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UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION
Vienna International Centre, P.O. Box 300, 1400 Vienna, Austria
Tel: (+43-1) 26026-0 · www.unido.org · unido@unido.org

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SAFETY, BIOTECHNOLOGY, AND THE PROBLEM OF INTERNATIONAL TRADE-OFFS

M. Morris L LEVIN OCT 29/1993

Risk analysis has become an increasing important component in the development, regulation, and promotion of biotechnology. While many countries, including the developing ones, are aware of the many benefits that biotechnology promises, the complex issues concerning the special risks in the environmental application of this technology are not well understood, especially when it comes to the international management of biotechnology risks.

To some extent the United States may appear to be a model. Not only does the US have an elaborate regulatory system, there have been almost 200 field tests of biotechnology products in the US with no adverse effects noted to date. In no other country has this scale of testing been approached. This article will examine the regulatory structure of the US in terms of its ability to ensure the safe development of the biotechnology industry. The article then proceeds to examine the special problems that arise when safety concerns take on an international dimension. The fundamental problem regarding safety begins with the realization that risks cannot be reduced to zero. Hence, determining safety requires making "trade-offs." Different countries might be drawn to make different trade-offs because of their differing national agendas and priorities. How ought these different trade-offs be reconciled? How ought the information and expertise needed for risk assessment be coordinated and made

available, especially when the safety of developing countries are involved? The article includes an assessment of the current international organizations, activities, and procedures for handling environmental biosafety issues. The article concludes with a number of specific recommendations to improve international cooperation leading to the development of safe methods for testing and utilizing engineered organisms in environmental situations.

Risk Analysis

The overall process of risk analysis has two components: risk assessment and risk management. Risk assessment is the determination of the probability or likelihood of harm. The assessment process consists of the collection and analysis of the appropriate data that can lead to an estimation of likelihood of harms. Risk management focuses on the actions that should be taken, given these risks. The risk management process begins with risk assessment but it also takes into account a number of other factors including the benefits of the product (e.g., less use of hazardous chemicals in the case of a biological pesticide) and the social implications of the risky activity (e.g., the impact of the use of Bovine Growth Hormone on the structure of the agriculture industry). Political factors must also be considered [1]. Managing risk requires striking a balance between all of these factors. Since many of these factors will often suggest different responses, proper risk management -- i.e., safety -- involves the necessity of making trade-offs.

Risk Communication

Recent events have demonstrated the importance of risk communication [2,3]. A number of authors have emphasized the need for involving the lay public early and the need for clearly communicating risk information [4,5,6].

Some commentators have suggested that all risk analyses share at least five elements that strongly affect the ability of experts to communicate risks to the public. These elements include (1) the path by which information reaches the audience (the path to the public is not direct), (2) the limited value of experts when the process becomes highly politicized, (3) the extent to which the local community believes it is affected (4) the role of the mass media, and (5) the technical or cultural background of the audience. Technical audiences are more responsive to data developed using defined sets of principles and data. The boundaries are kept narrow and there is a high degree of reliance on statistical methods. Non-technically oriented audiences are more interested in broad problem definitions and analyses.

Because of the involvement of life forms and the interaction with the environment, biotechnology risk analyses rely more heavily on probability estimates than other technology assessments. Consequently, they must incorporate a greater degree of uncertainty into the analysis. The differences in the background and perspective of the recipients of risk analyses information will affect the evaluation of the results and the

management decisions. The role of risk communication in establishing meaningful communication between assessor and those potentially affected becomes especially critical. Drawing these groups together to reach agreement also requires strong coordination efforts among those conducting risk assessments as well as attention to the means of communication.

Coordination within the US

Background

In order to understand the efforts to coordinate biotechnology risk management in the US, it is important to understand how the regulatory framework is structured. Three agencies are involved, each of which is required to comply with a general statute for environmental protection and each of which has a specific mission. A coordinating committee has been formed to harmonize activities between agencies, which has published a framework for regulation and a list of applicable statutes [7].

