COMPREHENSIVE BIOTECHNOLOGY

The Principles, Applications and Regulations of Biotechnology in Industry, Agriculture and Medicine

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The Principles of Biotechnology: Engineering Considerations

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United States and Canadian Governmental Regulations Concerning Biohazardous Effluents

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32.1 INTRODUCTION

32.1.1 Scope of the Chapter

The discovery of plasmid-mediated *in vitro* DNA recombination in 1972, resulted in a renaissance for commercial fermentation technology. The prospects of applying techniques in molecular biology to the development of a wide range of microbial products has given rise to several hundred new firms worldwide within a few years. While applications for genetically engineered microorganisms were being sought and commercial markets assessed, scientists and the public debated the safety of rearranging genetic material across disparate species. Some skeptics called for new laws, while others were satisfied to establish regulations under the authority of existing laws. Throughout a decade of intense controversy, primarily centered in the United States and Britain, many scientists emphasized that the risks associated with the manufacture of novel organisms were purely conjectural.

Much of the early discussion over biohazards was almost exclusively directed to gene-splicing experiments. As the debate over laboratory-scale recombinant DNA manipulations subsided, the focus shifted to industrial scale activities where environmental release and occupational health are highlighted. The question at the heart of the issue is: 'Will commercial biotechnology be clean in comparison to the chemical industry which is plagued with problems of treatment, transportation, storage and disposal of hazardous wastes?'

The decades of the 1960s and 1970s brought an unprecedented public response to the chemical hazards facing man and the environment. Throughout the industrial world, major pieces of legislation were enacted to protect land, water, air resources and the working environment from chemical contaminants. The commercial developments that were taking place to exploit the use of gene-splicing brought a new air of apprehension to some environmentally-minded individuals, government officials and public advocacy groups. Central to their concerns were the following possibilities: (1) a novel organism might be released into the environment with unpredictable and possibly irreversible effects on the environment; (2) a new microbial agent, infectious to humans or animals, might be released, or a conventional pathogen might have its host range broadened; (3) a rapid rise in large-scale biotechnology could result in bioeffluents that would place additional stresses on the quality of land and water resources; (4) organisms engineered to perform useful functions in the environment might produce adverse secondary effects of an unanticipated nature.

Initiated first by Britain (Working Party, 1976), followed soon after by the United States (National Institutes of Health, 1976), guidelines regulating experiments involving the production of recombinant DNA molecules were adopted by many countries actively pursuing research in this area. Scientists questioned the rationale that selects out genetically engineered organisms for regulation. The laboratory use of pathogens and infectious viruses has been an area of concern for the public health community. Infectious disease experts can point to studies of hospital-induced (nosocomial) infections traced in part to clinical laboratories and the lack of adequate attention to the disposal of infectious waste products. By 1980 many states had adopted regulations for the management of infectious wastes. Special treatment of infectious waste materials is required by some Canadian provinces. But in the laboratory uses of infectious agents, even in large clinical laboratories, the volumes have not been large relative to an industrial scale, and thus federal environmental initiatives which respond to the scale of pollution have been minimal.

In the food and pharmaceutical industries, the fermentation technology has utilized mainly non-pathogenic microorganisms cultured from natural environments, or their laboratory-induced hybrids. As a consequence, little attention has been given to regulating industrial effluent consisting of biological entities that are plentiful in nature. But as genetically engineered bacterial strains constructed in the laboratory are introduced into the industrial fermentation process, or released into the environment as pesticides or pollution degraders, new expressions of concern can be

heard among those who are inclined to draw connections between the developments in synthetic chemistry and those in synthetic biology.

The goals of this chapter are threefold. First, it examines six areas where the use of microorganisms in an industrial setting is expected to grow as a consequence of the revolution in applied molecular genetics that is currently taking place. Second, it reviews the laws in the United States and Canada which are or may be applicable to the regulation of biological agents released into the environment. Third, it summarizes statutory regulations and guidelines that have been issued in the United States and Canada pertaining to the release of biological agents. The inventory of environmental laws and regulations includes those in the area of occupational safety and health.

In contrast to the use of chemicals in industrial processes, the application of microbial agents in production or as pesticides has been small. This is reflected in the fact that few regulations have been established for contaminants from bioprocess sources. This study distinguishes between the authority to regulate and the actual regulations. For example, the United States Environmental Protection Agency may have a legal authority to regulate biological waste products, but it has not chosen to exercise this authority thus far.

32.1.2 Bioprocess Sources and Pathways for Environmental Release

The term bioprocess in this study is used in a general sense to mean any human activity that produces or transports microbial agents, disperses them into the environment, or uses them as part of a system of production. The laws and regulations reviewed were chosen with consideration of the following pathways through which biological agents are released into the environment: human to human, animal to animal, or plant to plant contact; transport of etiologic agents; laboratory and clinical wastes; manufacturing processes involving large cultures of bacteria or viruses; large-scale release of biological agents into the environment; release of biological agents from experimental laboratories, through drains, human, insect or rodent vectors.

In the pharmaceutical and food industries that employ fermentation technologies, biological agents may be released inadvertently during the venting of gases, through the wastewater effluent stream or by the disposal of the sludge resulting from the fermentation process. Some technologies, such as wastewater treatment, use the indigenous organisms within the effluent stream by enhancing their growth and thereby helping them break down organic contaminants. Some efforts are underway to improve the efficiency of secondary treatment plants by adding specially cultured or genetically engineered bacteria. In these uses, the microorganisms have a natural pathway into the environment unless these biodegraders of organic contaminants are themselves disinfected after their work is completed.

Relatively little legislation has been conceived with the release of biological agents in mind. It has been a small effort compared to the regulatory activities for chemical agents and radioactive materials. The legislation which has been enacted is concerned primarily with pathogenic agents infectious to humans, plants and animals. As an example, under the quarantine acts certain organisms or their hosts are prohibited from being imported into North America. Beyond direct infectivity, there are clearly other ways that biological agents can be ecologically troublesome. They may interfere with biochemical pathways, increase the coliform bacteria levels in drinking water or affect the biological oxygen demand in lakes, rivers and streams. The guidelines that were issued in the United States, Canada and elsewhere for genetically modified organisms are based upon a broader interpretation of biohazardous materials than what is understood by a pathogenic or infectious agent. That is also true with regulations for the use of biological pesticides, where studies are required that include host specificity, allergenic effects and toxicity prior to the granting of a permit for their use.

32.1.3 Overview of Environmental Laws

32.1.3.1 United States

Regulation has been the preferred method of dealing with environmental problems in the United States. American governments at all levels have chosen to regulate sources of environmental pollution, although alternative forms of governmental intervention have been suggested (Stewart and Krier, 1978).

Several major pieces of legislation have been enacted by Congress to deal with the problems of air pollution, water pollution and hazardous substances. The federal agency given primary responsibility for implementation and enforcement of government policy as directed by these laws is the Environmental Protection Agency (EPA). EPA's enforcement role covers a number of areas including stationary sources of air pollution, discharges into the nation's waters, mobile sources of air pollution, hazardous waste sites, toxic substances, solid wastes, drinking water and pesticides.

In many instances the federal and state governments share the burden of implementation and enforcement. State agencies analogous to the federal EPA regulate and enforce state environmental laws and state components of federal programs. Some federal programs are predicated on direct state regulation with varying degrees of federal overview, others on direct federal regulation only until states develop programs which are in compliance with federal guidelines. When compliance is achieved, the state directs the regulatory program. A third category of regulation involves direct federal regulation with little or no state involvement.

The Clean Air Act (33 U.S.C. § 7401 *et seq.*) established federal controls on air pollution. It was last amended in 1977 and it is that version of the Act which is now in effect. The requirements of the Act are expressed in terms of ambient air standards which are created by statute, federal or state regulations, or permits. It was intended by Congress that the states would be primarily responsible for administering the Clean Air Act requirements through state implementation plans (SIPs).

The Federal Water Pollution Control Act (FWPCA) (42 U.S.C. § 1251 *et seq.*) was shaped in its present form by the Amendments of 1972. The goals of the Act are: (1) the achievement of swimmable and fishable waters by 1983, and (2) elimination of pollution discharge by 1985. Under the law, effluent limitations were established for industrial and municipal sources of water pollution. The Clean Water Act went through certain revisions in 1982–83, including re-authorization of some programs and clarification of particular sections.

In response to the problems posed by hazardous waste and toxic substances which may enter the environment, Congress passed three major pieces of legislation. The Toxic Substances Control Act of 1976 (TSCA) (15 U.S.C. § 2601 *et seq.*) is a product control law in contrast to a pollution control law. TSCA regulates the manufacture, distribution and sale of chemicals which 'may present an unreasonable risk of injury to health or the environment'. The Resource Conservation and Recovery Act (RCRA) (42 U.S.C. § 6901 *et seq.*) gives authority to the federal government to provide technical and financial assistance to state and local governments and interstate agencies to promote improved solid waste management techniques, and to issue regulations for the treatment, storage, transportation and disposal of hazardous wastes. The Comprehensive Environmental Response, Compensation and Liability Act of 1980 (42 U.S.C. § 9601 *et seq.*) provides the EPA with authority to require generators, transporters, treaters and disposers of hazardous wastes to remedy actual or potentially endangering hazardous waste sites and associated damage to natural resources. The legislation established a 'Superfund' and authorizes use of the fund's resources to perform the remedy if the responsible party fails to do so.

Further examination of these basic elements in the United States regulatory arsenal is necessary to understand their applicability to the industrial release of biological agents. While EPA has principal jurisidiction over industrial waste streams, other federal and state agencies, under public health statutes, can regulate the release of pathogenic agents in the environment from non-industrial sources.

