Appendix F

Recombinant DNA Research Guidelines, Environmental Laws, and Regulation of Worker Health and Safety

Chapter 15: Health, Safety, and Environmental Regulation discussed the regulatory policies of the United States, the Federal Republic of Germany, the United Kingdom, France, Switzerland, and Japan as they pertain to biotechnology. This appendix elaborates on the material presented in that chapter.

Recombinant DNA research Guidelines

UNITED STATES

The National Institutes of Health "Guidelines for Research Involving Recombinant DNA Molecules" (NIH Guidelines) apply to all research involving recombinant DNA (rDNA) in the United States or its territories conducted at or sponsored by any institution receiving support for rDNA research from NIH (28). All Federal agencies require their own scientists to comply with the guidelines, and Federal agencies other than NIH funding rDNA research also require their grantees to comply. Compliance is enforced by the authority of the agency to suspend, terminate, or place restrictions upon its financing of the offending projector all rDNA projects at the institution receiving support.

Although the NIH Guidelines are not legally binding on private companies (unless the company receives Federal funds), the private sector has espoused voluntary compliance. Some States and localities have required industry to comply by law.

Administrative Framework.—The NIH Guidelines create an administrative framework for oversight that specifies the responsibilities of scientists, their institutions, and the Federal Government. The primary responsibility for ensuring compliance lies with the institutions and scientists doing the research. The institution must establish an Institutional Biosafety Committee (IBC) meeting certain requirements, appoint a biological safety officer if certain experiments are done, ensure appropriate training, and implement health surveillance, if appropriate. The principal investigator has the initial responsibility for determining and implementing containment and other safeguards and for training and supervising the staff.

The IBC oversees all rDNA work at the institution for compliance with the NIH Guidelines. The IBC must consist of at least five members who collectively have the expertise to assess the safety of rDNA experiments. TWO members must be otherwise unaffiliated with the institution and must represent the community's interest with respect to health and the environment. Institutions are encouraged to open IBC meetings to the public, and minutes of IBC meetings and certain other documents must be made available to the public on request. The institution must register the IBC with NIH by providing information about its members.

At the Federal level, the responsible parties are the Director of NIH, the NIH Recombinant DNA Advisory Committee (MC), the NIH Office of Recombinant DNA Activities, and the Federal Interagency Advisory Committee on Recombinant DNA Research (Interagency Advisory Committee). The Director of NIH is the final decisionmaker under the guidelines. For major actions, he or she must seek the advice of the RAC and must provide the public and other Federal agencies at least 30 days to comment on proposed actions. Every action taken by the Director of NIH must present "no significant risk to health or the environment ." RAC is a diverse group of experts that meets three or four times a year to advise the Director of NIH on the major technical and policy issues. * The NIH Office of Recombinant DNA Activities performs NIH's administrative functions under the guidelines. Additional oversight is provided by the Interagency Advisory Committee. This committee, which is composed of representatives of approximately 20 agencies, coordinates all Federal rDNA activities, and its members are nonvoting members of RAC.

Substantive Requirements.—The NIH Guidelines classify all experiments into four categories: 1) exempt, 2) those requiring RAC review and NIH approval before initiation, 3) those requiring IBC approval before initiation, and 4) those requiring IBC notification at the time of initiation. The first cate-

• In accordance with its charter, RAC is composed of not more than 25 members. At least eight must specialize in molecular biology or related fields; at least six must be experts in other scientific disciplines; and at least six must be authorities on law, public policy, the environment, public or occupational health, or related fields. As of June 30, 1983, RAC was Composed of 10 molecular biologists, 6 experts from other scientific disciplines, and 9 persons in the third category (6). An industry trade association has requested that an industry representative be appointed to the RAC as a nonvoting member.

gory-exempt-covers an estimated 80 percent to 90 percent of all rDNA experiments. Examples include work with *E. coli* K-12, S. *cerevisiae,* and asporogenic B. subtilis host-vector systems.

NIH approval is required for experiments involving formation of rDNA containing genes for the synthesis of certain toxins lethal to vertebrates, deliberate release of recombinant organisms into the environment, and transfer of drug resistance to certain microorganisms under certain conditions.

IBC approval is required for experiments involving certain pathogenic organisms, whole organisms or plants, or more than 10 liters of culture (except for certain exempt experiments). The last category experiments requiring IBC notification–is a catch-all category. Containment levels are specified for each category except the one requiring NIH approval, where containment is set on a case-by-case basis.

Application to Industry. -In the absence of legal authority over industry's work with rDNA, NIH has taken several steps to encourage voluntary compliance and provide a modest degree of Federal oversight. Part VI of NIH Guidelines, added in January 1980, sets up a mechanism for voluntary compliance. It creates a parallel system of project review and IBC registration, modified to protect proprietary information. * In addition, RAC established a subgroup in May 1979 to deal with large-scale work. "Physical Containment Recommendations for Large-Scale Uses of Organisms Containing Recombinant DNA Molecules" (Large-Scale Recommendations) (27) developed by that subgroup, RAC, and NIH specify physical containment requirements, suggest the appointment of a biological safety officer, and suggest the establishment of a worker health surveillance program for work done at higher containment levels. (They were added to the NIH Guidelines as Appendix K in June 1983.)

According to industry spokespeople, the NIH Guidelines are accepted and followed by the private sector.** Compliance with the Large-Scale Recommendations also appears to be widespread, but there have been few, if any, definitive statements by industrial spokespeople on this point. Regarding present Large-Scale Recommendations, one industry group stated that its experience has indicated that "the present [recommendations] are reasonable and workable, although they are quite stringent for work at the P1-LS level. The design requirements in the Recommendations make sense to us and are consistent with other regulations relating to the manufacture of products for use with human subjects" (4). The group went onto state that it also saw difficulties arising from the recommendation that the primary containment system not be opened until all microorganisms are inactivated because that could compromise that product in some cases (4).

