drinking Water Standards have been enforced as the national standard since 1962.

Etiologic agents are defined, and their transportation regulated, under 42 C.F.R. 72.25. Psittacine birds, lather brushes, and plain garbage are regulated under 21 C.F.R. 1230.63, 1240.70, and 1230.75, as a prophylactic measure to prevent disease.

For many years, the Public Health Service, and more recently FDA, has engaged in joint programs with State and local government agencies and with the regulated industry to promote sanitation in the production of milk products and shellfish, and in the provision of food in eating establishments, under the general provisions of Section 361. Development of the Pasteurized Milk Ordinance and Code, through the Interstate Milk Shippers Conference, has had a major impact on milk sanitation. The PMO provides detailed requirements for the handling of milk and dairy products on the farm, in order to prevent the possi-
bility of communicable disease. The growing conditions for shellfish have similarly been the subject of control since 1924 under the National Shellfish Sanitation Program, and FDA has proposed to establish regulations codifying this program in the Federal Register of June 19, 1975 (40 F.R. 25916), which are now being held in abeyance pending further study required by Congress in Section 16(b) of P.L. 94–370 (90 Stat. 1013, 1033). FDA proposed to codify its 40-year history of cooperation on food sanitation programs for food service establishments in the Federal Register of October 1, 1974 (39 F.R. 35438), and has since concluded instead to issue a model ordinance as announced in the Federal Register of March 22, 1977 (42 F.R. 15428). Under the same authority, FDA has announced a proposed Model Retail Food Store Sanitation Ordinance in the Federal Register of October 25, 1977 (42 F.R. 56367) and a Model Vending of Food and Beverages Ordinance in the Federal Register of October 7, 1977 (42 F.R. 54626).

Finally, in a variety of regulations in the past few years designed to implement a national blood policy, FDA has utilized Section 361 to control blood banking and blood labeling practices in intrastate as well as interstate commerce. The preambles to these regulations specifically mention the need for close control of all blood practices, in minute detail, in order to prevent communicable disease. Copies of the proposed regulations to establish current good manufacturing practice for blood and blood components published in the Federal Register of May 28, 1974 (39 F.R. 18614) and to require a label statement to distinguish volunteer from paid blood donors published in the Federal Register of November 14, 1975 (40 F.R. 53040), both of which discuss this subject, and both of which provide extraordinary detailed requirements, are enclosed.

V

Questions have been raised about the degree and nature of the potential harm that must be shown in order to invoke the authority of Section 361. It appears that the language of the statute itself, its legislative history, and the court opinion interpreting it, place broad discretion in HEW to determine when the scientific evidence warrants reliance on Section 361 to prevent the possibility of communicable disease. Absent evidence that the HEW decision is wholly irrational, it is highly likely that the courts would uphold this exercise of discretion.

Nor is there any limitation in Section 361 on the source from which the potential harm must come in order to justify regulation. The terms of Section 361 permit regulation of research or of commercial activity. Indeed, the present regulations governing transportation of etiologic agents directly affects basic research, and a number of regulations affect commercial activity. The law permits control of human beings, animals, plant material, and any other form of article, in order to prevent communicable disease.

With specific reference to research on recombinant DNA molecules, the question has been raised whether there is sufficient danger of communicable disease to justify invocation of Section 361. If indeed there is no significant possibility of this occurring, it is difficult to understand why the United States Congress, NIH, the entire scientific community, numerous state legislatures and city councils, and many citizens groups, have been spending such an inordinate amount of time debating it. The very nature of the controversy itself is sufficient, in my judgment, to establish the potential for harm that is required under Section 361. If that potential were agreed not to exist the entire issue of regulatory control over this research would never have been raised in the first place.

More specifically, some have questioned whether controls over certain types of research on recombinant DNA molecules, such as research on plant materials, can be justified under Section 361, since arguably the need for control arises from potential communication of disease from one plant to another rather than to man. Others have argued, however, that so little is known about research on recombinant DNA molecules that there is indeed a danger, which will remain until further experimentation proves otherwise, that research on plant materials could unleash pathogenic organisms to infect man, or could otherwise result in human infection in ways we cannot anticipate. Again, the mere existence of this controversy, which has been sufficient to engage the attention of the entire country, seems quite enough to provide a legally sufficient basis for invoking Section 361. Moreover, once jurisdiction is established the courts have held that the National Environmental Policy Act provides substantive authority over all

It is important, once again, to understand that Section 361 was intended by Congress broadly to authorize prophylactic public health measures to prevent disease before it occurs. All that is needed to support regulations under this provision is either apprehension or uncertainty about the possibility of potential harm, the lack of adequate information showing that the harm cannot occur, and the possibility that the harm would be serious (e.g., irreversible) if it did occur. The more serious the nature of the potential harm, the less is required in the way of apprehension of uncertainty about that harm in order to justify invoking regulatory controls under Section 361.

**VI**

Questions have also arisen about enforcement of any regulations issued under Section 361. Section 361 itself provides that any articles not in compliance with such regulations may be destroyed, and authorizes any other enforcement measures that may be concluded to be necessary. In initially promulgating its turtle regulations, FDA included a requirement for bacteriological testing and certification. In its proposed shellfish regulations, other enforcement mechanisms were included. Each of the PHS and FDA regulations issued under Section 361 has its own tailor-made enforcement provisions.

It seems clear that the statute authorizes regulations that require destruction of any materials resulting from activity not in compliance with regulations issued under Section 361. There is judicial authority for proposition that a Federal court, using its broad equitable powers, may enjoin violation of any validly-promulgated government regulation. Section 368 specifically provides for a fine and/or criminal incarceration. Section 361 specifically mentions authority for inspection as an enforcement tool. Administrative provisions requiring reports or imposing other enforcement mechanisms are also clearly authorized. Thus, it appears that there is an infinite variety of enforcement mechanisms available, and that any of a number could be incorporated into a regulation promulgated under Section 361.

**VII**

Questions have been raised about the way in which the recombinant DNA research guidelines could be enforced if they were proposed and promulgated as regulations under section 361. Clearly, it would not be necessary that the same government agency issue the regulations and enforce them. It would be possible, for example, for NIH to issue the regulations (as it presently does), and for CDC to enforce them. I mention CDC because it has jurisdiction over the Clinical Laboratories Improvement Act and thus has experience in inspection and enforcement with respect to scientific laboratories. FDA might also be in a position to enforce the regulations, but its other responsibilities are so overwhelming that enforcement of recombinant DNA research regulations might better be performed by CDC.

**VIII**

At the recent NIH meeting, representatives of the pharmaceutical industry stated that industry intends to comply with the NIH guidelines and would have no objection to making them mandatory if certain specific problems were overcome. The principal problem involved their concern about submission of trade secret information to NIH. I stated at that meeting that this issue exists with respect to all regulatory agencies, and that FDA, EPA, and the others have resolved it without significant difficulty.

A Federal statute, 18 U.S.C. 1905, explicitly provides that trade secret information provided to the government may not be released to the public by any government employee under pain of criminal penalty. FDA—which regularly receives trade secret information from the regulated industry with respect to food additives, new drugs, biological products, medical devices, and so forth—has issued extensive regulations providing that such trade secret information will be held in confidence by the agency and will not be released to the public. Enclosed is a copy of 21 C.F.R. Part 20, dealing generally with the release of information from FDA to the public, together with Section 314.14 relating to information in IND and NDA submissions (as an example of the way in which this information is handled). The court have now definitely held that 18 U.S.C. 1905 does in fact protect all trade secrets from public disclosure by government agencies. Thus, all
that is needed to resolve this concern of industry is to incorporate some of the routine practices for protection of trade secrets, that have long prevailed in other governmental agencies, into the regulations governing recombinant DNA research.

Sincerely yours,

PETER BARTON HUTT.

See page 73 for letter of Secretary Califano, February 27, 1978, to Senator Stevenson.

U.S. ENVIRONMENTAL PROTECTION AGENCY,

HON. ADELAI E. STEVENSON,
Chairman, Subcommittee on Science, Technology, and Space, Committee on Commerce, Science, and Transportation, U.S. Senate, Washington, D.C.

DEAR MR. CHAIRMAN: I am writing in response to your letter of November 30, 1977, which focused on various policy issues associated with recombinant DNA activities. Your particular concern was the extent to which the Environmental Protection Agency (EPA) can regulate the commercial applications of recombinant DNA research under the authorities contained in the Toxic Substances Control Act (TSCA).

I am in general agreement with your observations concerning the scope of TSCA and its application to the commercialization of chemical substances. However, I believe that effective regulation of all aspects of recombinant DNA research—including the commercial applications which may be derived therefrom—would be better achieved by the enactment of comprehensive legislation specifically addressing itself to the unique policy issues surrounding all recombinant DNA activities.