32.1.3.2 Canada

In Canada, the demarcation between federal and provincial jurisdictions is framed in the British North America (B.N.A.) Act of 1867, a principal document of the Constitution of Canada along with its amendments in the Canada Act of 1982. Most of the federal powers are provided through Section 91 of the B.N.A. Act while Section 92 delineates the powers of the provinces. Amendments to Section 92 are found in Part VI of the Canada Act of 1982.

The B.N.A. Act does not address the environment specifically. Legal authority in this area has evolved through judicial interpretation. Some environmental problems lie within the jurisdiction of both the provincial and federal governments. Water pollution is a case in point. Whereas federal laws are designed to protect the fisheries, provincial laws are enacted to protect the public health.

The full impact of the new Canadian Constitution on the B.N.A. Act and its delineation of

powers between federal and provincial jurisdictions is not fully understood at this time. Therefore, this chapter emphasizes historically-developed environmental jurisdictions.

Both federal and provincial governments have powers with respect to agriculture. Each can pass laws regulating fertilizers, feed products and pesticides. In the case of pesticides, the provinces have promulgated additional regulations beyond those of the Parliament. Where there are areas of overlapping jurisdictions, the federal government will at times resort to measures involving negotiation and coordination with provincial authorities. And when federal and provincial statutes are in conflict, federal laws generally prevail.

Chemical contaminants in the environment are regulated by the federal government under four main acts: The Fisheries Act, the Clean Air Act, the Canada Water Act and the Environmental Contaminants Act. In most instances these Acts define an environmental contaminant broadly enough to include biological agents. The exception is the Environmental Contaminants Act which applies exclusively to 'inanimate matter'.

According to Section 92 of the B.N.A. Act, the provinces are given authority over the working environment and waste disposal. The federal government can enact occupational health and safety statutes for a select number of industries that fall under its jurisdiction, subject to Part IV of the Canada Labour Code. Generally, federal legislation has been upheld where problems have taken on 'national dimensions' or become a matter of 'national concern'.

Ince (1976) makes the following observations about the genesis of environmental law in Canada: 'Because provincial powers of legislation are framed in such general terms, it is very difficult to limit provincial powers. Over the past century, the courts have, quite understandably, interpreted these powers very broadly which has enabled the provincial legislatures to deal with a vast number of areas. On the basis of the provinces' powers to control property, civil rights and local matters, a great deal of environmental legislation is authorized. We can safely say that these powers allow the provinces to legislate on land, air, water and noise pollution, land use control, parks and industrial regulation'.

Indeed, many provinces have enacted laws and issued regulations for chemical contaminants, radiation, clean air and water, waste management, pesticides and the working environment. These statutes were not developed with biological agents in mind, although in some cases the language is sufficiently broad to justify their application to microbial forms, if certain conditions are satisfied. In contrast to the strictly formal and mandatory framework for regulatory policy in the United States, Canada is known for a more informal and discretionary system of lawmaking. Within this framework there is considerable federal–provincial negotiation, consultation and cooperation, as well as industry–government consultations.

Before U.S. and Canadian laws and regulations are examined more fully with respect to the release of biological agents, a brief review is given of the major applications of microorganisms in industry.

32.2 POTENTIAL HAZARDS OF BIOPROCESSES

32.2.1 Pharmaceutical Industries

The conventional organisms that are used to manufacture antibiotics consist of a relatively narrow taxonomic range. Nearly a thousand distinct antibiotics are derived from six genera of filamentous fungi including molds of the genus *Cephalosporium* and the genus *Penicillium*. By inducing mutations through radiation and chemical substances, these two molds were the main source of antibiotics for 30 years. Other drugs manufactured by microbial fermentation techniques are viral and bacterial antigens, antifungal agents, antitumor drugs, alkaloids and vitamins.

Fermentation technology has been the principal process for manufacturing pharmaceuticals. Volumes produced in the fermentation vats may be as high as 100 000 l. A brief description of the process is given by Aharonowitz and Cohen (1981).

Recombinant DNA technology opens up opportunities for the biosynthesis of drugs, hormones and other biologically active substances by microorganisms containing the inserted relevant information. Somatostatin (a hormone made in the hypothalamus), insulin, growth hormone and interferons (antiviral agents) are currently being synthesized by *E. coli* K12 which have the requisite gene inserts. Gene-splicing techniques are also beginning to revolutionize vaccine production. Molecular cloning makes it possible to manufacture in large quantities non-virulent, nonselfreplicable segments of a virus that can be used to immunize a host.

32.2.2 Food Industries

The food processing industry uses microbial activity in two ways (Office of Technology Assessment, 1981): (1) inedible biomass is transformed by microorganisms into food for human consumption or animal feed; (2) organisms are used in food processing either by acting directly on food or by providing materials that can be added. Enzymes and vitamins are examples of the latter use. Food processing has utilized enzymes extracted from plants and animals. Microbial production of them has become economically competitive in some cases. Bacteria and molds also are used to make vitamins, such as riboflavin (*Ashbya gossypii*) and vitamin B12 (*Propionibacterium shermanii* and *Pseudomonas denitrificans*).

New developments in genetic engineering, *e.g.* protoplast fusion, are expected to broaden the use of fermentation in the food industry (Demain and Solomon, 1981). The genomes of two distinct species can be brought into a single cell. Recombinant DNA technology establishes genes as interchangeable elements capable of being transplanted between diverse organisms. Food processing need not depend exclusively on the enzymes found naturally in microorganisms; even human enzymes can be produced in large quantities by cloning their DNA in bacteria.

32.2.3 Energy Production

The production of liquid fuels through fermentation can be improved upon in two ways through genetic engineering (Office of Technology Assessment, 1981). First the genetic manipulation of plant seeds may yield better quality and greater quantity of biomass. Second, microbial mutants are being sought to improve the efficiency of converting agricultural and forest biomass into liquid fuel. Ethanol, among the most important organic substances in the chemical industry, has attracted significant attention in the biotechnology field. The genetic programming of conventional organisms used in the fermentation of ethanol, which include yeasts, *Zymomonas mobilis*, *Clostridium thermocellum* and *Trichoderma reesei*, has been proposed 'to increase the amount of certain enzymes in the cell or to replace one enzyme with another that has a higher specific activity' (Eveleigh, 1981, p. 168).

In a report entitled *Biotechnology: A Development Plan for Canada* (Task Force on Biotechnology, 1981), it was noted that the production of methane from the fermentation of agricultural, industrial and domestic wastes is another fuel prospect in addition to ethanol. Moreover, the report states, the bioproduction of substitute fuels to replace hydrocarbon-based conventional crude oil derivatives, 'could be of significance in determining alternate energy strategies for Canada'.

Some concern has been raised about the ecological impacts of genetically modified organisms released into the environment either purposefully or inadvertently through the waste stream. Potential hazards of disturbing biochemical pathways or altering ecological balances have been cited (Krimsky, 1982, p. 122; Wright, 1982). In Massachusetts, several communities have passed ordinances that regulate fermentation with recombinant organisms (Krimsky *et al.*, 1982) to insure that novel organisms are adequately contained or appropriately treated prior to being released in the waste stream.

32.2.4 Waste Treatment

Microbial activity is used in the detoxification and degradation of sewage and industrial wastes. Secondary sewage treatment facilities use some form of biological activity to degrade organic materials. The activated sludge process developed early in this century has depended upon the indigenous microorganisms in the waste stream. The activity of the microorganisms may be enhanced by additives or environmental controls, such as pH and temperature.

More recently, sludges have been inoculated with mixtures of microorganisms which are designed to accelerate the degrading process or broaden the types of chemicals broken down by bacteria. The next important breakthrough in this area will be made through genetic engineering. Microorganisms are being genetically constructed to degrade specific compounds found in industrial wastes. Organisms have been developed which are successful at the laboratory scale in degrading industrial organic compounds such as polychlorinated biphenyls (PCBs) and the herbicide 2,4,5-T. The Canadian Task Force on Biotechnology (Task Force on Biotechnology, 1981) cited two advantages offered by biological processes over other methods of detoxification of

effluents. First, biological processes are readily adaptable to the varied composition of wastes and conditions of degradation. Second, a large selection of microorganisms can degrade a wide variety of substances. The Task Force reported that 'increased pressure upon new and existing industries to invest more heavily in waste treatment and pollution control could spur more development in this application of biotechnology'.

Some policy experts are concerned that novel organisms developed for sewage treatment may constitute new forms of pollution. Johnston (1981) discussed some environmental outcomes of enhanced sewage treatment through new microbial systems. '[T]he use of microbes for pollution treatment and control must be viewed as an irreversible release of the organism and its DNA to the environment . . . . Even if consideration were restricted to a contained system such as a sewage treatment plant, where disinfection of sludge and effluents could be undertaken, it would be unrealistic to guarantee that no viable organisms would be released . . . . Unlike biological wastes from pharmaceutical manufacturers . . . the sheer volume of effluent from waste treatment facilities makes the disinfection impractical. Economic constraints alone negate the effective sterilization of such waste streams . . . . It is imperative therefore, that any use of engineered organisms for waste treatment be considered a deliberate, irreversible release of the organism and its DNA to the environment.'

32.2.5 Bioorganic Chemistry

Industrial organic chemicals including enzymes, acids and solvents have been manufactured by microbial fermentation. There are many organic chemicals which can be made either by chemical synthesis or by fermentation. The deciding factor has been economics. According to Eveleigh (1981), microorganisms yield products for some 200 substances of commercial value; only a few of those are currently manufactured by biological methods. This group includes ethanol, *n*-butanol, acetone, acetic acid, citric acid, lactic acid, amino acid and various enzymes. Solvents like *n*-butanol, acetone and glycerol, once manufactured by biological methods, are currently produced mainly by chemical synthesis. Efforts are underway to exploit the use of thermophilic bacteria and renewable-resource-based feedstocks to again manufacture solvents by fermentation.