Impact on Biotechnology.—The impact of the NIH Guidelines on biotechnology appears to be minimal. As essentially voluntary codes of practices that are fairly consistent with previously established good laboratory and manufacturing practices, they add little in the way of additional restrictions. Moreover, an estimated 80 to 90 percent of the experiments are exempt. On the basis of past history and what experts continue to learn about risks, the NIH Guidelines are likely to be further liberalized and may even disappear. In fact, whatever burdens they impose are probably offset by the gains in public confidence and the likelihood that they have headed off more restrictive mandatory controls.

EUROPEAN ECONOMIC COMMUNITY COUNTRIES: FEDERAL REPUBLIC OF GERMANY, UNITED KINGDOM, AND FRANCE

European Economic Community.—The European Economic Community (EEC) has considered at length the problems and prospects for rDNA research and the need for common Communitywide action to regulate and promote its development (13), but only a nonbinding recommendation has been made by the Council of the European Communities to member states on the question of guidelines applicable to rDNA research. The nonbinding EEC Guidelines were adopted in June 1982 (2). By that time, most of the individual member states with any significant amount of rDNA research had already adopted their own national guidelines. The EEC Guidelines impose no stricter requirements on rDNA research than those of the individual member states. They principally provide that any laboratory wishing to conduct rDNA research notify the competent national or regional authority in the member state and that the member states adopt a common definition of work involving rDNA (sees. 1-3).

More particularly, the EEC Guidelines suggest that notification of any rDNA research be given before work is commenced, except for research of very low-risk potential. * The notification should include infor-

"Proprietary information is protected in several ways. First, there is a presubmission review of data as to availability under the Freedom of Information Act. Second, NIH must consult with institutions applying for exemptions or approvals about the content of any public notice to be issued, if the application contains proprietary information. Finally, applications involving proprietary information are considered by RAC in nonpublic sessions,

.● Although there is no means for NIH to monitor compliance with the NIH Guidelines or Large-Scale Recommendations, there is no evidence suggesting noncompliance.

● The EEC Guidelines do not define the term "very low risk potential," but indicate that this be determined by the competent national authorities. The United Kingdom, France, and the Federal Republic of Germany have adopted somewhat different methodologies in their guidelines for defining risk potential

mation about the experimental protocol, the protective measures to be taken, and the general education and training of the staff working on the experiment or monitoring it. Such notification is thought desirable because it creates records that will be helpful in what the Commission of the European Communities believes to be the highly unlikely event of an accident or other misfortune involving rDNA (2). The authority receiving the notification must also, under the recommendation, protect the confidentiality of the information submitted (2). The EEC Guidelines do not call for specific approval of rDNA research of any type. As is discussed below, certain member states do require specific approval.

The EEC Guidelines do not address many issues which national guidelines, including those of the United States, have attempted to cover. The EEC Guidelines do not discuss the question of whether private laboratories should be subject to regulation, leaving this decision to the discretion of national authorities. Neither do they address how large-scale rDNA research should be regulated.

The fact that the EEC issued its rDNA guidelines despite the existence of more comprehensive guidelines in the member states reflects both the continuing concern over the safety of rDNA research and the difficulty in obtaining agreement on such matters. It is clear that the EEC has not yet determined its proper role in the regulation of rDNA research. Although discussions concerning rDNA as well as biotechnology generally are continuing within the EEC, it is likely to be some time before any agreement is reached concerning the respective roles of the EEC and the member states.

Federal Republic of Germany.—The Federal Republic of Germany has issued guidelines for rDNA research (3) that borrow heavily from the NIH Guidelines of the United States. The West German guidelines are theoretically broader than the NIH Guidelines because the German guidelines nominally apply to all research activities involving DNA. The only enforcement mechanism, however, is control over research funding from the German Federal Government.

The West German guidelines, like the NIH Guidelines, provide that the physical and biological containment measures required for particular experiments be determined according to the risk of the experiment. Risk is evaluated largely in terms of the source of the DNA. The German guidelines also prohibit certain specified experiments in the host organism E. *coli* K12 and other E. coli strains discussed in the NIH Guidelines (and the corresponding bacteriophages and plasmids of these strains), thereby requiring that the higher biological containment measures be used, regardless of the source of the DNA. * The guidelines also specify the appropriate containment methods required for various rDNA experiments. Physical and biological containment measures are divided into four and two levels (LI to L4 and B1 to B2), respectively.

The German guidelines for rDNA research are administered by the Central Commission for Biological Safety (Zentrale Commission ffi die Biologische Sicherheit), * * a biological safety officer or committee at each laboratory, and a project leader for each experiment. * * * The guidelines specify that the Central Commission must be notified of all rDNA experiments except those at the lowest physical containment level. For research at the next level, the Central Commission must authorize one of its scientist members to supervise the work and to keep the Commission informed. Experiments using mid-level containment measures require the prior approval of two members of the Commission. Prior approval must be sought from the Central Commission for all experiments using vertebrate cells as the host and for experiments using DNA from pathogenic organisms. In the case of the latter, the Central Commission must find that the expected benefits clearly outweigh the conceivable hazards. On request, the Central Commission will also authorize the use of new host-vector systems not enumerated in the German guidelines. The Central Commission also gives advice on research and safety measures.

United Kingdom.-The U.K. guidelines for rDNA research (26)T are similar to the NIH Guidelines in broad conceptual terms but differ with respect to

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"These specially restricted experiments are: 1) the production of recombinant DNA for the biosynthesis of powerful bacterial exotoxins such as botulinus toxin, tetanus toxic, diphtheria toxin, and snake toxin; z) the use of genomes of extremely pathogenic viruses such as Lassa, small pox, and hepatitis B; and 3) the transmission of genes which confer resistance to an antibiotic between micro-organisms that do not naturally exchange genes when the resistance gene has not previously been known in the receptor cell,

* ● West Germany's Central Commission for Biological Safety, the only Government body, has 12 members, 4 rDNA experts, 4 experts from related field of biology, and 4 "outstanding individuals" from unions, industry, or research-promoting organizations, all appointed by the Federal Minister for Research and Technology.