There are two principal factors underlying this recommendation. First, EPA's administration of TSCA is still in its infancy. The Agency is wrestling with the many difficult policy issues involved in the implementation of TSCA, resolution of which may take months or perhaps years. This effort will require a great commitment of Agency resources, and is critical to the ultimate success of the program. Regulation of recombinant DNA activities, however, will require consideration of additional questions which may not be directly relevant to other aspects of the regulation of toxic chemicals; resolution of those issues will require a significant diversion of Agency energy and expertise. As a matter of overall program priorities, therefore, I believe that regulation of all recombinant DNA activities should be placed under some statutory authority other than TSCA.

Second, any attempt to regulate the commercial applications of recombinant DNA research under TSCA may be hampered or obstructed by certain interpretative and conceptual problems. For instance, although 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 recombinant DNA molecules fits—or was intended to fit—that definition. Practical applications of recombinant DNA technology will utilize several generations of organisms which will inherit the implanted genetic information via natural biological reproductive processes. 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 interpretation which I am confident the Congress neither contemplated nor intended.

Similarly, with respect to products which may be derived from such organisms (e.g., enzymes), section 5 of TSCA will require a pre-manufacturing notice only if the product is a "new chemical substance" or will be put to "a significant new use". New methods (including recombinant DNA technologies) of production of chemical substances included in the inventory published under section 8 of TSCA are not per se subject to the notice requirements of section 5. Finally, it should be observed that a significant area of application of recombinant DNA research is likely to be in the economical and efficient production of certain drugs or pharmaceuticals, which are specifically excluded from the coverage of TSCA.

I do not believe that these and similar problems should be solved by amendments to TSCA. As illustrated above, adjustments to particular provisions of TSCA to embrace circumstances peculiar to recombinant DNA research may have

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Bartox 27, 1977; Stevenson.
much broader—and undesired—impacts upon the overall regulatory program for toxic substances. Rather, I believe that it would be more appropriate to enact comprehensive legislation regulating all aspects of recombinant DNA research—including all commercial applications—which would be sensitive to the unique problems and issues attendant to this frontier of science.

In closing, however, I would like to emphasize that in the absence of legislation which specifically addresses the unique problems associated with recombinant DNA research, the Agency will conscientiously attempt to protect the public to the fullest extent necessary against any unreasonable risk of injury to health or the environment which may be presented by any recombinant DNA activity, utilizing TSCA and other existing authorities.

Sincerely yours,

Douglas M. Costle,
Administrator.

U.S. Department of Labor,
Occupational Safety and Health Administration,

Hon. Adlai Stevenson,
Chairman, Subcommittee on Science, Technology, and Space, Committee on Commerce, Science, and Transportation, U.S. Senate, Washington, D.C.

Dear Mr. Chairman: This will respond to your letter of November 30, 1977 to Secretary of Labor Ray Marshall concerning the authority of the Occupational Safety and Health Administration as it pertains to recombinant DNA.

Generally, the Occupational Safety and Health Act of 1970 covers employees engaged in both DNA research and commercial activities. However, employees of State and local governments such as a State university or community college, are not covered under the Act unless the State has an approved OSHA plan. Nonetheless, research or other activities conducted by a private employer under a contract with the federal, State or local government are, like those of any private employer, subject to the OSH Act. In addition, protection of Federal agency employees is provided for under a special section of the Act which requires Federal agency heads to develop and implement occupational safety and health programs for their employees.

With respect to the regulatory authority of other Federal agencies, section 4 (b) (1) of the Act provides that OSHA shall not apply to any hazardous working conditions that are addressed by the standards or regulations of another agency and which are promulgated by that agency in the “exercise” of its statutory authority. The Committee-reported DNA bill, S. 1217, contains the following provision which is designed to ensure that section 4 (b) (1) of the Act would not, in the case of DNA-related activities regulated under the terms of the bill, displace the application of OSHA to working conditions involving DNA.

“(c) This title shall not affect the authority of the Secretary or the Secretary of Labor to exercise their respective authority pursuant to the Occupational Safety and Health Act of 1970. And provided further, that in exercising authority under this title, the Secretary, the Commission, or any person acting on behalf of the Secretary or Commission or pursuant to the provisions of this title, shall not, for the purposes of section 4 (b) (1) of the Occupational Safety and Health Act of 1970, be deemed to be exercising statutory authority to prescribe or enforce standards or regulations affecting occupational safety and health.”

Thus, OSHA would be the agency with primary statutory responsibility in matters dealing with occupational safety and health hazards of DNA.

While OSHA’s present capability to protect workers from the hazards associated with recombinant DNA is limited, this Agency’s responsibility for worker health and safety makes it essential for OSHA to acquire appropriately qualified personnel and technological capabilities. The acquisition of this expertise will be crucial in OSHA’s effectively setting and enforcing occupational safety and health standards to protect men and women working with recombinant DNA.

I hope this information clarifies OSHA’s role in protecting workers from possible hazards of exposure to recombinant DNA. If you need further information, please feel free to contact me.

Sincerely,

Eula Bingham,
Assistant Secretary, Occupational Safety and Health.
HOM. ADLAI E. STEVENSON,
Chairman, Subcommittee on Science, Technology, and Space,
U.S. Senate, Washington, D.C.

DEAR MR. CHAIRMAN: This is in reply to your inquiry dated November 30, 1977, regarding authorities to regulate products of DNA research and microbes or other organisms containing recombined DNA. Specifically, you requested to be advised whether the Animal and Plant Health Inspection Service (APHIS) of this Department has the authority to control microbes or other organisms containing recombined DNA in animals and plants, and whether authority exists to directly control organisms containing recombined DNA.

Since this is a relatively new area of scientific endeavor, and since the end results of DNA research are still mostly conjectural, we cannot specifically point to any statute administered by APHIS which would be definitely applicable to such research. However, there are several statutes which are administered by APHIS which may ultimately be affected by either the end products resulting from DNA research or by organisms containing recombined DNA.

The major programs that are administered by APHIS under which certain products of DNA research or organisms containing recombined DNA could be regulated are as follows:

A. The Animal Quarantine laws, especially 21 U.S.C. 111, 114, 114(b), 123 and 134(a)

The main purpose of these laws is to prevent the introduction into the United States, or the dissemination from one State or Territory or the District of Columbia to another of the contagion of any contagious, infectious, or communicable disease of animals and/or live poultry. Under these laws, the Secretary of Agriculture has the authority to promulgate such regulations and to take such measures as he may deem proper to prevent such introduction or dissemination. Any product of DNA research or any organisms containing recombined DNA which could be classified as such a “contagion” would be subject to the Animal Quarantine laws.

Section 122.2 of Title 9, Code of Federal Regulations, applies specifically to organisms and vectors. It states that no organisms or vectors shall be imported into the United States or transported from one State or Territory or the District of Columbia, to another State or Territory or District of Columbia without a permit. Organisms are defined in section 122.1(e) of Title 9, Code of Federal Regulations as “All cultures or collections of organisms or their derivatives, which may introduce or disseminate any contagious or infectious disease of animals (including poultry).”

B. The provisions of the Virus-Serum-Toxin Act (21 U.S.C. 151, et seq.)

The purposes of this Act, as stated in the Legislative History (See, e.g., Senate Committee Report No. 1288 on H.R. 28283, 62nd Congress) is to prevent “the introduction into the United States of dangerous and worthless viruses, serums, and analogous products for use in the treatment of domestic animals . . . and also for the purposes of controlling the use, by preventing the interstate shipment, of similar dangerous, and worthless products that may be manufactured within the United States”.

Therefore, products of recombinant DNA research which could be considered viruses, serums, toxins or analogous products (i.e., veterinary biologics), as well as any recombined DNA containing organisms used to produce them, which are subject to the provisions of the Virus-Serum-Toxin Act, would also be subject to APHIS regulation.

C. The Federal Plant Pest Act, particularly 7 U.S.C. 150bb and 150dd

This law is mainly concerned with the prevention of the dissemination of plant pests in the United States. The Secretary of Agriculture has the authority to prevent the introduction of such pests which are moved from a foreign country into the United States, or interstate. Therefore, any products of DNA research or organisms containing recombined DNA which fall under the category of plant pests would be subject to regulations by APHIS.