Zaugg and Swarz (1982) cite three genera of organisms that will probably be used in chemical production: *Pseudomonas*, *Acinetobacter* and *Flavobacterium*. The authors claim little is known about the effects these organisms have on man and express some apprehension about the introduction of genetically engineered organisms in production. 'The chemical industry has a poorer record than the pharmaceutical industry in areas related to worker safety and environmental protection, causing one to be apprehensive of the new technologies for which industry-wide experience is limited.'

32.2.6 Biological Agents Used in the Environment

Both current and contemplated uses of microorganisms in non-contained environments are designed to improve operations in the fields of metallurgy, agriculture and *in situ* pollution control. Bacteria have been used to extract metals from low grade ores. Copper and uranium are mined and commercially purified by a process that includes leaching by bacteria of the genus *Thiobacillus*. The bacterial leaching process takes two principal forms: organisms act directly on the ore to extract the metal, or they produce other chemicals which make separation of the metal possible.

Zaugg and Swarz (1982) cite some potential hazards in the use of organisms in the mining industry. '[A]ll foreseeable applications of biological processes . . . involve microbial systems operating in relatively open environments, such as slag heaps or tailings ponds. Consequently, there are risks that microorganisms or their metabolic products will inadvertently contaminate the local ecology'. The authors offer three examples: (1) bacterial leaching operations that generate large quantities of sulfuric acid could acidify water supplies; (2) *Thiobacilli* and related species may acquire the traits to infect humans; (3) metals concentrated by bacteria from dilute mine waters can accumulate in the food chain.

The organism *Xanthomonas campestris* produces xanthan gum which is used for oil recovery by increasing the viscosity of water used to displace the oil. And while some organisms are used in oil recovery operations, another has been developed to degrade crude oil. The General Electric Corporation was awarded the first patent on a microorganism *sui generis* in the United States

after the Supreme Court upheld a lower court decision to grant a patent for a strain of *Pseudomonas putida* (*Diamond* v. *Chakrabarty*, 1980). At the present time the organism has not been marketed by the company. According to the Office of Technology Assessment (OTA), bacteria have been used to degrade gasoline in underground spills and strains are available for breaking down highly toxic substances such as pentachlorophenol. Alexander (1981) reports on a growing interest in biodegradation of toxic chemicals.

The Office of Technology Assessment (OTA) cites some ecological risks over the release of such organisms into the environment (OTA, 1981, p. 118). 'Introducing large numbers of genetically engineered microorganisms into the environment raises questions of possible ecological disruption, and liability if damage occurs to the environment or human health . . . the present lack of sufficient scientific knowledge, scientists, and interdisciplinary teams, and the concerns for ecological safety present the major obstacles to the use of genetic engineering in microbial leaching.'

OTA raises some environmental concerns about the use of organisms in oil recovery also. 'All strains of *Xanthomonas*, which produce xanthan gum polymer, are plant pathogens. Other microorganisms with potential, such as *Sclerotium rolfii* and various species of *Aureobasidium*, have been associated with lung disease and wound infections, respectively' (OTA, 1981).

The OTA study (OTA, 1981) expresses a cautious optimism about the large scale use of microorganisms in the environment. 'Immediate environmental and legal concerns, therefore, arise from the potential risks associated with the release of microorganisms into the environment. When they naturally cause disease or environmental disease or environmental disruption, their use is clearly limited. And when they do not, genetic engineering raises the possibility that they might.'

An agricultural application which requires spreading organisms in the environment is the use of biological insecticides, fungicides and herbicides. It is estimated that 100 known species of bacteria are pathogenic to insects, but only a few species have been developed into commercial insecticides (OTA, 1981). The bacterial agents are *Bacillus popilliae*, *Bacillus thuringiensis* and *Bacillus moritai*. Here, too, genetic engineering may make it possible to increase the potency of bacterial strains by doubling the genes that code for the toxins which destroy the insect pests.

Supporters of biorational pesticides as a substitute for synthetic chemical agents believe that these organisms occupy a narrow ecological niche for which there is no evidence of departure. The viral pesticide agents have shown no potential for adverse human effects. Moreover, viruses may occur naturally at much higher levels than result from their intentional use as pest control agents. On the other side are those who support extensive testing. They cite the potential for the latency of viral agents in non-target species, including man, where the virus may interact with the host's genetic material and could be involved in a disease etiology. Second, they cite the capacity of the viruses to mutate which may change their specificity and selectivity (EPA, 1979b).

32.3 LAWS APPLICABLE TO BIOLOGICAL AGENTS

32.3.1 United States

32.3.1.1 Authority under the Federal Food, Drug and Cosmetic Act (FFDCA)

The Federal Food, Drug and Cosmetic Act (21 U.S.C. § 301 *et seq.*) and Section 351 of the Public Health Service Act (42 U.S.C. § 201 *et seq.*) give the Food and Drug Administration (FDA) authority to regulate food, drugs, biologics, medical devices and veterinary medicines. The statutes are broad enough to cover recombinant DNA (rDNA) techniques, and the agency's authority will extend to products it ordinarily regulates when they are manufactured by newly developed genetic engineering methods.

University and industrial laboratories are developing sophisticated techniques which will be used to create products for which FDA approval must be obtained before they can be marketed. Several examples of these products, some in the experimental stage, others closer to large scale production and marketing are given by Miller (1981): (1) drugs—human insulin, human growth hormone, thymosin, ACTH, endorphins; (2) biologics—interferons, vaccines, serum albumin, urokinase; (3) enzymes used in food processing; (4) medical devices—*in vitro* diagnostic tests for thalassemia or sickle cell anemia; (5) veterinary medicine—interferons, animal growth hormones.

Although the FFDCA focusses on products, the statute can be used to control production processes as well. FDA can regulate chemicals being produced for use in a product regulated by the agency. This authority extends to chemicals used in experiments designed to develop products

which are within the purview of FDA. In theory, FDA can regulate the development of genetically engineered host organisms, as well as plasmids and vectors used in rDNA processes, if the procedure involves making a product for which FDA approval is necessary. The agency has not determined how or whether it will exercise this authority, the extent of which is unclear.

32.3.1.2 Public Health Services Act (PHSA)

Section 361 of the Public Health Services Act (42 U.S.C. § 264) authorizes the Department of Health and Human Services (DHHS) 'to prevent the introduction, transmission, or spread of communicable diseases'. This might provide authority to require adherence to Section I-D-2 of the National Institutes of Health rDNA Guidelines (NIH, 1982), which currently restricts experiments that deliberately form rDNA molecules containing genes for the biosynthesis of certain toxins lethal to vertebrates. The Recombinant DNA Advisory Committee (RAC) of the NIH voted in February, 1982 to drop the prohibition for this type of experiment and requires instead prior approval by the committee, NIH and the local institutional biosafety committee. The recommendation has been approved by the acting director of the National Institute of Allergy and Infectious Diseases of NIH, who currently has authority to promulgate rDNA guidelines for institutions receiving funding from NIH.

Aside from the Guidelines, Section 361 of the PHSA could potentially be used if FDA concluded that an rDNA product could be harmful to humans or the environment, but no regulations have yet been promulgated.

32.3.1.3 Resource Conservation and Recovery Act of 1976 (RCRA)

One of the objectives of RCRA (42 U.S.C. § 6901 *et seq.*) stated in § 1003(4), is to promote the protection of health and the environment by 'regulating the treatment, storage, transportation, and disposal of hazardous wastes'. A 'hazardous waste' is defined in § 1004(5) as a solid waste which, because of its quantity, concentration, or physical, chemical or infectious characteristics may (a) cause, or significantly contribute, to an increase in mortality or an increase in serious irreversible, or incapacitating illness; or (b) pose a substantial or potential hazard to human health or the environment.

RCRA is administered by the Environmental Protection Agency (EPA), which has promulgated regulations for the generation, transportation, storage and disposal of hazardous wastes (40 C.F.R. Parts 261–264, 1980). Numerous provisions of these regulations are being litigated.

Solid wastes, considered hazardous wastes, and thus regulated under RCRA, are identified and listed in 40 C.F.R. Part 261, 1980. In addition to listing hazardous wastes, EPA has prescribed an 'extraction procedure' (EP) (40 C.F.R. Part 261, Appendix II). Solid wastes which exhibit EP toxicity as well as those listed as hazardous wastes in Subpart D will be regulated as hazardous wastes. EPA has also prescribed processes to reduce pathogens in solid waste (*Fed. Regist.*, 1979).

If pathogenic organisms remain in the waste after treatment or it contains substantial amounts of heavy metals or toxic chemicals, it is probably hazardous waste and the generator, transporter and disposer of the waste must comply with EPA requirements. EPA has issued standards applicable to generators (40 C.F.R. Part 262) and transporters (40 C.F.R. Part 263) of hazardous waste and owners and operators of hazardous waste treatment, storage and disposal facilities (40 C.F.R. Part 264). Section 3002 of RCRA authorizes the use of a 'manifest system' to track shipments of hazardous waste from the time it is generated until final disposal. If a manufacturer determines that his waste is hazardous, he must comply with EPA regulations establishing standards for the manifest system (40 C.F.R. § 261.5(c)(5)).

Manufacturers whose solid waste includes microorganisms will be subject to EPA hazardous waste regulations issued under RCRA if the waste after treatment contains pathogenic organisms, EP toxic substances, or is a listed hazardous waste in nonexempt quantities.

32.3.1.4 Clean Air Act (CAA) (42 U.S.C. § 7401 et seq.*)*

If an industrial process results in the release of 'criteria pollutants', *i.e.* hazardous air pollutants for which standards have been set by EPA, the company must comply with Parts A, C and D of

Title I of the Clean Air Act (40 C.F.R. Part 50). It is not likely, however, that the operation of a fermentation plant will result in emission of criteria pollutants unless the liquid wastes of the fermentation process were to be dried and incinerated (EPA, 1976).