.. ● The officer or at least one member of the committee must have the appropriate license, if the research work involves pathogenic or toxin-producing organisms. The project leader must possess adequate experience in microbiology and, for certain higher containment level work, knowledge about pathogens. The project leader is responsible specifically for planning and conducting the research, health monitoring of laboratory workers, informing the Central Commission and the biological safety officer or committee of the research and the planned safety measures, implementing Commission instructions, making regular reports to the Commission, maintaining a record of safety instruction, and training laboratory personnel.

†The term used in the United Kingdom to describe rDNA research is '(genetic manipulation. " Genetic manipulation is defined in the Genetic Manipulation Regulations as: the formation of new combinations of heritable material by the insertion of nucleic acid molecules produced by whatever means outside the cell, into any virus, bacterial plasmid, or other vector system so as to allow their incorporation into a host organism in which they do not naturally occur but in which they are capable of continued propagation.

scope, risk assessment, and enforcement. Like the NIH Guidelines, the U.K. guidelines have been gradually relaxed. Nevertheless, the guidelines in the United Kingdom are still regarded as more restrictive than those of the United States.

The guidelines for rDNA research in the United Kingdom are promulgated and administered by the Genetic Manipulation Advisory Group (GMAG) under the Health and Safety at Work Act of 1974 (24). * The guidelines apply to all research in the United Kingdom, not just that funded by the Government. Enforcement is the responsibility of the Health and Safety Executive (HSE), which is comparable to the U.S. Occupational Safety and Health Administration. HSE has taken no enforcement action to date.

As do the guidelines in all of the competitor countries, the GMAG guidelines establish four progressively more restrictive physical containment levels based on the perceived hazards of the research.** Facilities for the highest two levels must be examined by HSE inspectors before any rDNA research can be conducted to ensure that the GMAG requirements are met.

The GMAG guidelines also adopt the two-level biological containment approach of most of the other countries * * * which is based on the degree of disability of the host-vector system being used. However, GMAG has also developed special rules for rDNA research involving experimental animalsl and for work that involves the introduction of foreign nucleic acid into higher plants or into any plant pest. *

GMAG asssess the degree of potential hazard in a way somewhat different from the other countries, including the United States. GMAG considers three factors: access, expression, and damage. * As a general matter, the British classification system appears to require less stringent containment measures for some types of research than would be required in other countries. For example, the damage factors associated with interferon and insulin are quite low and work with these products would be classified as less risky in the United Kingdom than in some other countries (22).

The administrative framework for implementing the GMAG guidelines relies on institutional and governmental oversight. GMAG and HSE must be given advance notice of work involving rDNA except for certain selfdoning experiments.** Most work at the lowest two physical containment levels can go forward after notice. Although no express provision prohibits work at containment levels three and four before GMAG issues its advice, such premature work might violate the Health and Safety at Work Act, which carries criminal penalties. In addition, each institution conducting rDNA research is required to have certain personnel responsible for the research * * * review, to forward notifications of proposed rDNA research to GMAG, and to suggest other health and safety actions that the institution might take.

Industrial or large scale applications of rDNA—that is, research involving the growth of self-propagating products of genetic material in volumes of 10 liters or more—are subject to special rules. GMAG reviews proposals to conduct such large-scale research on a case-by-case basis and visits each site, commenting on the safety measures proposed. GMAG expects that this review will involve "integration" of questions about physical and biologic containment. Whether this means that review of large-scale work will be stricter or more relaxed is unclear. GMAG has stated, however, that vaccine and antibiotic production can be done safely using ordinary chemical engineering measures—measures probably more relaxed than the containment-level measures required for small-scale research (20).

GMAG has recognized the potential commercial and industrial importance of genetic manipulation by establishing special confidentiality requirements for work that raises questions about commercial proper-

● The Government department with responsibility for GMAG policy is the Department of Education and Science, although this department has little expertise in such areas, particularly in comparison to the Department of Health and Social Security, which has a very limited role, via the Medical Research Council, in the oversight of genetic manipulation safety (25). GMAG's status was recently reviewed by the Health and Safety Executive, and the subsequent report recommended the relocation of the group to the Department of Health and Social Security (12). GMAG, now called the Health and Safety Commission Advisory Committee on Genetic Manipulation, has been moved to the Department of Health and Social Security.

•*Certain Dh'A research is considered so safe as to not require containment. Laboratories conducting this research must instead follow simply the Guidelines for Microbiological Safety.

••● France has four levels of biological containment.

†These require isolation of the animal, safe disposal of refuse and waste, and stricter rules for research in category 111 and IV laboratories (23).

*Plant pest is defined as "any living organism, other than a vertebrate animal, or any pathogen which is injurious to any plant, and includes any culture of such organism or pathogen. " The work requires a special license from the Agricultural Ministries. The license will be issued only if the research is conducted according to the containment recommendation of GMAG, which include special rules for the handling of plants and preventing the dissemination of pollen and seed. The special plant rules do not cover experiments involving the introduction of plant nucleic acid into bacteria or other microorganisms (except #ant pests), which are covered by the existing GMAG guidelines (z I). It should be noted that the United Kingdom has adopted specific restrictions on the importation of such pests.

● "Access" is the possibility that escaped organisms will enter the human body and eventually reach susceptible cells. "Expression" is the possibility that a foreign gene incorporated into the gene sequence of an organism will be able to carry on or "express" its normal function, such as secretion of a toxin that the organism formerly did not secrete. "Damage" is the chance that a new gene sequence will cause physiological damage in the body to which it gains access once it is expressed (15,18, 19,22).

* ● These include experiments using *E.coli* K12, *B. subtilis*, and S. *cerevisae* (17).

••● These include a Biological Safety Officer familiar with the safety procedures for rDNA work and a Safety Committee to consider the containment and other safety measures proposed for genetic manipulation.

ty or patents. While confildentiality arrangements may vary from case to case, GMAG generally treats as confidential any material so labeled. Members of GMAG who have commercial interests in DNA work are prohibited from seeing such material or taking part in the discussion about it (17,20).