Each of the three Agencies is responsible for compliance with the National Environmental Policy Act (NEPA) which is binding on all US Federal Agencies. NEPA attempts to ensure that federal actions are environmentally sound. In essence it requires each Agency to evaluate the possible environmental outcomes of its proposed actions and look for a balance between benefits and possible adverse impacts. The Agencies must conduct and document a thorough review of all pertinent available information, including alternatives, and seek public comment.

Each Agency is also guided by its particular legislation. All of the relevant legislation is based in part on safety. Safety has been viewed from a number of perspectives. For example, safety can be viewed from the standpoint of workers in general, from the standpoint of particular categories of workers (i.e. laboratory or factory employees), from the standpoint of the potential impact of industrial emissions on the environment, or from the standpoint of the public health. Each of these standpoints has provided the basis for specific statutes. Implementing these statutes led to the establishment of the federal regulatory agencies. There are no statutes specifically dealing with the safety of biotechnology products.

The first effort to deal with the safety of biotechnology (molecular biology, as it was called then) was not the result of law making but grew out of concerns voiced by the scientists involved. The protocol was developed and administered by the National Institutes of Health, resulting in its Recombinant Advisory Committee and the well-known RAC guidelines [8,9]. The RAC guidelines focussed on laboratory worker safety. They functioned with a great deal of success by stressing containment. In the initial version of these guidelines, any type of release of genetically engineered organisms into the environment was completely prohibited.

Although only federally funded molecular biological research was covered, nonfederally funded researchers were expected to comply on a voluntary basis, which they did. An outcome of this

procedure was the creation of Institutional Biosafety Committees (IBC's). These committees were established at all research and at most industrial facilities involved in molecular biology. They provide a first line of review of safety requirements for specific research projects. Although they were developed to aid the RAC by providing local review of some applications for rDNA research, they currently review most of rDNA research requiring review in the US.

Specific Agencies

With the scaling up of molecular biology to industrial levels, safety emerged as an industrial issue. The safety of workers other than laboratory employees, of the environment, and of agricultural products as well as the safety of the public health in general became involved. Because of their stated missions, three Agencies -- the Food and Drug Administration (FDA), the Environmental Protection Agency (USEPA), and the Department of Agriculture (USDA) -- became heavily involved in biotechnology regulation.

The FDA has a large role in regulating biotechnology products because of the Food, Drug, and Cosmetics Act and the Public Health Services Act. The Agency has a mandate to ensure efficacy and safety of food and pharmaceutical products. The FDA's criteria for product evaluation focusses on purity, lack of adverse effects, and efficacy. It has been estimated that the FDA has already ruled on thousands of biotechnology products, although not many of them have any potential ecological impact.

FDA's environmental concerns and responsibilities result from the requirement to comply with NEPA.

The USEPA is the primary agency responsible for ecological and related public health issues. EPA administers seven environmental statutes. It regulates biotechnology under two of them, the Toxic Substances Control Act (TSCA) and the Federal Fungicide and Rodenticide act (FIFRA). These two acts are best described as "gateway legislation" since they are invoked before new products are released to the environment. Unlike other EPA statues which are oriented towards abatement, TSCA and FIFRA are oriented towards prevention. FIFRA covers all pesticidal products and is clearly applicable to biotechnology products. New chemicals or new uses for existing chemicals trigger TSCA. Recombinant DNA is considered a new chemical in order to invoke TSCA, and the new life form resulting from the genetic recombination is therefore included in what TSCA covers. The EPA reviews are considered the equivalent of NEPA reviews.