Section 112 (42 U.S.C. § 7412) authorizes EPA to set emission standards for non-criteria hazardous air pollutants which 'may reasonably be anticipated to result in an increase in mortality or an increase in serious irreversible or incapacitating reversible illness'. If EPA can demonstrate that a microorganism or a product synthesized by a microorganism which is emitted into the air poses such a risk it may promulgate hazardous air pollution regulations establishing emission standards. However, since the procedure for promulgating a hazardous air pollutant standard is time consuming, it has been suggested that EPA will be more likely to regulate airborne microorganisms containing recombinant DNA molecules or their hazardous by-products under the Toxic Substances Control Act (McGarity, 1981).

The term 'air pollutant' as defined in § 302(g) includes a 'biological . . . substance . . . which is emitted into or otherwise enters the ambient air'. Microorganisms which escape from a fermentation vessel would fit within this definition, however, if it is unlikely that they travel beyond the workplace, they would more likely be regulated by the Occupational Safety and Health Administration (OSHA).

As the biotechnology industry develops and microorganisms produce potentially hazardous products on a large scale, the danger of emission of hazardous air pollutants may increase. The CAA may play a larger role in regulation of the industry at that time.

32.3.1.5 Federal Water Pollution Control Act (FWPCA) as amended by the Clean Water Act of 1977 (CWA) (33 U.S.C. § 1251 et seq.*)*

The FWPCA regulates the discharge of conventional pollutants, which include biological materials, into navigable waters of the U.S. Under Sections 301, 304(b), (c) and 306(b), EPA may promulgate technology-based controls for new and existing dischargers of conventional pollutants. Conventional pollutants are defined in Section 304(a)(4) to include biological oxygen demanding pollutants (BOD), suspended solids, fecal coliform and pH. Dischargers of conventional pollutants are to be regulated assuming application of 'best conventional pollution control technology' (BCT) (Section 301). Even if a source does not belong to a category for which effluent limitations and guidelines have been promulgated, it must still obtain a National Pollutant Discharge Elimination System (NPDES) permit under Section 402. EPA has promulgated effluent limitations and new source performance standards for the pharmaceutical industry which specify the amounts of conventional pollutants that can be discharged into navigable waters by new and existing fermentation processes (40 C.F.R. Part 439).

The category of toxic water pollutants is regulated under a different scheme from conventional pollutants. Section 307 adopts the list of 65 toxic water pollutants (40 C.F.R. § 401.15) and empowers EPA to add or withdraw substances from this list.

EPA can prescribe, under Section 307(a)(2), toxic effluent limitations, which require the use of 'best available technology' (BAT) for treating toxic pollutants. In compiling a list of toxic pollutants, EPA must take into account the toxicity, persistence and degradability of the pollutant. For toxic water pollutants, there are no water quality based modifications of BAT. Under Sections 307(a)(2) and (a)(4), EPA is empowered to promulgate toxic effluent standards which are more stringent than toxic effluent limitations. They are ambient standards which must be set at a level that provides an ample margin of safety.

Depending upon the category into which waste products of the biotechnology industry fall, EPA can regulate discharges into navigable waters under the scheme provided by FWPCA for toxic, conventional or residual pollutants. The most stringent regulations apply to toxic pollutants which must be treated using BAT.

32.3.1.6 Toxic Substances Control Act (TSCA) (15 U.S.C. § 2601 et seq.*)*

The purpose of TSCA is to develop data concerning potentially hazardous chemicals and to authorize the EPA to regulate chemicals used both in research and commerce so as to minimize risk to human health and the environment (15 U.S.C. § 2601(b)). It was intended by Congress to be used to fill in regulatory gaps left by other environmental statutes. If EPA can regulate under another statute, it is obligated to do so before using TSCA. The provisions of TSCA apply to

research as well as manufacturing and only Section 5 which requires premarket notification for a 'significant new use' of an existing chemical substance is not applicable to university research.

A key legal issue with respect to the applicability of TSCA to genetically engineered microorganisms is whether the recombinant DNA within the microorganism will be considered a 'chemical substance' or a 'mixture'. A 'chemical substance' is defined in Section 3(2) to include 'any organic or inorganic substance of a particular molecular identity' including 'any combination of such substances occurring in whole or in part as a result of a chemical reaction or occurring in nature'. The statute excludes pesticides, tobacco and substances subject to FFDCA or the Atomic Energy Act. It is unclear whether the definition would include microorganisms containing recombinant molecules and the issue will have to be litigated if EPA chooses to use its authority under TSCA to regulate microorganisms.

In promulgating regulations under TSCA, EPA took the position that 'the definition of chemical substances does not exclude life forms which may be manufactured for commercial purposes . . . ' (*Fed. Regist.*, 1977). However, in a letter responding to a Senate inquiry, former EPA administrator Douglas M. Costle (1978) stated that although EPA agreed that rDNA molecules were 'chemical substances' within the meaning of Section 3, it wasn't clear that the host organisms containing these molecules were subject to TSCA. Some legal experts (McGarity, 1981) believe that if EPA were to assert such authority and its initiative survived legal challenge, TSCA could potentially be used to regulate the biotechnology industry.

Section 4 authorizes EPA to require testing of chemicals which 'may present an unreasonable risk of injury to health or the environment' and for which there exist insufficient data and experience to predict the risk, or chemicals which will be produced in substantial quantities and which may reasonably be expected to enter the environment in substantial quantities.

Assuming that spliced DNA is held to be a 'chemical substance' or a 'mixture', EPA must first find that it may present an 'unreasonable risk' before it could require testing. Although it is possible that in the future harmful strains will be developed, present scientific evidence does not support a finding that genetically altered microorganisms now being utilized for rDNA work present an unreasonable risk. However, the testing requirement in Section 4 could be imposed by EPA if new or less well-characterized host strains are used.

The second requirement of Section 4, that the chemical will be entering the environment in substantial quantities, also serves to reduce the probability that testing would be required of the genetic engineering industry. Since the fermentation process is enclosed, it is unlikely that escaping microorganisms or chemicals would cross the 'substantial quantities' threshhold. However, this may not be the case for non-pharmaceutical use of genetically engineered microorganisms, such as those used for the digestion of spills.

TSCA authorizes EPA to compel notification of new chemicals or mixtures before they are manufactured, to require submission of relevant records, to inspect manufacturing facilities and to require testing in order to generate adequate risk data on proposed new chemicals.

In 1983 EPA began exploring the agency's role in biotechnology. The EPA Administrator's Toxic Substances Advisory Committee recommended that the agency apply TSCA to regulate the release of genetically modified organisms into the environment. EPA will use its experience with regulating microbial pesticides as a basis for addressing the problem (see Section 32.4.1.1).

In conclusion, the authority of EPA to regulate the biotechnology industry and university researchers under TSCA will be established only if the courts hold that recombinant DNA molecules, vectors and host organisms containing altered DNA, or even natural biological entities that might present a hazard, are 'chemical substances' or 'mixtures' as these are defined in Section 3.

32.3.1.7 Marine Protection, Research and Sanctuaries Act of 1972

The Marine Protection, Research and Sanctuaries Act of 1972 (33 U.S.C. § 1401 *et seq.*) was passed by Congress in order to 'prevent or strictly limit' the use of the oceans for disposal of wastes of almost any type, including those generated by the pharmaceutical industry. Title I regulates ocean dumping and the transportation for dumping of waste materials through a permit program operated by the EPA and the Army Corps of Engineers. Title II directs the Secretary of Commerce to conduct research on the effects of ocean dumping through the Office of Marine Pollution Assessment.

The Act defined 'unreasonable degradation' of the environment in terms of a balance between environmental and public health factors and the availability of alternatives to dumping (33 U.S.C. § 1412(a)). Current regulations ban the dumping of sludge in the ocean unless it has been

determined that there is not a better alternative method of disposal. EPA makes this determination on a case-by-case basis after balancing the statutorily mandated factors.

Under 1982 draft proposals, EPA would make it easier to obtain permits to dispose of dredged material and low level radioactive wastes. EPA has identified the pharmaceutical industry as one which would benefit from the revised rules. There is uncertainty at this time as to whether these proposals will be promulgated as regulations.

32.3.1.8 Federal Insecticide, Fungicide and Rodenticide Act (FIFRA)

Chemical and biological pest control agents are regulated by EPA under the Federal Insecticide, Fungicide and Rodenticide Act (7 U.S.C. § 136 *et seq.*) as amended in 1972, 1975 and 1978. Section 2(u) of FIFRA defines a pesticide as 'any substance intended for preventing, destroying, repelling, or mitigating any pest, and . . . any substance or mixture of substances intended for use as a plant regulator, defoliant, or desiccant'. The language of FIFRA provides EPA with very broad regulatory authority. Each new pesticide must be registered by the agency before it can be marketed. Prior to registration EPA evaluates the safety and efficacy of the agents. The registration must be approved if the pest control agent performs its intended function without unreasonable adverse effects on the environment, and when used in accordance with accepted practice it will not cause unreasonable adverse effects on the environment. The term 'unreasonable adverse effects on the environment' is defined in the Act as 'any unreasonable risk to man or the environment, taking into account the economic, social and environmental costs and benefits of the use of any pesticide' (§ 136(a)(c)(5)). A pesticide which has been registered may be cancelled if its continued use poses a 'substantial question of safety' to man or the environment. EPA may also ban the production and distribution of a pesticide if it presents an imminent hazard.

Responding to the differences in biochemical activity between chemical and biological pesticides, EPA issued two sets of guidelines for registering pest control agents. (EPA, 1978a; EPA, 1980). The justification for the separate registration requirements is provided by the agency: 'The vast majority of the more than one thousand pesticide active ingredients regulated by EPA . . . are man-made organic and inorganic chemicals and are innately toxic. Less than one percent of the pesticide active ingredients registered by the Agency are inherently different in their mode of action from most organic and inorganic compounds. This small group is exemplified by the living or replicable biological entities, such as viruses, bacteria, fungi and protozoans. Naturally occurring biochemicals, such as plant growth regulators and insect pheromones, also function by modes of action other than innate toxicity'. EPA defines this group of pest control agents as 'biorational pesticides'. A discussion of regulations for 'biorational pesticides' is given in Section 32.4.