France.-The French guidelines for rDNA research (S) largely follow those of the United States. The guidelines were promulgated and are administered by the National Control Commission (Commission de Controle), which reports to the General Delegation of Scientific and General Research (Delegation Generale de la Recherche Scientifique et Technique). The French guidelines apply only to Government-funded research and require that scientists conducting such research notify the Control Commission of the planned research and in some cases obtain approval of the research. Local safety committees monitor ongoing research. The principal sanctions for failure to comply with the French guidelines are loss of Government funding or denial of approval to conduct research.

As in the United States, rDNA experiments in France must be conducted using certain physical and biological containment measures. The degree of containment depends on the risk of the work. Risk is assessed using a method very similar to that used in the United States. Research with DNA from oncogenic or highly pathogenic viruses is reviewed on a case-by-case basis but generally must be conducted according to the most stringent containment measures unless the oncogenic or highly pathogenic genes are eliminated before cloning.

In certain respects, the physical and biological containment requirements in the French guidelines differ from those in the United States, Although the French guidelines use four levels of physical containment as in the United States, they appear to be more flexible than the U.S. guidelines with respect to upgrading containment. In some cases, the French guidelines permit a laboratory's containment level to be upgraded without requiring construction of a new facility. Use of an approved safety cabinet will give the laboratory the next higher rating. If a safety cabinet is used to render a P3 laboratory equivalent to a P4 laboratory (the laboratory with the highest degree of containment), however, the National Control Commission must certify the facility. This upgrading system should expand the ranges of research that a French laboratory can do, as well as make research at higher containment levels less expensive. With respect to biological containment, the French guidelines use four levels, unlike the U.S. guidelines, which use two levels. Biological containment is based on the safety of the host-vector system. In effect, the French approach to biological containment appears quite similar to that of the United States, with the four levels of containment in France being finer gradations of the two levels used in the United States.

France allows biological agents containing rDNA to be imported and exported freely, although the French guidelines specify that certain measures must be met to safely transport and import rDNA materials. Large-scale research—i.e., experiments involving volumes of 10 liters or more—is not covered by the French guidelines for rDNA research, but Government oversight exists on a case-by-case basis.

SWITZERLAND

The Swiss have basically adopted the U.S. guidelines as their national rDNA research guidelines. Although the Swiss generally have amended their guidelines whenever the NIH Guidelines are amended, they are currently using a version based on the NIH Guidelines in effect in April 1982 (14).

There are other basic differences. The Swiss Government has no direct role in regulation of rDNA research; Swiss scientists instead have established a system of complete self-regulation. The Commission for Experimental Genetics (Commission fur Experimentelle Genetik) created by the Swiss Academy of Medical Sciences, is responsible for monitoring rDNA research. The guidelines that this commission has promulgated apply to all research involving rDNA in Switzerland, not only that funded by the Government. Moreover, the Swiss guidelines do not require special approval for work using cell culture volumes in excess of 10 liters.

The adminstrative structure for oversight in Switzerland is quite similar to that in the United States. The Commission for Experimental Genetics must approve certain experiments in advance, such as those involving the deliberate release into the environment of any organism containing rDNA. For two other classes of experiments, scientists must notify the commission but need not obtain approval. A final class of experiments are exempt from the guidelines. Principal investigators, safety officers, and institutional safety committees also bear oversight responsibility,

JAPAN

Japan's guidelines for rDNA research (11) are promulgated by the Ministry of Education (on recommendation by the Science Council). The guidelines apply only to publicly funded research, but private industry has followed them on a voluntary basis.

Each research institution is required under these guidelines to have laboratory supervisors, a safety committee, and a safety officer. The head of each research institution is also charged with specific duties

in **supervising the rDNA work. The laboratory supervisor must submit plans of experiments and changes in plans to the head of the research institution for his or her approval, The head of the institution then consults with the safety committee—a body consisting of "members representing the relevant fields, and having high standards of both professional and technical knowledge and judgment"—to determine whether the plans comply with the guidelines, what training will be necessary, and other issues relevant to the safety of the research. The safety officer's role is to monitor the safety of ongoing work and to make appropriate reports to the safety committee.**

The Japanese Government monitors rDNA research through two bodies: 1) the Council for Science and Technology, which advises the Prime Minister and which oversees work by private institutions; and 2) the Science Council, which advises the Ministry of Education and which supervises Government-funded university research. The Science Council and the Ministry of Education formerly had to approve university rDNA research; now it is only necessary that the university safety committee and the university president approve the experiment (7,9). Ministry authorization is still required, however, for experiments involving specified "especially dangerous" organisms and the release of such organisms into the environment. *

Certain experiments are effectively prohibited in Japan, because the Japanese guidelines for rDNA research specify no safety or containment rules for them. Effectively prohibited experiments include large-scale research (more than 20 liters of cell culture) and experiments in which recombinant organisms infect individual animals and plants, in which the source of the DNA is other than specified cells or host-vector systems. Such experiments can be done once containment standards are set, but setting such standards depends under the guidelines on confirmation of the safety of these experiments, which has not been completed for most types of this research. Large-scale research is possible if special permission is granted by the Ministry of Education; few companies have sought it successfully. Japanese companies using biotechnology are now lobbying heavily for relaxation of restrictions on large-scale research,

For permissible experiments, the Japanese rDNA research guidelines require physical and biological containment based on the perceived risk of each experiment. Under the guidelines, risk is assessed principally according to a **phylogenic scale** but also according to the biological characteristics of the source of the DNA, * the purified or unpurified nature of the DNA,** the size of the clone number,*** and the scale of the cultivation. † Required physical containment measures resemble those under the NIH Guidelines and are categorized in a similar P_1 to P, scale. Similarly, the Japanese guidelines provide for two levels of biological containment.