There are, of course, other authorities which might have an impact in this area, such as the Federal Meat and Poultry Inspection Acts (21 U.S.C. 601, et
seq. and 21 U.S.C. 451, ct seq.). These laws are mainly concerned with providing wholesome and safe meat and poultry products to the public. Any meat or poultry products which are "adulterated", within the meaning of that term, would come under the prohibitions of said Acts. If such "adulteration" were related to the administration of products resulting from DNA research or to exposure to organisms containing recombinant DNA, then the provisions of these Acts could have significance with respect to the area of DNA research.

Sincerely,

BOB BERGLAND, Secretary.

THE SECRETARY OF TRANSPORTATION,

HON. ADLAI E. STEVENSON,
Chairman, Subcommittee on Science, Technology, and Space, U.S. Senate, Washington D.C.

DEAR ADLAI: Thank you for your letter of November 30, 1977, asking whether the Hazardous Materials Transportation Act (HMTA) provides authority to deal with the transportation hazards of materials associated with recombinant DNA research or its commercial application, and whether the Department has any plans to examine those hazards.

The short answer to both questions is "yes." The Department has been active in the work of the Interagency Committee on Recombinant DNA Research, chaired by the Director of the National Institutes of Health (NIH), which examined Federal authority that might be used to control the hazards of recombinant DNA research, including transportation incident to research. In the course of examining our own authority under the HMTA, we concluded that the Act was adequate to insure transportation safety when recombinant DNA materials are moved in commerce.

We presently are considering the possibility of publishing a notice of proposed rulemaking which would include a proposal to designate recombinant DNA materials as hazardous materials subject to certain precautions when shipped. In this regard, we expect to follow the course set by existing NIH Guidelines by limiting our concern to "novel recombinant DNA," i.e., DNA segments inserted into species not known to exchange chromosomal DNA by natural processes with the species of origin. Suitable packaging could be required for novel recombinant DNA, such as that now required for shipment of etiological agents. The exact nature of any needed transportation safety requirements will depend on the hazards associated with the particular material. Varying degrees of hazards are recognized by the NIH Guidelines based on the nature of the genetic material involved.

One of the peculiarities of assessing the hazards of novel recombinant DNA is the extent to which those hazards are unknown. However, the Secretary, under the HMTA, is directed to designate as a hazardous material any material which he finds "may pose an unreasonable risk to health and safety or property" when transported in commerce in a particular quantity and form. Thus, a finding that a particular quantity and form of a material may pose an unreasonable risk is sufficient to bring that material under the HMTA.

It is not possible to give you a precise estimate of when a final decision will be made to publish either a notice of proposed rulemaking on recombinant DNA or a final rule. This is a complex, technical field that is in a state of flux. Elements of the scientific community have recently re-evaluated the hazards of recombinant DNA research and suggest that the hazards may be less than initially believed. At the present time, NIH is considering revision of its guidelines and has solicited public comment on its proposals with a notice in the Federal Register. However, as a general matter, we expect that some form of transportation control on novel recombinant DNA materials, whether generated by research or commercial activities, will be established by the Department. We also believe it advisable that such transportation controls as are necessary be established under the HMTA, to avoid difficulties and confusion that may arise from conflicting transportation requirements that State or local governments may impose. Please let me know if you have any further questions or desire an update on our activities in this matter.

Sincerely,

BROCK ADAMS.
Hon. Adlai E. Stevenson, III
Chairman, Subcommittee on Science, Technology, and Space, U.S. Senate, Washington, D.C.

Dear Senator Stevenson: On November 29, 1977, you wrote me with regard to a request made to the Department of Commerce by Dr. Frank Press, Director of the White House Office of Science and Technology Policy. This request was that the Office of Environmental Affairs in my office explore the feasibility of establishing a program of "voluntary compliance and meaningful surveillance" in the area of recombinant DNA (RDNA) research carried out by the private sector.

During the period between our receiving Dr. Press' request and the present, the Office of Environmental Affairs has consulted at length with industrial representatives and with other Federal agencies. A preliminary plan was developed for voluntary surveillance of a private sector RDNA program. Several troublesome issues were raised, most of which we believe could have been resolved. However, in the opinion of industry the proposed plan did not contain adequate protection for proprietary information and rights. For this reason, a voluntary surveillance program entirely satisfactory to both industry and Government is unlikely at this time. The Department, however, continues to maintain its contacts with the appropriate industrial representatives.

You also asked for a summary of RDNA research activities in the private sector. As nearly as can be determined, there are now four pharmaceutical manufacturing companies carrying on this research in their own laboratories:

- Upjohn Company, Kalamazoo, Michigan.
- Eli Lilly and Company, Indianapolis, Indiana.

Two companies are supporting research in university laboratories, under contract:

- Miles Laboratories, Inc., Elkhart, Indiana.

Three companies, not in the pharmaceutical manufacturing business, are known to be engaged in RDNA research:

- Genentec Corporation, Berkeley, California.
- Cetus Corporation, San Francisco, California.

Other companies, however, are probably preparing to do RDNA research, by building containment facilities and hiring specialized personnel. The private sector picture, therefore, may change considerably over the next few months depending on establishment of standards of operation applied to private institutions.

I shall keep you informed about further developments as they occur.

Sincerely,

Jordan J. Baruch.

Natural Resources Defense Council, Inc.,

Hon. Adlai E. Stevenson, III.
Chairman, Subcommittee on Science, Technology, and Space, Committee on Commerce, U.S. Senate, Washington, D.C.

Dear Senator Stevenson: Enclosed is a memorandum I have prepared which considers existing statutory authority for regulating recombinant DNA.

I have also enclosed a memorandum prepared for me by two patent attorneys, which describes the effect of disclosure on patent rights. Since NRDC believes that full disclosure by industry of its recombinant activities is essential to public decision-making about this new technology, we recommend that your committee consider legislation which will resolve these problems. Specifically we recommend that the patent laws be amended to make it clear that disclosures made pursuant to a recombinant DNA regulatory statute do not jeopardize patent rights. Also the State Department should be asked to seek similar protection of foreign patent rights in international conventions governing patents.
Thank you for allowing NRDC this opportunity to supplement its testimony before your committee.

Sincerely, 

Marcia J. Cleveland

45 Rockefeller Plaza, 

Marcia Cleveland, Esq.,
Natural Resources Defense Council, Inc.,
122 East 42nd Street, New York, N.Y.

Dear Marcia: You have asked us to explain how certain provisions of the patent laws of the United States and other countries may affect proposed legislation relating to recombinant DNA research. The specific area of interest is the relationship between, on the one hand, disclosure requirements needed to implement a regulatory program for assuring the health and environmental safety of recombinant DNA research and, on the other hand, the waiver-by-publication provisions common in national patent systems. This topic is large, and our response is not exhaustive. We hope, however, that it may be a useful first effort.

The United States Patent Act provides, in Title 35, United States Code, Section 102(b), that a person shall not be entitled to a patent for an invention if (a) the invention was . . . described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The "date of application for patent in the United States" is the date on which the inventor, or the assignee of the inventor, submits to the Patent and Trademark Office the written description of the invention that is known as the patent application. In the normal course of events, that date precedes by about two years the date a patent would ultimately issue for that invention.

Therefore, once an invention has been described in a printed publication, placed in public use or offered for sale, a one-year countdown begins. At the end of that year, patent rights to the invention in the United States are irretrievably lost, unless a patent application has already been submitted.

The terms "printed publication", "public use" and "on sale" are, of course, the operational terms in Section 102(b), the terms whose meaning often determines whether a patent that was issued by the Patent and Trademark Office is valid or invalid. An extensive body of decisional law has grown up around those terms. For present purposes there are two significant facts about that body of case law: first, the precise meaning of each of those terms in Section 102(b) is not fixed; and second, those terms cause patent owners a great deal of concern.

The uncertain scope of the terms used in Section 102(b) leads patent owners to act cautiously when they realize that they are skirting the periphery of one of those forbidden acts. This tendency toward caution is encouraged by the fact that, in litigation, alleged infringers regularly claim that the patented invention was in use, on sale or described in a printed publication sufficiently early to destroy the validity of the patent. Pre-trial discovery on the issue can be extensive.

Moreover, the one-year "grace period" included in United States law is not found in the patent laws of all other countries. Several countries, including Italy, France, the Netherlands, Norway, Spain, Sweden and Uruguay, do not give any grace period for acts like those listed in Section 102(b), no matter where in the world those acts occur. In France, for example, no patent may be obtained if the invention "has been made available to the public by written or oral description; by use or by any other means prior to the date of filing of the patent application. . . ." French Patent Law, Article 8.

Since patent applications must be filed in every country in which patent protection is sought, the more severe foreign requirements respecting prior disclosure, use or sale often become controlling. That is, a United States company interested in obtaining worldwide patent coverage on an invention will file a patent application in at least one country before making any publication of the invention. (An international convention adhered to by most countries allows subsequent patent applications filed up to a year later in signatory countries to relate back to the filing date of that first application).