32.3.2 Canada

In a pattern similar to that of the United States, during the 1970s the Canadian Parliament responded to societal concerns over chemical contamination of the environment with the passage of new laws followed by a host of regulations. However, in contrast with the United States, the federal government in Canada does not have principal jurisdiction over the release of hazardous agents into the environment. The authority is divided between the federal and provincial sectors. In effect, Canada has two tiers of pollution control statutes and occupational health and safety laws, those passed by Parliament with application to federal jurisdictions and those passed by the provinces. In cases where jurisdictions overlap, the federal government has preemptive authority. Many of the laws reviewed in this section were not explicitly enacted for controlling biological agents but where the statutory language is framed broadly enough, their applicability to such agents becomes manifest.

32.3.2.1 Environmental Contaminants Act (S.C. 1974–75, C.72)

The goal of the Environmental Contaminants Act (ECA) is 'to protect human health and the environment from substances that contaminate the environment'. The Act defines 'substance' quite explicitly in a way that excludes biological agents. 'A "substance" means any distinguish-

able kinds of inanimate matter' capable of becoming dispersed or transformed in the environment, into something of the same chemical moiety or having similar chemical properties (Sec. 2).

The Act is under the joint jurisdiction of the Minister of the Department of Environment and the Minister of the Department of National Health and Welfare. Under the law, the Governor in Council may establish the maximum quantity or concentration of a substance released into the environment in the course of any commercial, manufacturing or processing activity, and to establish a schedule of substances which may not be imported, manufactured, processed, offered for sale or used.

If the Ministers have reason to conclude that a substance may endanger human health or be a threat to environmental quality they may (1) require commercial producers of the substance or class of substances to notify the government of such activities and provide information about the substances; (2) require producers and importers of the substance or any product containing it to conduct tests which the Ministers may reasonably require. Like the Toxic Substances Control Act in the United States, the ECA is designed to regulate chemicals before they are put into the market place. The Act requires the Canadian federal government to consult with the provinces and industry prior to taking any regulatory action (Sec. 5(1)(b)). Like other federal environmental control statutes, the ECA is an enabling law which becomes realized when specific regulations are made under it.

While the ECA is directed at the regulation and control of inert chemical substances and not organisms, it could have jurisdiction over chemicals produced by microorganisms. If chemical-producing bacteria are used in an industrial process, and the release of the organisms into the environment is tantamount to a release of the chemicals, then it is plausible that the ECA might be applied, but as a control measure for the chemical substances. The applicability of the law to microbially-produced chemicals will depend upon the large release of organisms that synthesize chemicals which endanger humans or the environment. A distinct area of ambiguity is whether toxin-producing bacteria fall under the Act since the toxins themselves are chemical products with harmful side effects. In whichever manner the chemicals are produced, there is a 500 kg cut-off for manufacture or import below which the law does not apply, making its application to biological agents even a more remote possibility.

32.3.2.2 Pest Control Products Act, 1968–69 (R.S.C. 1970, C. P-10)

The Pest Control Products Act (PCPA) regulates products used for the control of pests and the organic functions of plants and animals. It applies to any 'product, device, organism, substance or thing that is manufactured, represented, sold or used as a means for directly or indirectly controlling, preventing, destroying, mitigating, attracting or repelling any pest' (Sec. 2). The Minister of Agriculture administers the Act and is responsible for 'prescribing the form, composition and other standards for (pest) control products' (Sec. 5).

Under the PCPA, any pest control product sold or imported into Canada must be registered, conform to prescribed standards, and be labeled and packaged as determined by the Minister (Sec. 4). To satisfy the registration requirement, a producer or importer must provide data that demonstrate the product is both safe and effective under acceptable standards of use.

The use and manufacture of pesticides is controlled not only by federal laws and regulations in Canada, but also by a variety of provincial legislation and regulations.

The regulations issued under the Act provide the registration requirements for pest control products. Despite the broad statutory language, the regulations issued are targeted toward chemical agents, *i.e.* hazard information refers to toxicological data, but not information about infectious agents.

32.3.2.3 Clean Air Act (S.C. 1970–71–72, C.47)

This Act gives the Governor in Council authority to establish national ambient air quality standards for contaminants emitted into the air by stationary sources. To be regulated, the emissions must impose risks to health or be in violation of an international agreement. For the purpose of the Act, an air contaminant is defined as 'a solid, liquid, gas or odour, or a combination of any of them that, if emitted into the ambient air, would create or contribute to the creation of air pollution' (C.47, Sec. 2). Air pollution is defined as a condition of the ambient air that, from the presence of contaminants, 'endangers the health, safety or welfare of persons, interferes with the

normal enjoyment of life or property, endangers the health of animal life, or causes damage to plant life or property' (C.47, Sec. 2).

Three ambient air quality objectives are specified: maximum tolerable limit; maximum acceptable limit; and maximum desirable limit. The government's standards are only guidelines and not legally enforceable. The objectives provide a signal to industry about potential federal regulations, and to the provinces that they might adopt the emission standards into their own regulations. The Minister of Fisheries and Forestry may enter into agreements with the provincial governments for the purpose of 'facilitating the formulation, coordination and implementation of policies and programs designed for the control and abatement of air pollution . . . ' (C.47, Sec. 19).

The description in the Act of an air contaminant would seem to include biological organisms that might be released in large-scale fermentation processes as part of the gaseous effluent. For regulation, the burden is on the government to demonstrate that the gaseous effluent, if it contains viable organisms, represents a hazard to human health, endangers the environment or interferes with the normal enjoyment of life.

32.3.2.4 Canada Water Act (R.S.C. 1970, 1st Supplement, C.5)

This Act authorizes the establishment of water quality management areas and comprehensive water resource management programs by the federal government in collaboration with provincial governments. Under the management of water quality are included the establishment of waste treatment facilities and water quality management plans. These plans make recommendations about the types of wastes and the quantities that may be discharged into the water as well as the conditions for such discharge. Waste is defined broadly as 'any substance that, if added to any waters, would degrade or alter . . . the quality of those waters to an extent that is detrimental to their use by man or any animal, fish or plant that is useful to man . . . ' (Sec. 2). This Act is an appropriate vehicle for two types of biological releases into the environment. It would appear to cover the processing of sludges from wastewater treatment plants that may contain viable organisms. The Act may also have jurisdiction over the use of novel organisms in the waste treatment process, since it includes recommendations for the types of treatment facilities necessary to achieve prescribed standards.

32.3.2.5 Fisheries Act (R.S.C. 1970, and amendments S.C. 1977, C.35)

Authority for the Federal Fisheries Act (FFA) arises out of federal jurisdiction over the seacoast and inland fisheries. The Act has broad powers making almost any discharge to waters inhabited by fish under its purview. It prohibits the disposal of deleterious substances into such waters. The substances referred are considered to be those which, when found in water, make it 'deleterious to fish or to the use by man of fish that frequent that water' (Sec. 7). The federal government may specify substances it classifies as deleterious under the Act and establish conditions under which substances can be legally disposed.

The Water Pollution Control Directorate of Environment Canada has issued regulations and guidelines under FFA for certain industrial sectors pertaining to the control of the discharge of conventional pollutants. According to Cornwall (1982), 'none of these regulations and guidelines have included biological agents as parameters; nor do they involve the fermentation industry directly'.

The Water Pollution Control Directorate is actively addressing the control of the discharge of toxic chemicals; the regulation of biological agents in wastewaters is not currently under consideration. However, the Directorate has issued a report on the lack of effective treatment processes for the reduction of *Salmonella* populations in the liquid effluent from meat and poultry plants (WPCD, 1976). The report recommended disinfection of the treated effluents before the *Salmonella* organisms are discharged into the environment.

32.3.2.6 Quarantine Act (R.S.C. 1970, C.33, 1st Supplement)

This Act gives the Minister of National Health and Welfare authority to prevent the introduction into Canada of infectious agents or contagious diseases. The Minister publishes a schedule of

such agents or diseases that fall under the regulations. A quarantine officer may order the quarantine of any person arriving in or departing from Canada who may be in possession of such agents, be a carrier of infections, be infected with insects that may be carriers of such agents, or may have been in close proximity with a person satisfying these conditions. The officer may also require the disinfection of any conveyance found to be carrying agents of an infectious or contagious disease. The Act has no jurisdiction over industrial process releases of microorganisms, the disposal of infectious materials, or the inter- or intra-province transport of biological agents.

32.3.2.7 Canada Shipping Act (R.S.C. 1970, C.S-9 as amended in S.C. 1971, C.27)

The Governor in Council may issue regulations prohibiting the discharge from ships of pollutants to all Canadian waters and fishing zones under federal jurisdiction. A pollutant is defined (C.27, Part 19, Sec. 736) as 'any substance that, if added to any waters, would degrade or alter or form part of a process of degradation or alteration of the quality of those waters to an extent that is detrimental to their use by man or by any animal, fish, or plant that is useful to man . . . '. The Act would apply to the discharge from ships of fermentation sludges containing biological materials if they threaten to alter the ecological balance of nature. However, for the purposes of implementation, the Governor in Council classifies substances as pollutants.

32.3.2.8 The provinces

Under Section 92 of the British North America (B.N.A.) Act, provincial legislatures have authority within their provinces over matters of manufacturing, municipal institutions, property and civil rights, the working environment, and waste disposal. Although the B.N.A. Act provides no federal–provincial division of authority on environmental affairs, the provinces have developed considerable responsibility and autonomy for the regulation of environmental contaminants. Most of the provinces have a variety of pollution control statutes in conjunction with more established public health laws that regulate the discharge of effluent into the air, water or land. Ilgen (1981) finds that 'while provincial governments have found their own department of environment, there seems thus far to be a willingness to cede these residual powers in the control of toxic substances to the federal government'.