Historically, the Japanese guidelines have been among the most restrictive in the world. Although Japan's guidelines have recently been relaxed considerably to bring them more into line with the guidelines in other countries, they are still the most restrictive of the ones surveyed in this appendix, Japanese companies applying biotechnology consider themselves handicapped in competition against their foreign counterparts for two principal reasons. First, hosts are limited in Japan, with a few exceptions, to E. ***coli*** and B. ***subtilis;*** other micro-organisms such as the actinomycetes, which is effective in producing antibiotics, therefore cannot be used. Second, work in Japan is limited to volumes of 20 liters or less, and successful commercial development requires larger fermenters (8). Japanese companies using biotechnology have mounted an intensive lobbying campaign to eliminate the 20-liter rule (10).

Environmental laws and regu1ations

UNITED STATES

The United States has no laws specifically directed toward biotechnology, but, as discussed in ***Chapter IS: Health, Safety, and Environmental Regulation, the*** Toxic Substance Control Act (15 U.S.C. $2601-2629) and the Federal Insecticide, Fungicide, and Rodenticide Act (47 U.S.C. **~136(a)-(y)) will play a** major role in preventing any adverse environmental impacts from biotechnology products. In addition, there are several statutes dealing with pollution that would apply because they generally define pollutants or wastes so as to cover biological materials. They are:

- The Federal Water Pollution Control Act, as amended by the Clean Water Act of 1977 (33

● "Especially dangerous" experiments indude the transplant of manipulated genes with toxicity into animal and plant cells. University presidents may still approve work with disease pathogens, including influenza and hepatitis viruses (7).

• 'DNA donor organisms closer phylogenically to humans are considered riskier.

● The relevant biological characteristics of the DNA are pathogenicity, toxin-producing ability, carcinogenicity, parasitic quality, drug resistance, likelihood of becoming an allergen, masked infective factors such as nucleic acids related to C-type virus, vulnerability to contamination by viruses, bacteria, or other parasites, ability to produce substances such hormones or metabolic intermediates affecting the metabolism of human beings, and possibility of causing ecological disturbances.

" ● Purified DNA, proved to carry only Nonhazardous genr,) is deemed safer than unpurified DNA,

•" ● The fewer the number of clones, the safer the experiment is, on the reasoning that a lower number will reduce the probability that harmful genes will appear.

†Smaller-scale experiments are considered safer than large-scale ones.

U.S.C. **$$1251-1376, as amended by Public Law No. 95-217, 91 Stat. 1566 (1977)).**

- **The Marine Protection, Research and Sanctuaries Act of 1972 (33 U.S.C. j$1401, 1402, 1411-1421, 1441-1445).**
- **The Clean Air Act (42 U.S.C. $$7401-7508, 7521-7574, 7601-7626).**
- **The Solid Waste Disposal Act, as amended by the** Resource Conservation and Recovery Act of '1976 (42 U.S.C. f\6901-6987, as ***amended by*** Public law No. 94-580, 90 Stat. 2795 (1976)).

Under the Federal Water Pollution Control Act, as amended, the Environmental Protection Agency has promulgated regulations on wastewater from the manufacture of pharmaceuticals by fermentation (4 C.F.R. Part 439 (1982)).

EUROPEAN ECONOMIC COMMUNITY COUNTRIES: FEDERAL REPUBLIC OF GERMANY, UNITED KINGDOM, AND FRANCE

European Economic Community.–Although the EEC has issued no directives or taken any other action specifically to regulate the environmental effects of biotechnology, several general directives concerning waste disposal and water pollution will be applicable to biotechnological products (30,31,33). The EEC'S environmental regulations are general and flexible, giving maximum discretion and authority to the bureaucrats that implement them.

Companies using biotechnology will encounter environmental regulation in manufacturing biotechnological products in the EEC member states and in exporting products to those states. Under the premarketing notification requirement imposed by the Sixth Amendment to the EEC'S dangerous substances directive (32), * a firm must test a new chemical before marketing, must provide the proper authorities in the member states where the product is to be marketed with the results of the "base test" (minimum testing requirements), and must conduct such further tests as those authorities may deem necessary before approval may be granted. Since many biotechnology products will likely qualify as "new chemicals," the Sixth Amendment's requirements would apply. Of course, a firm seeking to build a plant to manufacture biotechnology products in a member state would be required not only to secure "new chemical" approval, but also to comply with the more comprehensive system of environmental regulation in the member state.

Federal Republic of Germany.-The Federal Republic of Germany is a federal state, and under its Constitution, the 11 ~"nder (States) share power with the Federal Government. In controlling pollution, poisonous substances, and waste, the Federal Government and the ~"nder have concurrent jurisdiction, but the Lander may pass laws in these areas only if the Federal Government has not done so. In environmental protection, land use, and water law, the Federal Government may enact broad "framework" legislation, but the Lander must implement the general Federal laws by enacting detailed legislation adapted to the conditions of each State.

The Ministry of the Interior (Bundesministerium Des Innern) coordinates the environmental policies of the West German Federal Government, including environmental planning, waste and water management, and control of air pollution. The Federal Environmental Agency (Umweltbundesamt), which is more concerned with environmental protection, furthers Federal environmental policies by developing planning programs and performing research. Coordination of Federal environmental programs also is conducted by a Cabinet Committee for Environmental Questions (Arbeitsgemeinschaft fur Umweltfragen E.V.).

The only environmental regulations directed specifically at biotechnology are contained in the Federal Republic of Germany's guidelines for rDNA research (39). **The Gerrnm guidelines** impose requirements on disposal of waste from rDNA experiments, requirements that depend on the containment level of the work involved. In no case may biological agents containing rDNA be released into the environment. Experimental plants and animals containing rDNA must be kept under conditions of isolation. All rDNA material may be removed from the laboratory only in airtight packaging and must eventually be destroyed, usually by incineration. All wastes containing microorganisms or nucleic acids must be sterilized or denatured. Waste water from experiments at the L3 or L4 level must be decontaminated.

Apart from the rDNA research guidelines, it appears that the Federal Republic of Germany's legislation and implementing regulations do not specifically regulate environmental impacts from biotechnological products and processes. Instead, companies using biotechnology would appear to be subject, like other firms in West Germany, to a series of general environmental protection laws and regulations.