For these reasons, patent-oriented entities involved in recombinant DNA research will be uneasy about disclosing information relating to that research
prior to the date on which patent applications directed to the work are filed. Causing this uneasiness will be the possibility that a litigation opponent might allege years in the future that the disclosure constituted a publication, a public use or an offer for sale. The key fact is not the outcome of such an allegation but the present fear of the future possibility. Since a governmental regulatory program presupposes the disclosure of information about intended research before that research is undertaken and therefore well before any patent applications based on the outcome of the research are filed, the patent laws in their present embodiment are not ideally structured to mesh with a recombinant DNA regulatory program.

If in the recombinant DNA area the needs of the government regulatory function could be satisfied by an early and confidential disclosure of information, then a statute so providing should be considered. The difficulty probably lies in assuring that information submitted in confidence remains confidential throughout the regulatory process.

Time constraints force us to stop at this point. If we can be of further help in the future, please do not hesitate to contact us.

Sincerely yours,

STEPHEN D. KAHN.
ALAN D. GILLILAND.

NATURAL RESOURCES DEFENSE COUNCIL, INC., NEW YORK, N.Y.

Re regulation of recombinant DNA under existing statutory authorities.

Date: December 2, 1977.

Memorandum to: Senator Adlai E. Stevenson, Chairman, Subcommittee on Science, Technology and Space.

From: Marcia J. Cleveland, Staff Attorney, Natural Resources Defense Council, Inc.

INTRODUCTION

This memorandum reviews existing statutory authority which might be used to regulate recombinant DNA activities to determine whether they are adequate, and if not, to identify significant omissions. It discussed the Toxic Substances Control Act (TSCA; 15 U.S.C. §§ 2601, ff.); the Food, Drug and Cosmetic Act (FDCA; 21 U.S.C. §§ 301 ff.); the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA; 7 U.S.C. §§ 136 ff.); the Occupational Safety and Health Act (OSHA; 29 U.S.C. §§ 651 ff.); the Clean Air Act (CAA; 42 U.S.C. §§ 1857, ff.); the Federal Water Pollution Control Act (FWPCA; 33 U.S.C. §§ 1251, ff.); the Public Health Services Act (PHSA; 42 U.S.C. §§ 264); and the National Environmental Policy Act (NEPA; 42 U.S.C. §§ 4321, ff.).

This memorandum concludes that existing authorities are not adequate. In addition to specific gaps in each statute, they share some common shortcomings. None of the regulatory statutes (TSCA, FDCA, FIFRA, OSHA, CAA, FWPCA and PHSA) is designed to prevent environmental damage and health hazards which are as poorly understood as those posed by recombinant DNA. The premarket testing statutes (TSCA, FDCA, and FIFRA) are better designed to deal with incomplete scientific information than the pollution control statutes (OSHA, CAA, and FWPCA), but even the testing statutes are of limited value when we know so little about the hazards to be tested for that we cannot have standardized tests, like bioassays for cancer, which dependably evaluate those hazards. Only NEPA, which requires federal agencies to evaluate environmental impacts regardless of the amount of information available, can be applied to recombinant technology in spite of the present state of our knowledge. None of the statutes except NEPA requires technology assessment of recombinant DNA, and NEPA provides only partial review because it applies only to federal actions. Finally, none of the existing statutes provides adequate regulation of research activities.

AUTHORITY NECESSARY FOR EFFECTIVE REGULATION OF RECOMBINANT DNA

This evaluation of existing statutory authority is based on what the Natural Resources Defense Council believes to be essential elements of a regulatory program for recombinant DNA. Such a program must be designed to prevent release of recombinant organisms into the environment and provide a means for society
to decide whether and to what extent it wishes to develop this technology. To achieve these goals the regulatory program must:

1. Apply uniformity to all persons and institutions engaged in recombinant activities.
2. Prevent release of organisms, rather than control emissions or remedy environmental damage after it has occurred. A preventive program is essential, because the consequences of recombinant technology are largely unknown, but likely to be irreversible. Licensing which requires containment facilities and regulates work practices is the most effective form of preventive legislation.
3. Protect the environment as well as human health.
4. Provide continuing evaluation of risks as more information becomes available.
5. Provide technology assessment of proposed uses of recombinant organisms and techniques.
6. Provide public participation in all phases of regulation.
7. Require full disclosure of all recombinant DNA research, development, manufacturing and use.
8. Establish civil liability of institutions engaged in recombinant DNA activities, for injury to individuals exposed to recombinant DNA organisms.

The following discussion of statutes focuses on points 1 through 5. Points 6, 7, and 8 would each require extensive legal research which was not feasible in the time available for preparing this memorandum.

TOXIC SUBSTANCES CONTROL ACT

Although the Toxic Substances Control Act (TSCA) is one of the broadest regulatory programs available, it does not provide uniform regulation of all chemical substances. It is explicitly designed to fill in the gaps left by existing statutes. Consequently, regulation of recombinant activities under TSCA will only be meaningful if supplemented by regulation under other statutes. Even if used in combination with other statutes, TSCA would provide incomplete protection. TSCA only provides for selective testing of chemical substances; many chemicals will be marketed without any evaluation of their safety or environmental impact because there is no requirement under TSCA that every chemical substance be tested for health and environmental impacts before it is used. Any chemical substances can be marketed free of constraints unless EPA takes affirmative action. Also, it may be difficult to apply TSCA to recombinant DNA because most of the regulatory authority depends on an affirmative finding of unreasonable risk. The paucity of concrete information about risks may make it hard to support such a finding. Finally, TSCA does not provide effective regulation of research.

TSCA's strengths are that it provides a vehicle for requiring research into the hazards of recombinant organisms and can be used to require reporting and monitoring of recombinant activities by industry.

Definitions and jurisdiction: Section 3

The regulatory sections of TSCA (§§ 4–8) apply to chemical substances which are manufactured, distributed in commerce, processed or disposed of. A chemical substance is defined as: “any organic or inorganic substance of a particular molecular structure.”

Substances subject to the Food, Drug and Cosmetic Act (FDCA) or the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) are excluded from this definition. Manufacture means “import, . . . produce, or manufacture.” Commerce includes any trade or transportation of a chemical substance. Consequently, TSCA gives EPA jurisdiction over recombinant DNA molecules, any protein or enzyme produced by a recombinant organism as well as restriction enzymes and vectors used in recombinant technology. It also provides jurisdiction over all activities from research through use.

Notice of new chemicals, inventory of existing chemicals: Sections 5(a) (b) (c) (d), (h) (i), 8(a) (b)

The notice, reporting and inventory provisions of TSCA are central to its effectiveness. Unless EPA knows the chemicals it may have to regulate it cannot protect the public from their hazards. Under these requirements, the manufacturer of a chemical substance is required to report its identity, intended uses and whatever is known about its toxicity and environmental impacts. However, re-
searchers are not required to give notice of new substances and small businesses may not be required to report on existing substances. Non-commercial institutions, such as universities, are exempt from both requirements.

**Testing orders: Section 4**

If EPA concludes that a chemical substance "may present an unreasonable risk of injury to health or the environment" or "may reasonably be expected to enter the environment in substantial quantities or . . . there is or may be significant or substantial human exposure," it can issue an order requiring testing. The terms "unreasonable risk," "substantial quantities," "significant exposure" are not defined precisely in the statute. However, the legislative history indicates that the Administrator is to have broad authority to issue testing orders and that he will necessarily have to act on incomplete information about risks. Given the breadth of the authority under this section, the Administrator would be able to require research into the hazards of recombinant DNA. If such research involves the use of recombinant techniques, the Administrator could use his authority to set testing protocols and require that strict safety procedures be followed.

**Interim regulation: Section 5**

EPA has the authority to regulate toxic substances while testing is being conducted, but this authority does not apply to persons and institutions exempt from the notice requirements of § 5. This means that TSCA does not authorize any interim regulation of research or non-commercial institutions since they are not subject to the notice requirements.

**Permanent regulation under Section 6**

Once EPA finds that a chemical substance "will present an unreasonable risk of injury to health or the environment," it can issue a wide variety of orders to prevent that harm. However, the "will present" standard may require more information about the risks of recombinant DNA than is now available and therefore may not allow preventive regulations until far more is known about the consequences of recombinant technology. Also it is not clear that EPA could establish a facilities licensing system or regulate work practices under § 6. However, § 6 can be applied to research and non-commercial activities.