The regulatory instrument used most frequently in provincial regulation for the discharge of pollutants is a system of licensing, permitting, or issuance of guidelines. In cases where the federal government establishes minimal environmental quality standards or performance criteria for air or water, the provinces build upon these standards in their regulations. For those situations where there is overlapping jurisdictions, coordinated regulatory agreements are established between federal and provincial governments.

For this section it will suffice to illustrate a few examples of provincial statutes that pertain to biological effluent.

In Alberta, air pollutants are regulated by the Clean Air Act (1971, amended 1972, 1974) and Standards for Incineration. Bacteriological agents and viruses may fall under the incineration classification 'animal solids and organic wastes'. There are no standards for incineration of pesticide materials and other hazardous wastes, and disposal of these materials in this way is not allowed. No standards have been issued which regulate airborne microorganisms.

The disposal of biological agents into the waters of Alberta fall under the Clean Water Act of Alberta (1971, amended 1972, 1974). Industrial plants discharging their wastewater to municipal sewage systems are exempted from the Clean Water Act, but municipalities are responsible for meeting effluent standards. A water contaminant according to the Alberta statutes means 'any solid, liquid, gas or combination of any of them . . . '.

The land disposal of sludges from municipal and industrial wastewater treatment are regulated by the province, as is the burial of biological waste which is governed by the Public Health Act.

For Ontario, the principal law for controlling emissions is the Environmental Protection Act (1971). The Act prohibits discharges into the natural environment of any contaminant that exceeds what is prescribed in regulations. Discharge of contaminants must be approved by the Ministry according to waste management criteria and approved disposal sites. The Water Resources Act (1970, amendments, 1972) prohibits the release into the water of any substance which may impair its quality. Impairment may be said to take place if the material discharged

causes or may cause injury to any person, animal or other living thing.The Act established authority over sewage treatment systems and accidental discharges of contaminants.

In British Columbia, the chief legislation for protecting water quality is the Pollution Control Act (1967). This law allows the province to set objectives for the discharge of effluent from a variety of industrial sources (including those that use fermentation processes, such as breweries and distilleries) to marine and fresh waters. Water quality objectives are in terms of BOD levels, suspended solids and pH range. A Pollution Control Board designated by the provincial government sets environmental quality objectives for specific industries. These objectives function as unenforceable guidelines. The Director of the Pollution Control Branch exercises considerable discretion in issuing permits for specific emission sources, in holding hearings and in response to permit objections. The discretionary powers of pollution control agencies exists in all the provinces and has come to be understood as Canada's flexible approach to regulation.

32.4 GUIDELINES AND REGULATORY ACTIONS FOR THE RELEASE OF BIOLOGICAL AGENTS

32.4.1 United States

32.4.1.1 Environmental Protection Agency

Under the Resource Conservation Recovery Act, the EPA acquired authority to promulgate regulations for any waste, chemical or biological, that may be harmful to man or the environment. On 18 December 1978, EPA published a proposed plan for the disposal and treatment of hazardous wastes (EPA, 1978b). The plan included infectious wastes as a special category of hazardous wastes. Listed in the category of infectious wastes was the classification of etiologic agents issued by the Centers for Disease Control (1974). Subsequent to the publication of the proposed rule, EPA decided not to adopt regulations for infectious waste materials. It chose instead to develop an infectious waste management plan. This is purely an information report on state of the art procedures for handling infectious wastes. Although the plan has not yet been released by the agency it indicates that EPA will not be regulating infectious wastes, but merely providing industry with a range of options for managing their handling and disposal.

Most states have laws and regulations for the treatment of infectious wastes. These laws generally require autoclaving, incineration or processing by an approved treatment method before disposal in a sanitary landfill or discharge into the sewers. Some states treat infectious wastes as a subcategory of hazardous wastes, but many in this group have not yet promulgated regulations.

EPA's regulatory umbrella extends to pesticides through the Federal Insecticide, Fungicide and Rodenticide Act. As previously discussed (Section 32.3.1.8), before distribution or sale, a new pesticide must be registered with EPA. Under authority of FIFRA, the agency evaluates the safety and efficacy of the product. The registration must be approved if the pesticide performs its intended function without unreasonable adverse effects on man or the environment.

Prior to 1979, EPA had no formal policy on the registration of biological pesticides. Organisms were registered on an *ad hoc* basis. Only a few microorganisms were accepted as pest control agents over a period of 30 years. *Bacillus popilleae* was registered by the Department of Agriculture in 1948; *Bacillus thuringiensis* received its registration by that agency in 1960.

In May 1979, EPA issued a policy statement on the regulation of biorational pesticides, a subcategory of which includes microbial and viral agents. Biorational pesticides are defined as 'biological pest control agents and certain naturally occurring biochemicals (*i.e.* pheromones) which are inherently different in their mode of action from most organic and inorganic pesticide compounds currently registered with EPA. Among the organisms covered in the policy are viruses, bacteria, fungi, protozoa and algae' (Environmental Protection Agency, 1979a).

On 24 March 1981, EPA published a proposed rule exempting from regulation under FIFRA certain classes of biological control agents (defined as 'any living organism applied to or introduced into the environment to control the population or biological activities of another life form which is considered a pest under Section 2(t) of FIFRA' (*Fed. Regist.*, 1981).

Section 25(b)(1) of FIFRA states that EPA can exempt certain biological control organisms from regulation, if they are adequately regulated by another federal agency or are of a character which is unnecessary to be subject to the Act. Under FIFRA, the definition of pesticide includes many diverse forms of macroscopic life such as birds, insects and aquatic mammals. EPA has not attempted to regulate the macroscopic control agents.

Everything except the following biological control agents are exempted from EPA pesticide

registration: (1) viruses; (2) bacteria, including actinomycetes, rickettsia, mycoplasmas; (3) protozoa; (4) fungi of lower taxonomic order than the subdivision Basidiomycotina, or as members of the class Teliomycetes, or the sub-class Phragmobasidiomycetidae of the Basidiomycotina; (5) organisms classified as members of Class I, Schizophyceae, of Division I of the Plant Kingdom, Protophyta, including blue-green algae.

The EPA has drafted a 433 page set of working guidelines for registration of biological control agents (EPA, 1980). Under these guidelines, EPA sets requirements for the performance, toxicology and registration procedures of biorational pesticides. It also establishes criteria for the assessment of the environmental survival of released agents, their host range and their potential effects on non-target organisms. The draft guidelines stipulate that data requirements for genetically engineered bacteria will be determined on a case by case review.

The following biological agents have received registration for use in the United States: (1) *Bacillus popilliae*, reg. 1948; (2) *Bacillus lentimorbus*, reg. 1948; (3) *Bacillus thuringiensis*, reg. 1969; (4) *Heliothis*, nuclear polyhedrosis virus (NPV), reg. 1975; (5) *Agrobacterium radiobacter*, reg. 1979; (6) *Nosema locustae*, reg. 1980; (7) *Hersitella thompsoni*, reg. 1981; (8) *Bacillus thuringiensis, israliensis* variety, reg. 1981; (9) *Bacillus thuringiensis, aiswaga* variety, reg. 1981; (10) *Phytophthora palmivora*, reg. 1981

32.4.1.2 Department of Health and Human Services

The Public Health Service of HHS has played a role in establishing guidelines for the handling of biological agents primarily in laboratory settings. Two agencies under the PHS relevant in this regard are the Centers for Disease Control (CDC) and the National Institutes of Health (NIH).

The CDC publishes the voluntary guidelines entitled *Classification of Etiologic Agents on the Basis of Hazard* (CDC, 1974). This document provides a standard for assessing the hazards of numerous infectious agents. It also defines a set of minimal safety conditions for four classes of etiologic agents. Physical containment recommendations for handling the agents are made according to the degree of hazard.

Since 1976, the National Institutes of Health has issued guidelines (National Institutes of Health, 1976) for experiments that involve the use of recombinant DNA technology. Since NIH is not a regulatory agency, the guidelines apply exclusively to institutions receiving funding from HHS. However, other agencies of government have also made the NIH Guidelines a requirement for projects that they fund. NIH has no statutory authority to mandate the use of its guidelines by private companies, but it has instituted a program of voluntary compliance that allows industry to demonstrate adherence to the rules.

Until recently, large-scale work with recombinant DNA technology was prohibited by the NIH Guidelines and could be undertaken only with approval of the Director of NIH after review by the Recombinant DNA Advisory Committee. In the latest revisions of the Guidelines (NIH, 1982) the prohibitory language has been eliminated.

For large-scale experiments, defined as experiments with greater than 10 l of culture, investigators are required to obtain approval from their local Institutional Biosafety Committee (IBC) before initiation. The containment for such experiments is decided by the IBC with guidance from the large-scale containment recommendations published by the NIH. An experiment involving the deliberate release into the environment of any organism containing recombinant DNA can only be initiated when it has been reviewed by the RAC and NIH and approval has been obtained by the IBC (NIH, 1982).

Private firms that register their IBCs with the NIH and participate in the Voluntary Compliance Program are making a non-binding commitment to follow the same procedures for the review of experiments and containment requirements as any institution funded by NIH.

The interstate shipment and packaging of etiologic agents in transit is regulated by the Public Health Service of HHS through the CDC. According to the regulations, no person may transport an etiologic agent through interstate traffic unless the material is packaged to withstand leakage of contents, shocks and pressure changes experienced in ordinary handling. The list of etiologic agents covered by the regulations include bacterial, fungal, viral and rickettsial agents. The shipping regulations specify packaging for volumes less than and exceeding 50 ml, labeling, and responsibility when leakage is discovered in a package bearing an etiologic agents/biomedical materials label (42 C.F.R. § 72.1–72.5).