The most general of these laws is the Chemicals **Act** (40), **which is designed to** protect humans and **the en**vironment from **all types of** dangerous substances. This **law set** up compulsory testing **of** substances and compulsory classification, labeling, and packaging of dangerous substances and materials. It implements in the Federal Republic of Germany **the** Sixth Amendment **to the** EEC'S environmental protection directive.

● **The first directive in the field of dangerous substances was Council Directive of June *27, 1967 (29).***

Other relevant statutes in the Federal Republic of Germany are the following: the Law for the Prevention of Harmful Effects on the Environment Caused by Air Pollution, Noise, Vibration, and Similar Phenomena (Federal Emission Control Law) (37), the Law on Disposal of Wastes (36). Act on Regulation of Matters Relating to Water (Federal Water Act) (35), and the Waste Water Charges Act (Waste Water Law) (38).

A Committee of the German Society for Chemical Engineering (Deutsche Gesellschaft fur chemisches Apparatewesen E. V.) completed a study of the risks specifically associated with biotechnology and of the relevant statutory and regulatory provisions that could be used to control those risks (34). The study concluded that adequate legal authority exists in the Federal Republic of Germany for regulating the kinds of hazards most likely to arise in connection with biotechnology.

United Kingdom.—Responsibility for protection of the environment in the United Kingdom lies primarily with the Department of the Environment. In addition, a Royal Commission on Environmental Pollution was established in 1970 to advise the government on environmental issues. As in the United States, much environmental regulation in the United Kingdom is the responsibility of local governments.

Although the United Kingdom has an extensive statutory environmental protection scheme, there is no legislation or regulation specifically concerned with environmental impacts of biotechnological products and processes. Companies using biotechnology, therefore, would be subject to the general environmental protection laws and regulations.

The Control of Pollution Act of 1974 (53), provides in chapter 40 for licensing of sites for the disposal of '(controlled waste, " defined as household, industrial, and commercial waste, both on land and in water. The penalties for unlicensed disposal are fines and imprisonment. The law is to be phased in between July 1983 and July 1986. Waste products of biotechnological processes would appear to be covered by this law.

France.—The principal environmental protection agency in France is the Ministry of the Environment (Ministdre de lEnvironnement). Environmental protection legislation applies broadly to activities that degrade the environment in a variety of ways. The touchstone of most regulation is not the nature of a particular activity, but whether it produces environmentally adverse effects. To the extent that biotechnological products and processes produce such effects, they would be subject to these laws.

The most general environmental statute is the Law on Installations Classified for Purposes of Environmental Protection (44). This law covers all types of risk to humans and the environment resulting from the activities of various types of facilities, including but not limited to industrial and commercial establishments. These facilities are subject to requirements specific to the type of danger or inconvenience involved. This determination rests largely in the hands of local authorities, who have a continuing right of access to the regulated facilities, Failure to comply with the law may result in administrative and criminal *penalties. No* rules specifically aimed at biotechnology facilities have yet been adopted under the authority of this law.

The Chemicals Control Law of France (45), which predates the Sixth Amendment to the EEC'S dangerous substances directive, would apply to chemical compounds produced by biotechnology. This law aims to protect human beings and the environment against risks arising from both naturally occurring and industrially produced chemicals. Any producer or importer seeking to import or manufacture commercially a chemical which has never been placed on the French market before must notify the relevant authority, provide certain information, and submit to whatever conditions may be imposed. *

Two other statutes would be particularly relevant to biotechnology. They are the Law on Waste Disposal and Recovery of Materials (43) and the Act on the Administration and Classification of Waters and the Control of Water Pollution (42).

SWITZERLAND

Although the Swiss rDNA research guidelines prohibit the release of biological agents containing rDNA into the environment, they do not mention effects on the environment from other forms of waste which may result from applications of biotechnology. These would presumably be regulated in Switzerland under Article 24 *septies* (seventh) of the Federal Constitution, which gives the Federal Government far-reaching powers to pass environmental laws.

Legislation under this article has been sparse, however, and there are apparently no nonfederal rules in Switzerland on air pollution, noise abatement, or waste disposal. Only in the area of water pollution has legislation been enacted. The Water Protection Act of October 8, 1971 (51), seeks to ensure the quality of the nation's water by means of sweeping protective measures which cover all natural, artificial, ground, and surface waters.

In addition, Article 6 of the Federal Act on Work in Industry, Trade, and Commerce (52) requires employers to protect the area surrounding their business enterprise from harm or discomfort by taking all measures shown necessary by experience and found to be technically feasible and appropriate.

* Decree No. 79-35 desrribes the technical dossier to be provided when providing notice concerning a new chemical substance (41),

JAPAN

Specific measures governing environmental effects of biotechnology applications have not been prepared by the Japanese Government. The regulations applicable to biotechnology are those applicable to all industry. The agencies with responsibility for environmental protection in Japan include the Environmental Protection Agency, the Ministry of International Trade and Industry (MITI), the Ministry of Health and Welfare, and the Ministry of Agriculture, Forestry, and Fishery. The Environmental Protection Agency has jurisdiction over basic policy, general coordination of governmental pollution control activity, budgetary policy, and research and investigation.

The Basic Law for Environmental Pollution Control (46) establishes fundamental national principles and policies and establishes the basic regulatory framework for environmental protection in Japan. The law applies to air, water, soil, and other pollution. It empowers the Central Government to promulgate and enforce environmental quality standards necessary to protect the public health and conserve natural resources. This and other environmental laws are supplemented by and implemented through Cabinet orders issued by the Prime Minister, and through ministerial orders and Environmental protection Agency notifications. Administrative guidance is used to regulate pollution from specific industrial plants and industries. Local governments have responsibility with the Central Government in monitoring pollution and for regulation, and they may set more stringent standards than those set by the Central Government.

Japan's Basic Law for Environmental Pollution Control is supplemented by laws aimed at specific types of pollution. These include the Air Pollution Control Law (47), the Water Pollution Control Law (49) and the Waste Management Law (48).