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**THE FOOD, DRUG AND COSMETIC ACT**

The regulatory system of the Food, Drug and Cosmetic Act is based on pre-marketing approval—i.e. the requirement that a manufacturer demonstrate the safety of his product before it is marketed. Although this is one of the most powerful regulatory tools for protecting human health, it provides only incomplete protection against the hazards of recombinant DNA. First, the FDCA is only designed to protect human and animal health, not the environment. Second, its regulatory provisions apply only at the point that a product is marketed or after: non-commercial activities are not covered at all. Third, only a limited number of products—food additives, color additives, new drugs, new animal drugs, devices and pesticide residues—are subject to premarketing approval. Other substances covered by the act—food, environmental contaminants or other impurities in food and cosmetics—can only be regulated after the fact, if FDA has evidence that they are unsafe. Finally, the FDCA provides no technology assessment. If a product meets the safety and efficacy requirements of the Act, it must be approved regardless of whether risks outweigh benefits or alternatives are available.

**Jurisdiction over recombinant organisms or products: Sections 201, 301, 402, 501, 601**

The FDCA prohibits the sale in interstate commerce of any adulterated food, drug, device or cosmetic (§ 301(a)). Food is considered adulterated if it "bears or contains any poisonous or deleterious substance which may render it injurious to health" or contains an additive, or residue which does not comply with premarketing approval requirements or tolerances (§ 402). Similarly, drugs and devices are adulterated if they are "injurious to health" or have not complied with approval and quality control requirements or contain unapproved color additives. Cosmetics are adulterated if they contain any "poisonous or deleterious substances" or are not manufactured according to quality control requirements. If recombinant organisms or recombinant DNA molecules themselves are ever used as food, drugs or cosmetics, they could be prohibited under the Act if they
posed a health risk to humans. If as is more likely, recombinant organisms are used to produce food or drugs, these products could be regulated to assure that no harmful, or avoidable residues of recombinant organisms, or DNA molecules, are left in the product.

Premarket approval and pesticide tolerances: Sections 408, 409, 505, 512, 515, 706(a)

All of the premarket approval sections of the Act require the manufacturer to prove the safety and effectiveness of his product and assign him the burden of developing safety and efficacy data. However, these provisions suffer from the same weakness as testing orders under TSCA; the risks of recombinant organisms do not lend themselves to standardized testing for risks. A manufacturer may conduct enough safety tests to satisfy the FDCA, and not uncover a significant hazard because we do not know how to look for hazards. These premarketing approval sections will also have the effect of requiring complete reporting of products made with recombinant techniques, but this reporting will occur too late to permit any effective technology assessment.

Nonpremarketing approval sections: Sections 401, 406, 601

The sections of the FDCA which do not require premarketing approval and safety testing provide virtually no protection against the hazards of recombinant technology. These provisions leave FDA with the burden of showing that a recombinant organism which contaminates a food or cosmetic is injurious to health or avoidable. Both of these requirements will be difficult to meet with our limited knowledge of risks.

Good manufacturing practices, registration of producers of drugs and devices, batch certification of insulin and antibiotics: Sections 505, 506, 507, 510, 512, 515

The FDCA has several provisions which require a drug or device producer to follow good manufacturing practices (GMP's) to insure that the purity of drugs is maintained. These GMP's are specified by regulation and are enforced by a requirement that producers register each facility where drugs and devices are produced. Registered facilities are subject to regular inspection and are required to report regularly which drugs are being produced at that facility. Insulin and antibiotics are subjected to the additional requirement that each batch be certified by FDA to insure that it meets the purity standards established for these drugs. The GMP, registration, reporting and certification provisions of the FDCA provide only limited regulation of recombinant technology, but they may provide a useful model for licensing recombinant research and production facilities.

FEDERAL INSECTICIDE, FUNGICIDE AND RODENTICIDE ACT

FIFRA establishes a regulatory structure very similar to the FDCA. It requires premarketing approval of pesticides, registration of facilities which produce pesticides, and in addition requires certification of users of pesticides. However, FIFRA differs from the FDCA in that approval of a pesticide includes consideration of environmental costs. A pesticide can only be approved if its use "will not generally cause unreasonable adverse effects on the environment." Although this standard provides for cost/benefit balancing, it does not provide the kind of technology assessment necessary for recombinant DNA. The Administrator is not required to consider alternatives to a given pesticide and is specifically prohibited from refusing registration because a pesticide is not essential.

FIFRA would cover any use of recombinant technology for pest control or to promote or regulate the growth of plants. Any micro-organism which imparted nitrogen fixing abilities to plants which do not now have that ability would be covered. However, FIFRA suffers from the same weaknesses as FDCA. It does not regulate research and development, or non-commercial activities, and it presumes that studies can be conducted by an applicant for registration which accurately assess the hazards.

OCCUPATIONAL SAFETY AND HEALTH ACT

OSTIA establishes national standards for substances which pose a health hazard to employees and requires all employers to comply with those standards
and provide their employees a place of employment “free from recognized hazards that are causing or are likely to cause death or serious physical harm to his employees.” States can administer the Act within their borders, as long as they have approved programs at least as strict as the federal program. The principal limitation of OSHA is that it only protects employee health, the health of the general public and the environment are not within scope of the Act and employees of states which do not administer their own OSHA programs are exempt from the Act. This means that researchers at some state universities cannot be covered by OSHA standards. Also, OSHA is designed to apply to health hazards, for which information is already available. Unlike the premarket testing statutes, it is not designed to compel research on hazards which are either unknown or poorly understood. Finally, OSHA contains no provisions for technology assessment. Indeed, it requires that standards promulgated under the Act be feasible. This feasibility requirement presumes that at some point the health of workers may be compromised to insure the continued availability of their products. This kind of compromise should not be available in the regulation of recombinant DNA.

One feature of OSHA is sound and should be incorporated into any regulatory program for recombinant DNA. Standards promulgated under OSHA can require an employer to install control technology, modify work practices and give his employees protective clothing and equipment, changing rooms, showers and lunch rooms. OSHA is the only statute which provides for control of workplace design and work practices.

THE CLEAN AIR ACT AND THE FEDERAL WATER POLLUTION CONTROL ACT

These two acts are primarily designed to remedy existing pollution problems. They establish national standards, which define maximum ambient levels for pollutants and limit discharges from each source. These standards are achieved either by federal enforcement programs or by state programs pursuant to approved plans. Although both these statutes provide comprehensive regulatory programs, they are poorly suited to regulating recombinant DNA. They are designed to regulate pollutants, the health and environmental impacts of which are relatively well understood, rather than a technology the consequences of which are largely unknown. Both the air and water acts place limitations on the discharge of pollutants based on the control technology which is either available or can be developed. They are not designed to completely prevent discharge as is necessary with recombinant DNA. Unlike OSHA they do not regulate work practices, but rather focus on controlling emissions.

THE PUBLIC HEALTH SERVICES ACT

§ 361 of the Public Health Services Act gives the Secretary of Health, Education and Welfare broad discretion to regulate recombinant DNA technology to protect human health. It empowers the 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 State or possession into any other State or possession...”

It further provides that: “for purposes of carrying out and enforcing such regulations, the [Secretary] may provide for such inspection, ... disinfection ... and other measures, as in his judgment may be necessary.”

The problem with the PHSA is that it does not explicitly provide for protection of the environment. In other regulations under this section a communicable disease is defined as “an illness due to an infectious agent or its toxic product ...” transmitted by persons, animals, plants or the inanimate environment. (42 C.F.R. §§ 71.1 (b), 72.1(b)). Another weakness of § 361 is that it leaves the regulatory structure for enforcement to the discretion of the Secretary.

THE NATIONAL ENVIRONMENTAL POLICY ACT

NEPA is the only federal statute that provides for technology assessment. NEPA requires all federal agencies to consider the impact their activities will have on the environment and the alternatives to a proposed action. But even NEPA does not require that nonessential technology be avoided or that the environmentally least damaging alternative must be chosen. Furthermore, NEPA
only applies to recombinant activities regulated or funded by the federal government. Because the federal government’s authority to reach private recombinant activities is limited, the value of NEPA as a vehicle for evaluating the consequences of recombinant technology is also limited.

THE LIBRARY OF CONGRESS,
CONGRESSIONAL RESEARCH SERVICE,

To: Senate Committee on Commerce, Science, and Transportation, Subcommittee on Science, Technology, and Space.

From: American Law Division.

Subject: Regulation Under Current Law of the Products of Recombinant DNA Research.