Under the regulations an 'etiologic agent' means 'a viable microorganism or its toxin which causes, or may cause, human disease' (42 C.F.R. § 72.25). The regulations of etiologic agents

derive from Section 361 of the Public Health Service Act, which authorizes the Secretary of HHS to 'make and enforce . . . such regulations as in his judgement are necessary to prevent the introduction, transmission, or spread of communicable diseases . . . from one state . . . into any other state . . . '. This section, although broad in scope, is limited to those agents or bioprocesses that involve the transmission of communicable diseases.

Section 353 of the PHS Act gives CDC the general authority to license and control the operation of clinical laboratories.

32.4.1.3 Food and Drug Administration (DHHS)

The Federal Food, Drug and Cosmetic Act authorizes the Food and Drug Administration to regulate the manufacture of drugs and biologics. The rules promulgated for this purpose are designed primarily with the quality of the drug in mind. FDA has no statutory powers to establish regulations pertaining to the release of organisms into the environment or to the exposure of workers to biological agents. However, environmental safeguards are a by-product of regulating the manufacture of pharmaceuticals or food products. The conditions required for preventing contamination of drugs are similar to those necessary for containing organisms during the manufacturing process. Under Part 211 of the FDA regulations for the manufacture of biologics (21 C.F.R.), standards are established for the construction and maintenance of facilities and equipment. By minimizing the contamination of drugs during the manufacturing process, the regulations also serve to inhibit the release of organisms into the environment. The regulations state in part: '(1) Minimize contamination of products of extraneous adulterants, including cross-contamination of one product by dust or particles of ingredients, arising from the manufacture, storage, or handling of another product; (2) Minimize dissemination of microorganisms from one area to another'.

In 1978 FDA published a Notice of Intent to Propose Regulations which would require all experimental work using rDNA techniques to be done according to the NIH Guidelines (*Fed. Regist.*, 1978), or the resulting product would be rejected when submitted to FDA for approval. No further action has been taken pursuant to this notice; however, FDA strongly encourages industry to comply with the Guidelines and to inform FDA that they have done so (Miller, 1981).

In the 1978 Notice of Intent, FDA also proposed that the Guidelines be incorporated into the Good Manufacturing Practice (GMP) Regulations for those products produced by rDNA technology. However, it is unlikely that FDA has the authority to require adherence to all the provisions of the Guidelines (Korwek, 1981).

The purpose of the food and drug GMP Regulations is to assure that products affected are safe for human consumption. A very different focus is given in the Guidelines, which specify practices for conducting basic research in order to minimize risks to workers, the public and the environment. The legal authority to incorporate the Guidelines into GMP Regulations remains unclear since the aims of each set of rules are different.

The Good Laboratory Practices (GLP) Regulations (21 C.F.R. § 58.1 (1980)) are intended to insure the quality and integrity of safety data submitted in support of work on which FDA regulations are based. They are not directed to the safety of laboratory workers, the public or the environment and do not apply to basic research. They cover personnel, animal care and supply facilities, laboratory areas, testing facilities, operations, records and reports but are designed only to enhance the reliability of submitted data. It is unclear whether FDA has the authority to issue similar regulations to protect laboratory workers and the public. The primary focus of FDA is on products, ensuring their safety, effectiveness and purity, not environmental protection.

32.4.1.4 Department of Agriculture

The Department of Agriculture (USDA) has two important functions in the regulation of biological agents. Under the federal Quarantine Laws it has jurisdiction over the importation and interstate shipment of plants and animals and host pathogens. The Department also regulates vaccines, serums and related products used in the treatment of domestic animals under the auspices of the Virus, Serum, Toxin Act. This Act provides for premarket clearance and licenses for both product and factory. Similarly, under the Quarantine Laws, permits are required for the interstate or internation transport of plant and animal pathogens.

A plant pathogen is defined as any living organism that is injurious to plants including insects,

nematodes, fungi, bacteria and viruses. Before plant pathogens or any vector for such can be imported from any country or transferred between states, permits must be obtained from USDA's Animal and Health Inspection Service (APHIS). Vectors are defined by APHIS as all animals which have been treated or inoculated with organisms which are diseased or infected with any contagious, infectious, or communicable diseases of animals or poultry, or which have been exposed to any such diseases. USDA maintains a similar, but voluntary quarantine and permit program for importation and release of non-pest biological control organisms.

32.4.2 Canada

32.4.2.1 Medical Research Council

In February 1977, seven months after the United States published gene-splicing rules, the Medical Research Council of Canada issued its *Guidelines for the Handling of Recombinant DNA Molecules and Animal Viruses and Cells* (Medical Research Council of Canada, 1980). The Guidelines have been revised on several occasions. The MRC requires all research it funds to conform to the rules established in this document. But it has no jurisdiction over privately funded work. The Guidelines contain standards of practice, safety procedures and physical containment levels for different classes of organisms. Where large volume work is underway, the Guidelines state: 'It appears evident that, as the volume or concentration of agent used in an experiment increases, the problems encountered in minimizing risk to investigators or the environment also increase. The procedure described in these Guidelines relate mainly to the scales of operation normally encountered in a research laboratory'.

It is notable that the MRC Guidelines require a case by case review of two types of activities that are especially pertinent to commercial operations: (1) deliberate release into the environment of any organism containing recombinant DNA; (2) large-scale experiments (more than 10 l) unless the recombinant DNA molecules are rigorously characterized and shown to be free of harmful genes. If such work is permitted, the MRC may set the physical and biological conditions for executing the experiments.

32.4.2.2 Department of Agriculture

Under authority of the Pest Control Products Act (see Section 32.3.2.2), the Minister of Agriculture has issued regulations for the registration of pest control products (C.R.C., Vol. XIII, C.1253). The regulations also apply to microorganisms that are imported for personal use and in small quantities. Under Section 4 of the regulations, control products other than live organisms are given an exemption if they are 'imported into Canada for the importer's own use', and 'if the total quantity of the control product being imported does not exceed 500 grams by mass and 500 millilitres by volume and does not have a monetary value exceeding ten dollars'.

Three categories of exemptions are written into the regulations for agents covered by the Food and Drugs Act: (1) viruses, bacteria or other microorganisms used in humans or domestic animals; (2) control of microorganisms on articles intended to come directly into contact with humans or animals for the purpose of treating disease; (3) the control of microorganisms in premises in which food is manufactured, prepared or kept. Currently the Minister of Agriculture has registered *Bacillus thuringiensis* and will soon extend limited registration to the *israliensis* variety. The Department of Agriculture is in the process of issuing guidelines for the registration of biological pesticides.

In addition to falling under the federal Pest Control Products Regulations, a biological control agent also falls under the authority of provincial pesticide registration requirements.

32.4.2.3 Provincial regulations

It is not within the scope of this chapter to undertake a review of provincial regulations that apply to biological agents. But we can draw some conclusions from a preliminary survey. The primary body of Canadian provincial regulations that restrict the release of biological agents into the environment are in the area of hazardous waste and pesticide controls. Some provinces have adopted sludge management regulations and guidelines for disposing of infectious wastes. For

example, Alberta has standards for the incineration of animal solids and organic wastes including carcases, organs, and hospital and laboratory wastes. A permit and licensing system specifies design and operational requirements for facilities. Alberta also issues *Guidelines for the Application of Municipal Wastewater Sludges to Agricultural Lands* (Alberta Environment, undated). Four categories of potential human pathogens found in domestic wastewater cited in the Guidelines are bacteria, protozoan parasites, Helminth parasites and viruses. The land application of sludge is cited as a public health risk because: (1) survival of various infectious agents in soil will result in the contamination of forage and edible crops; and (2) runoff and percolation will result in the contamination of water. The Guidelines emphasize proper site selection, proper sludge handling and application, proper crop selection and appropriate land use as a way to reduce health risks. A 'letter of permission' from Alberta Environment must be obtained by the owner of a sludge-producing facility before sludge can be applied to land.

Provinces have issued guidelines respecting the discharge of industrial wastes into municipal sewerage systems. These guidelines are not enforced by statute but rather provide suggested procedures for a municipality to use when dealing with industry. According to guidelines published by Alberta (Alberta Environment, 1978), special care should be taken in treatment of pharmaceutical wastes. 'Wastes from pharmaceutical plants producing penicillin and similar antibiotics are strong (high BOD) and generally should not be treated with domestic sewage, unless the extra load is considered in the design and operation of the treatment plants.'

No special regulations or guidelines have been issued in the provinces as a response to the developments in recombinant DNA technology.

Clean Air Regulations at the provincial level are framed sufficiently broadly to include airborne infectious wastes. Alberta's Clean Air Regulations (216/75 Part I, Sec. 5), which prohibit the release of toxic contaminants into the atmosphere, include debris from animal cadavers, animal manure and pathological wastes.

British Columbia publishes *Pollution Control Objectives for Food-processing, Agriculturally-oriented, and Other Miscellaneous Industries* (Water Resources Service, 1980). These are recommended minimum objectives in issuing orders to industry for waste discharges to air and water. They reflect the more flexible and less formal regulatory orientation that has come to be characteristic of Canadian environmental policy.

32.5 OCCUPATIONAL HEALTH AND SAFETY

32.5.1 United States: Occupational Safety and Health Act

The Occupational Safety and Health Act (29 U.S.C. § 651 *et seq.*) (OSH Act), gives the Secretary of Labor power to require employers to provide a safe workplace for their employees. Every employer, under Section 5(a)(1), has a general duty to furnish each of his employees with a place of employment 'free from recognized hazards that are causing or are likely to cause death or serious physical harm'.