Finally, the Chemical Substances Control Law (50) requires manufacturers to notify the Japanese Government and to test all new chemical substances to be produced in quantities exceeding 100 kilograms. Chemicals are tested for their biodegradability and bioaccumulation. Manufacturers and importers of chemical substances must notify MITI of their intent to use or market a new chemical. Japan's Environmental Protection Agency monitors the effect of chemicals in the air and water, and the Ministry of Health and Welfare administers laws on chemical products.

Regulation of worker health and safety

UNITED STATES

The Occupational Safety and Health Administration (OSHA), which is part of the U.S. Department of Labor, is the agency primarily responsible for worker safety and health. OSHA'S authority derives from the Occupational Safety and Health Act of 1970 (29 U.S.C. $$651-678) which creates a broad mechanism for protecting workers from workplace hazards, Section 5(a)(1) of the act requires U.S. employers to furnish their employees with a workplace "free from recognized hazards that are causing or are likely to cause death or serious physical harm." Section 5(a)(2) requires employers to comply with safety and health standards set by the U.S. Secretary of Labor. Under a recent U.S. Supreme Court decision (62), the Secretary of Labor can promulgate permanent standards for toxic substances or harmful physical agents only after a finding that the standard is "reasonably necessary to remedy a significant risk of material health impairment." Section 6(c) of the act permits the Secretary of Labor to promulgate emergency temporary standards after a finding that employees are "exposed to grave danger." The statute also creates the National Institute for Occupational Safety and Health to gather data, assess risks, and recommend safety and health standards to OSHA. Other sections grant OSHA authority to require record keeping and medical surveillance and to enforce the act and its regulations through civil and criminal penalties.

Given the language quoted above regarding risk and hazard, the applicability of the Occupational Safety and Health Act to biotechnology would be limited when risk is conjectural. However, the act would be applicable to large-scale processes using known human toxins, pathogens, or their DNA. It also would be applicable to physical hazards presented by the fermentation process, such as temperature, pressure, and toxic solvents. OSHA has not promulgated health and safety standards for bioprocesses and has made no statements on how it might apply the act to biotechnology.

OSHA arguably has authority to require a medical surveillance program, although this is not clear cut. Section 8(c)(1) of the Occupational Safety and Health Act requires employers to "make, keep and preserve" such records as the U.S. Secretary of Labor prescribes

by regulation as "necessary or appropriate for the enforcement of this act or for developing information regarding the causes and prevention of occupational accidents and illness." Further, section 8(c)(2) of the act authorizes the Secretary of Labor to require employers to "maintain accurate records of, and to make periodic reports on, work-related deaths, injuries and illnesses other than minor injuries . . . ." Since the purpose of a surveillance program would be to develop information on any occupational disease related to biotechnology, section 8(c)(1) of the Occupational Safety and Health Act would seem to apply. In addition, the information developed in such a program would also be the kind of information necessary for compliance with regulations promulgated under section 8(c)(2). Employers, on the other hand, might argue that both sections require an initial showing that biotechnology causes occupational disease.

EUROPEAN ECONOMIC COMMUNITY COUNTRIES: FEDERAL REPUBLIC OF GERMANY, UNITED KINGDOM, AND FRANCE

European Economic Community.–Although its powers in the area of worker health and safety regulation are limited and indirect, the EEC has attempted to ensure at least minimal protection for most industrial workers. In 1980, the EEC adopted a directive that required each member state to adopt a variety of measures to protect workers' health and safety (54). * The directive covers work that does or may involve a "chemical, physical or biological agent . . . likely to be harmful to health." The directive is quite general; the specific content and substance is left to the discretion of the member states.

The directive does not refer explicitly to rDNA work or other applications of biotechnology. Thus, the question of how worker health and safety laws will affect the biotechnology industry is left to the discretion of each member state.

Federal Republic of Germany.-The rDNA research guidelines of the Federal Republic of Germany (57) provide specifically for the health-monitoring and training of laboratory workers. Each worker at an rDNA laboratory that is above the lowest containment level must have a pre-employment examination by an authorized doctor. If the results of this examination reveal a susceptibility to hazards which may be involved in the contemplated research, the worker may not be employed. Appropriate immunizations are required for work with pathogenic microorganisms. Blood serum from the worker must be taken at the first examination and at the end of employment and stored until at least 2 years after the end of participation in the research. All workers must receive instruction before the research begins and annually thereafter in the methods to be used, the conceivable hazards of the experiment, and the protective measures to be applied.

- The Federal Republic of Germany's general worker health and safety regulations would also apply to commercial uses of biotechnology. At the Federal level, substantive workplace health and safety requirements are stated in the Act Respecting Plant Physicians, Safety Engineers, and Occupational Safety Specialists (55), * in the Ordinance Respecting Workplaces (56),** and in rules that are issued by the Dangerous Industrial Substances Committee (Ausschus fur Gefahrliche Arbeitsstoffe) of the Federal Ministry of Labor and Social Affairs (Bundesministerium fur Arbeit und Sozialordnung) concerning the marketing and handling of dangerous substances (70).

Within this Federal framework, a significant regulatory role is played in the Federal Republic of Germany by accident insurance funds. These funds are authorized by statute to issue regulations setting standards for workplace health and safety (58). When approved by the Federal Minister of Labor and Social Affairs, the regulations become binding on covered employers. The funds, which are organized by indus -

● The required measures include the following:
1. limitations on the use of chemical, physical or biological agents in the workplace;
2. limitations on the number of workers exposed or likely to be exposed to such agents;
3. engineering controls;
4. establishment of exposure limit values for such agents and methods of assessing their level;
5. safe working procedures and methods;
6. collective protection measures;
7. individual protection measures, where exposure cannot reasonably be avoided by other means;
8. hygiene measures;
9. information for workers on potential risks associated with the exposures to such agents, technical preventive measures workers should take, and precautions to be taken by the employer and the workers;
10. use of warning and safety signs;
11. surveillance of workers' health;
12. maintenance of current records of exposure levels, workers exposed, and medical records;
13. emergency procedures; and
14. if necessary, general or limited bans on an agent from which protection cannot be adequately ensured.