In response to your request for a determination as to whether products of recombinant DNA research may be regulated under current federal statutes, we have analyzed the following laws:

1. The Patent Laws (Title 35);
2. Toxic Substances Control Act (15 U.S.C. 2601 et seq.);
4. Federal Water Pollution Control Act (33 U.S.C. 1251 et seq.);
5. Solid Waste Disposal Act (42 U.S.C. 3251 et seq.);
8. Occupational Safety and Health Act (29 U.S.C. 631 et seq.);
10. Public Health Service Act (42 U.S.C. 201 et seq.);

In brief, comprehensive regulation of the products resulting from recombinant DNA research techniques does not appear feasible under current laws. At best, regulation will be piecemeal and dependent on the uses for which those products are intended. Regulation will be dispersed throughout several federal agencies, where the research activities involved come under the respective department or agency mandate and it will be limited by the purposes enumerated in the appropriate authorizing legislation.

There has been very recent, rather curious development that could have far-reaching effects in the realm of genetic experimentation. In an October decision, the United States Court of Customs and Patent Appeals, as a matter of first impression, held that a biologically pure culture of a micro-organism, that apparently did not exist as a biologically pure culture naturally, was a “manufacture” within the meaning of the patent statutes. Thus, the fact that the claimed invention was alive did not remove it from the category of patentable things. Two judges dissented from the court’s decision and whether the decision will stand upon appeal is a matter of speculation. If it should, then the patent laws may offer the most wide-reaching means of regulating the uses to which DNA research products may be put. See, Application of Bergy, U.S. Court of Customs and Patent Appeals, October 6, 1977.

The Constitution confers upon Congress the power to secure authors and inventors, for periods of limited duration, the exclusive right to their writings and discoveries. This power is implemented by legislation which vests an inventor with the right to exclusive use of his invention provided he has perfected his right by proceeding in the manner required by law. (The patent laws may be found in Title 35 of the U. S. Code.)

Ultimately, the decision as to whether new life forms may be patented is a matter for Congress. The Constitution does not spell out the subject matters which are proper ones for patent protection. The exercise of the patent power is a permissive one and Congress may restrict or enlarge the granting of patent rights by specifying categories of discoveries or inventions appropriate for patent protection. In Application of Bergy the court found a new genetic composition to fall within the statutorily recognized category of “manufacture” or an “article of manufacture.” While new life forms have not been treated as patentable hereto-
fore, the Supreme Court has simply stated that "to obtain a patent for a product made from raw material, it must possess a new or distinctive form, quality, or property." American Fruit Growers, Inc. v. Brodax Co., 283 U.S. 1, 8 U.S.P.Q. 131 (1931). (A thorough discussion of the patent laws is outside the scope of this paper, but for a very good introduction to patent law, see, Peter D. Rosenberg, Patent Law Fundamentals (New York, 1975).)

Generally speaking, as the law now stands, regulation of scientific research or its products must be predicated on some legitimate governmental interest such as receipt of federal funding or on a federal power such as Congress's power to regulate interstate commerce. Although legislation may bring within its regulatory ambit all persons engaged in an activity which affects commerce (see, e.g. OSHA, 29 U.S.C. 652 (5)), it is doubtful whether such regulatory authority would extend to private recombinant DNA research conducted by a private individual with very few, if any, research associates in a small, local facility. On the other hand, there is no doubt that DNA research may be regulated to some extent (and probably insofar as use of its products are concerned) in research facilities receiving federal funds. Should the patent laws be construed as encompassing the products of genetic research, then federal regulation of DNA research could be predicated on still another federal power.

The Toxic Substances Control Act, effective since October 1976, gives authority to the Environmental Protection Agency (EPA) to ban or restrict the manufacture, processing, distribution, commercial use or disposal of chemical substances and mixtures which will present "an unreasonable risk of injury to health or the environment." 15 U.S.C. 2601. Of the laws we have analyzed, this Act presently has the greatest potential for regulation of DNA research products. Initially however, to be subject to the Act a "processor" of chemical substances or mixtures must be involved in an activity which affects interstate trade, traffic or transportation. 15 U.S.C. 2602 (3) (4). As noted previously, the private, independent researcher conducting an entirely local research activity may not be within the Act's regulatory scope.

Providing this threshold condition is met the Act applies, where there is an unreasonable risk, to the production of a "chemical substance." i.e. "any organic or inorganic substance of a particular identity" which occurs in nature or as a result of a chemical reaction. Any combination of chemical substances which does not occur in nature or as the result of a chemical reaction, i.e. a "mixture," is also subject to the regulatory provisions of the Act provided that "there is a reasonable basis to conclude" that the activity "presents or will present an unreasonable risk of injury to health or the environment." 15 U.S.C. 2605(a). Thus, the EPA may not restrict or ban such chemical substances or mixtures unless the risk is unreasonable. In making that determination the Administrator of the EPA must consider and publish a statement, with respect to the effects and magnitude of the exposure of the substance or mixture, the benefits of its uses and the availability of substitutes and "the reasonably ascertainable economic consequences of the rule, after consideration of the effect on the national economy, small business, technological innovation, the environment, and public health." 15 U.S.C. 2605(c) (1) (A) -(D).

Three key provisions serve to effectuate the EPA's regulatory authority under the Act and are potential methods of regulating DNA products somehow involved in or affecting interstate commerce. First, EPA may require the testing of any chemical substance or mixture if there is potential for an unreasonable risk of injury. 15 U.S.C. 2603 (a) (1) (A) (i). The Senate Conference Report indicates that testing may be required whenever "there is a basis for concern." S. Rept. 94-1302, 94th Cong., 2d Sess., at 61. Furthermore, testing may be required if there is insufficient data on which to base a prediction as to the dangers of such substances. 15 U.S.C. 2603 (a) (1) (A) (ii) (iii).

The Act also provides for a pre-market review mechanism. Notice to EPA is required prior to the manufacture or processing of any "new chemical substance," but such notice is not required for "mixtures" unless the mixture contains a new chemical substance or is a "significant new use" of an existing chemical substance. 15 U.S.C. 2604 (A mixture is a combination of chemical substances where the combination does not occur in nature or does not result from a chemical reaction.) Nor does the pre-market notification requirement apply to the production of "small quantities" of chemicals to be used solely for research and development, though persons working with such chemicals must be notified of any risks to their health. 15 U.S.C. 2604(h) (3). Furthermore, to come under the provisions,
the manufacture or processing of chemical substances must be “for commercial purposes.” 15 U.S.C. 2604 (i).

The most far-reaching of EPA’s regulatory powers under the Act is its authority to require maintenance of records and submission of reports by processors and manufacturers. 15 U.S.C. 2607. “Small manufacturers and processors” are not covered by this requirement, however other persons who manufacture or process small quantities of mixtures or chemical substances “solely for purposes of scientific experimentation or analysis, etc.” must submit reports as the Administrator determines to be necessary. Again, this activity, to be regulated, must affect commerce.

The Act indicates a preference for use of applicable laws other than the Toxic Substances Control Act to regulate chemical hazards where it is possible. 15 U.S.C. 2608 (a) (b). It also requires the Administrator of EPA to cooperate with any other federal agency to achieve maximum enforcement of the Act. Thus, other agencies that regulate chemical hazards, such as the Department of Transportation (transport of hazardous materials), the Consumer Product Safety Commission (safety of consumer products), and the Department of Labor (OSHA), must consult with and coordinate their regulatory efforts with those of the EPA. Where the actions taken by the other agencies or by the Administrator of EPA under other laws provide insufficient protection, then the EPA may have authority to require additional protective measures. More specifically, if the Administrator determines that the risk “may be prevented or reduced to a sufficient extent” by another agency’s action, then he must submit a report outlining those risks to the other agency. If the agency determines such a risk does not exist, or it initiates its own action, then EPA is precluded from further action. 15 U.S.C. 2608 (a). If, on the other hand, the risks come under laws also administered by EPA such as the Federal Water Pollution Control Act, the Marine Protection, Research, and Sanctuaries Act, the Clean Air Act, the Safe Drinking Water Act, or the Solid Waste Disposal Act, the Administrator may proceed under the Toxic Substances Control Act if he determines that to do so is “in the public interest.” That is true even if the “risk could be eliminated or reduced to a sufficient extent by actions taken under” the other law. 15 U.S.C. 2608 (b). (For a more detailed analysis of the Act and discussion of some additional provisions, see Robert F. Zener, “The Toxic Substances Control Act: Federal Regulation of Commercial Chemicals,” 32 The Business Lawyer 1685 (July 1977).)