OSHA's general authority to promulgate occupational health or safety standards is found in Section 6(b)(2). A standard as defined in Section 3(8) must be 'reasonably necessary or appropriate to provide safe or healthful employment and places of employment'. Section 6(b)(5) of OSH Act gives the Secretary of Labor authority to promulgate 'standards dealing with toxic materials or harmful physical agents'. OSHA 'shall set the standard which most adequately assures, to the extent feasible, on the basis of the best available evidence, that no employee will suffer material impairment of health or functional capacity even if such employee has regular exposure to the hazard . . . for the period of his working life'.

The U.S. Supreme Court has twice interpreted this section. The court has held that before invoking Section 6(b)(5), OSHA must make the threshold determination that there exists a significant risk (*Industrial Union Dept.* v. *Am. Pet. Inst.*, 1980). Once the threshold is crossed, however, OSHA can require an employer to do whatever is feasible to limit the risk (*Am. Text. Manu. Inst.* v. *Donovan*, 1981).

OSHA's authority under Sections 6(b)(2) and 6(b)(5) appears adequate to set standards regulating the physical environment in research areas and in the fermentation plant (McGarity, 1981). It could set standards for ambient air levels or enhanced physical containment for the fermentation process, and in general has statutory authority for regulating the working conditions of employees involved in all phases of the biotechnology industry. But before OSHA can initiate regulations, it is generally conceded that the existence of a hazard will have to be demonstrated;

mere speculations will not suffice to meet the standards of 'recognized hazards'. Reviewing OSHA's role in industrial bioengineering, Korwek (1982) concludes: ' . . . hazards associated with commercialization of biotechnology could not easily be made the subject of a permanent standard until definitive data become available demonstrating that a particular type of danger exists, that it is significant and that it is likely to cause material impairment as well'.

The National Institutes of Occupational Safety and Health (NIOSH), the research agency created by the OSH Act, evaluates new technologies to determine whether they may have associated occupational health and safety risks. NIOSH conducted a walk-through industrial hygiene survey of four companies involved in research and development of rDNA techniques applied to fermentation processes. For each company, NIOSH assessed the following areas: (1) potential for worker exposure; (2) engineering controls of physical containment design; (3) work practices; (4) medical surveillance; (5) validation procedures; (6) emergency and accident procedures; (7) environmental monitoring; (8) number of exposed workers; (9) employee training and education. In a preliminary report which has not been formally released by NIOSH and does not represent NIOSH policy the following recommendations were made: (1) a medical surveillance program should consist of pre-employment and periodic follow-up examinations; (2) systematic preventive maintenance should be established; (3) a registry of all workers using rDNA processes should be established; (4) environmental monitoring programs should be implemented; (5) physical containment of the fermentation process should be extended through the cell lysis and product extraction stages; and (6) the P1-LS production area should be segregated from other production or research operations.

Currently both OSHA and NIOSH are monitoring the industrial developments in biotechnology. Both agencies have representatives on a large-scale working group of the Recombinant DNA Advisory Committee (RAC). A report of the CDC/NIOSH Ad Hoc Working Group on Medical Surveillance for Industrial Applications of Recombinant DNA (CDC/NIOSH Ad Hoc Working Group, 1981) concluded that 'medical surveillance of industrial workers engaged in commercial applications of recombinant DNA techniques can play a valuable auxiliary role in protecting worker health'. The CDC/NIOSH study also emphasized the importance of physical containment of recombinant DNA organisms and their products, as a first line of defense against occupational exposures; a second level of protection cited was the use of attenuated or debilitated organisms, commonly known as biological containment.

32.5.2 Canada Labour Code

Jurisdiction over occupational health and safety is granted to the provinces by Section 92 of the British North America Act. Although the provinces have been primarily responsible for occupational environments, the Canadian Parliament can regulate the workplaces of a small number of industries that fall under federal jurisdiction. The provinces are also restricted from enacting worker safety legislation which pertains to issues of interprovincial trade or commerce.

Federal occupational health and safety regulations are authorized through the Canada Labour Code and administered by Labour Canada. Chapter 997 of the Labour Code entitled the Canada Dangerous Substances Regulations spells out the responsibilities of employers for the use of hazardous substances in the workplace. A dangerous substance is defined (Sec. 2) as 'any substance that, because of a property it possesses, is dangerous to the safety or health of any person who is exposed to it'. The Act was written for chemical substances and radiation emitting devices, although the statutory language clearly is broad enough to include biological agents should they be designated a dangerous substance by the Minister of Labour. The regulations consist of a set of general performance standards where there is considerable room for discretionary interpretation.

The general duties of the employer are stipulated in Section 4 of the regulations. 'No employer shall use in his operations a dangerous substance or radiation emitting device, if it is reasonably practicable to use a substance or device that is not dangerous. Where it is necessary for an employer to use a dangerous substance or a radiation emitting device in his operations and more than one kind of such substance or device is available, he shall to the extent that is reasonably practicable use the one that is least dangerous to his employees.'

The Act also requires that every employer 'ensure that any dangerous substance that may be carried by the air is confined as closely as is reasonably practicable to its source' (Sec. 9). The airborne contaminants in question refer to those on a published list where recommended threshold values are given.

The Minister of Labour is also given authority to require employers within federal jurisdiction to institute a medical examination for an employee who might be endangered by working with a dangerous substance.

When federal and provincial statutes are in conflict, the federal legislation preempts the provincial statute. And as a general rule, the legislation in the jurisdiction with the more stringent rules prevail.

There is nothing in the Act which requires pretesting of new substances to determine their effect on workers. In general, the evaluation of substances occurs after they have been introduced into the workplace. The Ministry of Labour utilizes toxicity information compiled by the Departments of the Environment and National Health and Welfare. No regulations at the federal level are specifically concerned with the exposure of workers to biological agents.

By the early 1970s new occupational health and safety legislation was passed in most of the provinces. Like their federal counterpart, the provincial regulations concentrated on chemical contaminants, radiation and pesticides.

32.6 CONCLUSIONS

Microorganisms have been put to the service of society in a variety of industrial processes, most extensively in the food and pharmaceutical sectors. Until recently, organisms employed in the fermentation technology of these industries originated from natural sources. This is one of the reasons why the use of biological agents and their release into the environment through the waste stream has not been viewed as a public health problem. Other factors affecting past regulatory responses to bioprocesses include their low volume of use compared to chemical processes, and the fact that microbial agents can be rendered harmless by disinfection or steam sterilization, unlike many toxic chemicals which require high temperature incineration.

As a result of the revolution that has taken place in applied genetics, especially with the recombination of genes *in vitro*, microorganisms can be engineered with the capacity to synthesize products which are coded for by exogenous DNA. These developments have brought about a renewed interest in microbial fermentation. In the chemical industry it is being pursued as an alternative to the costly synthesis of industrial chemicals from petroleum stocks.

The application of molecular genetics to industrial processes has raised concerns about the dissemination of novel organisms into the environment. Except for guidelines that regulate government-funded research, there have been no new statutes enacted in the U.S. or Canada responding to the developments in biotechnology. The federal governments of these countries actively regulate the release of biological agents in three general areas. First, quarantine laws restrict the movement of humans, plants and animals harboring infectious pathogens. Second, biological pesticides must meet registration criteria before they can be imported, marketed or disseminated. Third, as previously noted, federal agencies in both countries have issued regulations for laboratory experiments involving the use of hazardous or potentially hazardous biological agents and recombinant DNA molecules. The guidelines for the experimental use of microorganisms are not mandatory for the private sector.

The three areas of government regulation of the release of biohazardous materials are not applicable to industrial processes, such as those where genetically engineered organisms are employed in large-scale fermentation vessels.

Many of the laws enacted in Canada and the U.S. to protect the environment are broad enough in their statutory language to include the discharge of biohazardous materials. However these same laws that protect the air, water and land from contaminants require for their implementation the establishment of a performance or environmental quality standard. Unless a clear case can be made that biological agents are a viable part of the effluent and that they represent an endangerment to human health or the environment, existing laws such as the Clean Air and Clean Water Acts are not likely to be applied.

In the U.S. and Canada, federal, provincial and/or state laws regulate the disposal of hazardous wastes. It is generally accepted that pathogenic and infectious materials fall under this category. The U.S. Environmental Protection Agency has decided against taking action under RCRA to regulate the disposal of biological waste products. Canada has no comprehensive federal hazardous wastes regulations similar to RCRA within which infectious agents could be included. At a subindustrial scale, states and provinces concerned about the release into the environment of pathogenic wastes from clinical laboratories regulate the disposal of such materials under the public health laws.

Both Canada and the U.S. have enacted laws regulating the introduction of toxic agents into the industrial process with passage of the Environmental Contaminants Act and the Toxic Substances Control Act, respectively. But these Acts may not be applicable to life forms, since their statutory language refers explicitly to chemical substances.

In the food and drug industries, U.S. and Canadian federal roles have been principally to ensure the safety, efficacy and purity of the products. The protection against the release of organisms into the environment or against worker exposure is only a secondary effect of the governments' responsibilities to certify good manufacturing practices designed to protect the public from poor quality or contaminated drugs.

Certain uses of microorganisms in the environment (except for pesticides) such as oil-eating bacteria, microbial leachates, or organisms that degrade toxic chemicals, do not fall unambiguously within the jurisdiction of current statutes in the U.S. or Canada. No regulations exist for the private sector that cover the dissemination of novel biotypes into the environment. The NIH Recombinant DNA Guidelines have incorporated a voluntary compliance program for industry which covers such releases. But these Guidelines cannot be enforced on industry. Furthermore, if present trends continue in the U.S., the rDNA Guidelines will be non-existent in a few years. The Canadian rDNA Guidelines have followed the general trend toward relaxation.

Both U.S. and Canadian laws can be used to control occupational exposure to hazardous biological agents. However, no special regulations have been promulgated in this area. Occupational health and environmental agencies in the U.S. have taken a wait and see posture to the burgeoning biotechnology industry. Provincial authorities which have principal jurisdiction over worker health and safety have not initiated any rule-making or guidelines for the genetic engineering industry.

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