● The Act Respecting Plant Physicians, Safety Engineers, and Occupational Safety Specialists requires each employer to appoint a plant physician and an occupational safety specialist. The appointed physician must conduct medical examinations of employees, advise the employer concerning health and safety precautions (including technical equipment and personal protective devices), supervise workplace safety, investigate and report to the employer on the causes of work-related illnesses, and instruct employees concerning the dangers to which they are exposed in the course of their work and the measures available to avert such dangers.

●● Section 3(1)1 of the Ordinance Respecting Workplaces imposes a general obligation on employers to operate workplaces in accordance with both the law and the "generally recognized rules of safety engineering, occupational medicine and hygiene and any other scientifically established findings in the labor field." Its specific requirements, however, relate to physical design and construction.

try, are authorized not only to promulgate the applicable standards, but also to enforce them through inspections and fines. Because all employers must carry accident insurance, the funds have a large role in occupational safety and health.

United Kingdom. -Guidelines promulgated by GMAG contain specific requirements regarding the health and safety of laboratory workers who are involved in rDNA research (67,68,69) (see discussion of "Recombinant DNA Research Guidelines" above). Each laboratory must appoint a supervisory medical officer with experience in public health, infectious diseases, or occupational medicine, and conduct health reviews of all workers before they start work involving genetic manipulation. The reviews are designed to check workers for particular susceptibilities and to assist in determining whether any laboratory-contracted illnesses have developed. If a worker's medical history indicates that the worker's participation in genetic manipulation may be particularly hazardous, appropriate steps may be required to prevent his or her exposure to genetic manipulation work. The institution must also investigate any unexplained illiness, and if a laboratory contracted infection is suspected, the institution must inform both the worker and the worker's physician as well as GMAG and other authorities.

Companies using biotechnology in the United Kingdom must also fulfill the obligations imposed on virtually all employers and manufacturers by the Health and Safety at Work Act of 1974 (66). In general, an employer must ensure so far as reasonably practicable that employees are not exposed to health and safety risks and to inform them of the risks that are created. Employees also have certain obligations under the act.

Health and safety regulations in the United Kingdom, under the Health and Safety at Work Act, are promulgated by the Secretary of State, on the advice of the Health and Safety Commission. The Health and Safety Commission also supervises efforts to improve worker health and safety, makes necessary investigations, and may approve codes of practice for particular industries.

There is no code of practice for biotechnology other than the GMAG guidelines for rDNA research. If a broader code were developed, it would be only advisory; violation of a code is not per se a violation of the Health and Safety Work Act but is only evidence tending to show a violation of the act. HSE (and local authorities) enforce the act through appointed inspectors, who may issue "notices" prohibiting certain activities as too risky or requiring remedial actions. Violators of the act are subject to civil and criminal penalties.

France.—The guidelines for rDNA research in France contain no provisions dealing expressly with the health or the health-monitoring of laboratory workers. The guidelines do require, however, that scientists and technicians be familiar with the physical and biological containment measures involved in rDNA research and be prepared to take emergency action in the event of an accident.

The formulation and implementation of general policy on the prevention of occupational hazards in France is the responsibility of the Central Council for the Prevention of Occupational Hazards (Conseil Central pour la Prevention des Risques Professionally). So far, the council has not specifically addressed worker health problems arising from biotechnology.

Specific employee health and safety regulations are promulgated and enforced in France by the Minister of Labor, who is in charge of conditions in industrial and commercial establishments, and by the Minister of Agriculture, who is granted the same authority over agricultural facilities.

An occupational safety and health committee must be set up in any industrial establishment normally employing 50 or more workers (59,60). The committee advises management on safety procedures and periodically inspects the establishment to ensure that the safety laws and regulations are being applied. It also is supposed to take immediate action to avert imminent danger at the facility and to conduct an inquiry into the causes of any accident or serious occupational disease.

The manufacture of chemical substances potentially harmful to workers is also regulated by statute (61). Prior to the marketing of any substance or preparation that may involve a danger to workers, the manufacturer, importer, or seller must file with a Government-approved laboratory the information necessary to assess the risks of the manufacturing process. If the chemical substance has already been placed on the market, its manufacture, sale, transfer, or use may be restricted or prohibited in the interests of occupational health and safety,

SWITZERLAND

By following the U.S. guidelines for rDNA research, Switzerland applies to rDNA work the worker health and safety rules set out therein. Thus, each research institution in Switzerland must ensure that laboratory workers receive appropriate training, determine whether a health surveillance program is appropriate, and report to the Commission for Experimental Genetics any work-related accidents or illness. The re-

sponsibility for assessing the training provided to personnel and the adopting emergency plans for accidental spills and personnel contamination rests with the institution's biohazards committee. The biological safety officer must report work-related accidents or illnesses and assist in developing emergency plans. The group leader is obligated to train and supervise his or her staff.

Worker health and safety not specifically related to rDNA research is regulated in Switzerland on the cantonal rather than the nonfederal level. In one canton, Geneva, an advisory committee has been established to serve as a channel of communication between public authorities and business and to develop proposals on worker health and safety. The committee meets four times a year (63). The other cantons do not have such committees.

JAPAN

The basic law governing worker health and safety in Japan is the Industrial Safety and Health Law of 1972 (64). * This law imposes on employers health and safety obligations which are comprehensive in scope but very general in actual language. Among these obligations is the duty to take necessary measures to prevent health impairment caused by substances, agents, and conditions found in the workplace. The law vests broad discretion in the Japanese Ministry of Labor to determine when regulation is appropriate and what kinds of precautions an employer must take. Employers who manufacture, import, or use "chemical substances" may be subject to special requirements. Medical examinations must be conducted on all employees, but employers may also be required to provide special tests for employees engaged in harmful work. At the present time, no regulations have been addressed specifically to biotechnology.

The Industrial Safety and Health Law includes a stringent enforcement mechanism. Substantial criminal penalties and fines are imposed for violations. For the most serious violations, offending employers may also be **ordered to close or alter their operations.**

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