Other federal laws administered by the EPA offer potential authority for limited regulation of DNA research products. Under the Marine Protection, Research and Sanctuaries Act, 33 U.S.C. 1401 et seq., EPA prohibits (or strictly limits) the dumping into ocean waters of “any material which would adversely affect human health, welfare, or amenities, or the marine environment, ecological system, or economic potentialities.” 33 U.S.C. 1401 (b). The definition of “material” includes “matter of any kind or description, including radiological, chemical, and biological warfare agents, radioactive materials, chemicals, biological and laboratory waste, etc.” 33 U.S.C. 1402 (c). The Act appears sufficiently broad to encompass disposal of DNA research products. Unless EPA has issued a permit (after notice and opportunity for a public hearing) specifying sites and times, etc., then ocean dumping of dangerous materials as defined by the Act is prohibited. Violations of the Act are punishable by civil penalties and/or criminal fines. 33 U.S.C. 1415 (a) (b).

The Federal Water Pollution Control Act, 33 U.S.C. 1251 et seq., while of limited applicability in the regulation of DNA products, prohibits the discharge into navigable waters of pollutants (including toxic pollutants). 33 U.S.C. 1251 (a) (1) (3). Potentially, if a DNA research product should be classified by EPA as a pollutant, the Administrator has authority to restrict and control or prohibit its discharge into the Nation’s waters in order “to restore and maintain the chemical, physical, and biological integrity of the Nation’s waters.” 33 U.S.C. 1251 (a).

The Solid Waste Disposal Act, 42 U.S.C. 3251 et seq., administered by EPA, may also be of limited utility in attempts to regulate use and disposition of DNA products. In response to a Congressional finding “that inefficient and improper methods of disposal of solid wastes results in scenic blights, create serious hazards to the public health, including pollution of air and water resources, accident hazards, etc.,” one of the purposes of the Act is “to provide for the promulgation of guidelines for solid waste collection, transport, separation, recovery and disposal systems.” 42 U.S.C. 3251 (a) (4), (b) (4). Solid waste is defined to include “garbage, refuse, and other discarded solid materials, including
solid waste materials resulting from industrial, commercial, and agricultural operations." 42 U.S.C. 3552(4).

The Federal Hazardous Substances Act, 15 U.S.C. 1261 et seq. gives the Consumer Product Safety Commission authority to regulate labeling and interstate transportation of hazardous and toxic substances intended for household use. The household use condition undoubtedly limits the Act's applicability in the DNA research situation. If the hazardous substance is intended by the manufacturer or producer to be used for non-household commercial or industrial purposes, and is packaged and distributed for non-commercial purposes, it is outside the Act's jurisdiction unless it is actually diverted for household use. Consumer Product Safety Commission Advisory Opinion No. 136 (October 9, 1974). Thus, while the definition of hazardous substance includes any toxic substance "(other than a radioactive substance) which has the capacity to produce personal injury or illness to man through ingestion, inhalation, or absorption through any body surface," to be banned under the Act the substance must be "intended or packaged for use in the household." 15 U.S.C. 1261 (g), (q) (1).

Under the Hazardous Materials Transportation Control Act, 18 U.S.C. 834 et seq., the Department of Transportation has regulatory authority over the interstate transport of explosives, radioactive materials, etiologic agents, and other dangerous articles. The Department is entrusted with formulating regulations, which may be changed on its own motion or upon application by any interested party, for the safe transportation of all listed hazardous materials. A wide-ranging list of materials presently subject to the Act's requirement may be found at 49 C.F.R. Part 17. While the authority of the Department of Transportation does not go to direct regulation of the uses to which DNA products may be put, it may be used to limit and control the extent and manner of dissemination of those products by vehicles which are operated on land by "any for-hire carrier engaged in interstate or foreign commerce." 18 U.S.C. 832(a). Again, as under many federal laws, the non-commercial, independent researcher conducting a private, local experimental facility may not come within the scope of the Act so long as he does not engage commercial vehicles to transport materials he uses or produces.

With respect to the Occupational Safety and Health Act (OSHA), 29 U.S.C. 651 et seq., the Congress expressed, as the basic purpose of the Act, to assure "so far as possible every working man and woman in the Nation safe and healthful working conditions" and provided for the Secretary of Labor to promulgate standards for places and conditions of employment which are free from "recognized hazards." 29 U.S.C. 654. However, the Act specifically excludes State or political subdivision of a State from the definition of employer and while the Act brings within its orbit all employers engaged in a business which affects commerce, it is questionable, here, as under other federal laws, whether OSHA's regulatory authority extends to private recombinant DNA research conducted by an individual with a few employees in a small, local laboratory.

In Dekle v. Todd, a state court held that OSHA did not apply with respect to a two man farm roof repair job, 207 S.E. 654 (Ga. App. 1974). However, a federal court of appeals did apply the Act to a local building service maintenance supply company which supplied services to businesses engaged in interstate commerce, Brennan v. Occupational Safety and Health Review Commission, 492 F. 2d 1027 (1974). Thus, OSHA may very well be applicable to recombinant DNA research, generally, so long as there is at least a minimal contact with interstate commerce. It is also probable that the Act will not be applicable to a private researcher conducting experimentation in a small, local research facility, even if he does have a few employees. The Act certainly will not apply absent an employer-employee relationship.

Another aspect of the Act limits its potential utility for regulation of DNA products. Under OSHA, the authority of the Secretary of Labor is limited to recognized hazards and to the working environment. The courts have recognized that protection of the workplace under OSHA extends to those hazards which are identifiable by technical instruments. For instance, a federal court has upheld the use of air sampling pumps to collect contaminants in the air that an employee would normally breathe and the Commission's consequent order that action be taken to reduce the contaminant. American Smelting and Refining Company v. Occupational Safety and Health Review Commission, 501 F. 2d 504 (1974). However, the contaminant in that case was airborne concentrations of lead and the regulatory requirements were based on a recognized national standard for airborne lead. Thus, American Smelting supports the concept that
the regulatory authority of the Secretary of Labor under OSHA extends to airborne contaminants known to be dangerous, but whether OSHA's authority extends to unquantifiable and speculative dangers is certainly questionable. Another federal court relied on the legislative history of the Act in determining that a recognized hazard is one which is known to safety experts in the industry:

An activity may be a “recognized hazard” even if the defendant employer is ignorant of the activity’s existence or its potential for harm. The term received a concise definition in a floor speech by Representative Daniels when he proposed an amendment which became the present version of the general duty clause: “A recognized hazard is a condition that is known to be hazardous, and is known not necessarily by each and every individual employer but is known taking into account the standard of knowledge in the industry. In other words, whether or not a hazard is ‘recognized’ is a matter for objective determination; it does not depend on whether the particular employer is aware of it.” 116 Cong. Rec. (Part 28) 3877 (1970). The standard would be the common knowledge of safety experts who are familiar with the circumstances of the industry or activity in question—National Realty and Construction Company, Inc. 489 F. 2d 1257 (D.C. Cir. 1973).

It is dubious as to whether a court would uphold authority of the Secretary to promulgate and enforce standards for unknown dangers or hazards so as to prevent the inadvertent escape of an organism with a combination of unknown genetic characteristics. No specific authority was found to support the concept that the Secretary of Labor has authority to issue and enforce standards which would provide protection beyond the immediate working environment, or which would regulate, control, limit or possibly prohibit DNA research or use of its products. Under OSHA, it appears that the authority of the Secretary would be limited to the regulation of working conditions and the environment of employees engaged in such research where there is some relationship to commerce and then that such regulations could extend only to known or recognized hazards.

Presently, the National Environmental Policy Act (NEPA), 42 U.S.C. 4331 et seq., may in effect, have the most far reaching applicability to the initiation and monitoring of DNA experiments. While the Act only requires environmental impact statements (EIS) for federal projects and work conducted with federal grants or loans (40 C.F.R. 1500.5(a) (2)) the requirement does apply to any major federal project with the potential to significantly affect the environment. (40 C.F.R. 1500.6(a)). Currently all National Institutes of Health sponsored DNA research projects are required to submit an EIS assessing:

(i) the environmental impact of the proposed action,
(ii) any adverse environmental effects which cannot be avoided should the proposal be implemented,
(iii) alternatives to the proposed action,
(iv) the relationship between local short-term uses of man’s environment and the maintenance and enhancement of long-term productivity, and
(v) any irreversible and irretrievable commitments of resources which would be involved in the proposed action should it be implemented. 42 U.S.C. 4332(2) (C) (i) – (v).

In addition, the regulations require submission of a draft EIS for comment and review by the Council on Environmental Quality (CEQ) and other outside reviewers (including other agencies). While the preparation of an EIS is generally a pro forma exercise and review is usually cursory, the regulations do provide a basis for careful and meaningful monitoring of the proposed activity. To further assure safety of NIH funded DNA experiments, where there appear fundamental risks, the CEQ has authority to issue supplemental guidelines for EIS preparation as are necessary, 40 C.F.R. 1500.14.

Currently, according to a recent newspaper report, virtually all DNA research, some $10 million worth this year, is NIH funded. The Washington Post, Friday, November 18, 1977, p. A-8. Thus, the regulatory potential under NEPA may be one of the most comprehensive means of monitoring, indirectly, the uses to which DNA products are put.

The Public Health Service Act, 42 U.S.C. 264, provides for the promulgation of regulations to prevent the introduction, transmission, or spread of communicable diseases from abroad or from one State into another. Under the Act, the Secretary of Health, Education and Welfare (HEW) is authorized to provide for “such inspection, fumigation, disinfection, sanitation . . . destruction of animals or articles found to be so infected or contaminated as to be sources of dangerous
infection to human beings." 42 U.S.C. 264(a). There are limitations, however, with respect to detention of persons who are believed to be infected with a communicable disease. 42 U.S.C. 264(b) (c) (d). These limitations, apparently, do not apply to articles.

The appropriate HEW regulations, insofar as regulation of DNA products are concerned, control the interstate transportation of "biologic products" and "etio-
logic agents." The applicable definitional sections are reprinted here for your convenience:

SUBPART C—SHIPMENT OF CERTAIN THINGS

§ 72.25 Etiologic agents.1

(a) Definitions. As used in this section:

(1) An "etio-
logic agent" means a viable microorganism or its toxin which causes, or may cause, human disease.

(2) A "diagnostic specimen" means any human or animal material including, but not limited to, excreta, secreta, blood and its components, tissues, and tissue fluids being shipped for purposes of diagnosis.

(3) A "biological product" means a biological product prepared and manufactured in accordance with the provisions of 9 CFR Part 10, Licensed Veterinary Biological Products, 42 CFR Part 73, Licensed Human Biological Products, 21 CFR 130.3, New drugs for investigational use in humans, 9 CFR Part 103, Biological Products for Experimental Treatment of Animals, or 21 CFR 130.3(a), New drugs for investigational use in animals, and which, in accordance with such provisions, may be shipped in interstate traffic.

(b) Transportation; etiologic agent minimum packaging requirements. No person may knowingly transport or cause to be transported in interstate traffic, directly or indirectly any material, including but not limited to, diagnostic specimens and biological products, containing, or reasonably believed by such person to contain, an etiologic agent unless such material is packaged to withstand leakage of contents, shocks, pressure changes, and other conditions incident to ordinary handling in transportation.

(c) Transportation; etiologic agents subject to additional requirements. No person may knowingly transport or cause to be transported in interstate traffic, directly or indirectly, any material, other than diagnostic specimens and biological products, containing, or reasonably believed by such person to contain, one or more of the following etiologic agents unless such material is packaged in accordance with the requirements specified in paragraph (b) of this section, and unless, in addition, such material is packaged and shipped in accordance with the requirements specified in subparagraphs (1)–(6) of this paragraph:

BACTERIAL AGENTS

Actinobacillus—all species.
Arizona hinshawii—all serotypes.
Bacillus anthracis.
Bartonella—all species.
Bordetella—all species.
Borrelia recurrentis, B. vincti.
Brucella—all species.
Clostridium botulinum, Cl. chauvoei, Cl. haemolyticum, Cl. histolyticum, Cl. novyi, Cl. septicum, Ct. tetani.
Corynebacterium diphtheriae C, equi, Cl. haemolyticum, C. pseudotuberculosis, C. pyogenes, C. renale.
Diplococcus (Streptococcus) pneumoniae.
Erysipelothrix insidiosa.
Escherichia colli, all enteropathogenic serotypes.
Francisella (Pasteurella) tularensis.
Haemophilus ducreyi, H. influenzae.
Hericella vaginicola.
Klebsiella—all species and all serotypes.
Leptospira interrogans—all serotypes.
Listeria—all species.

1 The requirements of this section are in addition to and not in lieu of any other packaging or other requirements for the transportation of etiologic agents in interstate traffic prescribed by the Department of Transportation and other agencies of the Federal Government.
Mima polymorpha.
Moraxella—all species.
Mycobacterium—all species.
Mycoplasma—all species.
Ncisseria gonorrhoeae, N. meningitidis.
Pasteurella—all species.
Pseudomonas pseudomallei.
Salmonella—all species and all serotypes.
Shigella—all species and all serotypes.
Sphaerophorus auriculatus.
Sphingobacterium monteiliformis.
Streptococcus pyogenes.
Treponema pallidum, and T. pertenue.
Vibrio fetus, V. comma, including biotype El Tor, and V. parahemolyticus.
Yersenia (Pasteurella) pestis.

**Fungal Agents**

Actinomyces (including Nocardia species, Actinomyces species and Arachnia propionica).
Blastomyces dermatitidis.
Coccidioides immitis.
Cryptococcus neoformans.
Histoplasma capsulatum.
Paracoccidioides brasiliensis.

**Viral, Rickettsial, and Chlamydial Agents**

Adenoviruses—human—all types.
Arboviruses.
Coxiella burnetii.
Coxsackie A and B viruses—all types.
Cytomegaloviruses.
Dengue virus.
Echoviruses—all types.
Encephalomyocarditis virus.
Hemorrhagic fever agents, including Crimean hemorrhagic fever (Congo), Junin, and Machupo viruses, and others as yet undefined.
Hepatitis-associated antigen.
Herpesvirus—all members.
Infectious bronchitis-like virus.
Influenza viruses—all types.
Lassa virus.
Lymphocytic choriomeningitis virus.
Marburg virus.
Mawes virus.
Mumps virus.
Parainfluenza viruses—all types.
Polioviruses—all types.
Poxviruses—all members.
Psittacosis-Ornithosis-Trachoma-Lymphogranuloma group of agents.
Rabies virus—all strains.
Reoviruses—all types.
Respiratory syncytial virus.
Rhinoviruses—all types.
Rickettsia—all species.
Rubella virus.
Simian viruses—all types.
Tick-borne encephalitis virus complex, including Russian spring-summer encephalitis, Kyasanur forest disease, Omsk hemorrhagic fever, and Central European encephalitis viruses.
Vaccinia virus.
Varicella virus.
Variola major and Variola minor viruses.
Vesicular stomatitis virus.
Yellow fever virus.
Again, however, these quarantine sections relate only to the shipment of products rather than the uses to which they are put. It is suggested that even if that requirement is met, the Secretary of HEW has no authority to regulate DNA products until they have already been determined to be a "source of dangerous infection to human beings."

The Federal Food, Drug and Cosmetic Act, 21 U.S.C. 301 et seq., provides authority for regulation of the manufacture and interstate transportation of drugs and new drugs. Drug means (among other things) "articles (other than food) intended to affect the structure or any function of the body of man or other animals." 21 U.S.C. 321 (g) (1) (c). The definition also includes "any material used as a component of such a drug," such as component raw materials. United States v. Dianovin Pharmaceutical, Inc., 475 F.2d 100 (1973), cert. den. 424 U.S. 830. Provided that products of DNA research are intended for use as a drug product or as a component thereof, and will be introduced into interstate commerce, then they will be subject to the Act's requirements.

The Consumer Product Safety Act, 15 U.S.C. 2051 et seq., is unlikely to have any utility in the regulation of either DNA research or its resulting products. A consumer product must be just that, one intended "for sale to a customer for use in... a residence, a school, in recreation... or (ii) for personal use, consumption, or enjoyment of a consumer" under the same circumstances. 15 U.S.C. 2052(1). Thus, before any DNA research product is likely to be subject to the provisions of this Act, it very probably will have had to meet more stringent requirements under one or more of the other Acts described in this report.

To conclude, our review of the statutes discussed above suggests that one or more questions need to be asked to determine if the particular DNA research activity, and its products, are subject to regulation under current federal law. One of two threshold requirements must be met in order for the activity to be subject to any of the laws:

(1) Is the activity federally funded?
(2) Does the activity bear any relationship to interstate or foreign commerce? or is it an entirely private, local endeavor? Do the end products, or components thereof, enter commerce or affect commerce?

Some other, more specific, questions are:
(3) Is the research activity being conducted with a specific identifiable purpose? For what are its products intended?
(4) Does the activity present an "unreasonable risk?"

Even where the research is determined to be subject to one or more federal laws, it will be dependent on the specific nature of the activity involved. Current law, as we indicated at the outset of this report, does not provide for comprehensive regulation of DNA products. If this is to be accomplished additional legislation is necessary.

We hope the information provided is helpful. Should you require additional information or materials please feel free to contact us.

**Donna C. Parratt, Legislative Attorney.**