The USDA has the responsibility for enhancing production and for assuring the safety and nutritional quality of food and fiber. The Agency's primary environmental concerns are the safety of crop plants and cattle. The USDA has three divisions that deal with biotechnology. The Agricultural Research Service deals with research issues and has formed an equivalent to the NIH RAC to review proposals. It is also instituting an information service as part of it National Biological Impact Assessment Program and has an office that serves to coordinate

activities within the Agency. The Agency's Food Service and Inspection Service functions to ensure the safety and the wholesome characteristics of all food products. Through the Animal and Plant Health Inspection Service the Agency meets its responsibilities for licencing veterinary biological material and for issuing permits for the transport of biological material. The USDA has formed the Biotechnology, Biologics, and Environmental Protection Division (BBEPD) with responsibility for all biotechnology products. As a result of NEPA the USDA has the responsibility for ensuring safe ecological utilization of engineered crops, cattle, and veterinary products.

The International Situation

The US regulatory structure reflects the growing concern in the US for developing a safe biotechnology industry. The concern and enthusiasm for biotechnology is certainly not confined to the US. Various other nations engaged in or planning to engage in biotechnology research and development have produced regulatory structures that are distinctly different from the US's. Nevertheless, regardless of the quality of these national regulations and safety measures, there are several reasons for focussing international attention on the issue of biotechnology safety.

First of all, genetically engineered organisms do not respect national borders. A common public fear is that a harmful microorganism might be released into the environment. Such organisms cannot be "recalled," and, if they successfully adapt

to the environment, they will increase exponentially. An exponential increase of a harmful engineered organism would soon pose a threat to neighboring countries. And there is no practical way of securing borders against microorganisms.

In one respect this concern is like the international concern over nuclear energy. As the Chernobyl disaster made vivid, a nuclear accident in one country can have widespread effects in others. But there is an important difference between nuclear energy and biotechnology: Although both may be linked to weapons development, for the most part nuclear power is an expensive and complex technology, requiring sophisticated installations. This provides de facto international regulation of nuclear power. In contrast, biotechnology is not a secret technology; and the technology has become so easy that students in some US high schools perform recombinant DNA experiments as part of their course work.

This suggests a second reason for focussing international attention on the issue of biotechnology safety. While many scientists believe that the possibility of harmful genetically engineered microorganisms running amok is low, this belief is based on experienced researchers following safe laboratory practices. The easy availability of this technology raises the possibility that some work with genetically engineered organism might not be done with as much preparation and care as many scientists assume is the case.

Problems Facing International Biotechnology Regulation

There are three main issues facing international regulation in biotechnology.

The first, and perhaps the most obvious issue is the issue of authority. When disagreements about trade-offs occur within a country, the political structure of that country will typically identify an authority that sets a procedure by which disagreements are resolved into a national policy. A good example in the US is the establishment of the Council on Environmental Quality. The Council was established to review environmental issues and recommend a course of action to the President. The recommendations led to the passage of the NEPA. Resolving disagreements between nations is a different matter, for insofar as we acknowledge national sovereignty, there is no super-national authority.

The issue of authority is not at all peculiar to biotechnology regulation. Every kind of international arrangement -- from specific trade agreements to military treaties to the establishment of common manufacturing standards -- faces this issue. Our discussion of biotechnological risk has little to say on this issue. The issue of authority is a general issue, requiring a more general discussion.

Our discussion focuses on the other two issues. In order to understand these issues, we need to say more about what a trade-off problem involves.

A trade-off problem starts with the general assumption that we cannot completely eliminate risk. We can lower the risks

involved in many situations, but this is always at a price. We might install more safety devices or double and triple check possible sources of harm, but at some point we must stop. The possible increase in safety doesn't warrant further cost. It may not be worth any further expense of time, money, or energy to make a small probability of harm even smaller. This point can be called the "trade-off solution."

Trade-off problems are notorious for admitting of more than one "solution." Or, to put it more accurately, people can rationally disagree over the acceptability of particular solutions. Much of this disagreement is due to the role values play in identifying an acceptable level of risk since reasonable people can disagree within a limited range on the significance of these values.

The role values play in trade-off problems takes two forms. Values enter by their identifying certain loses as costs or harms. Is the loss of a particular species a cost or harm? Surely not unless (the preservation of) the species is of some value. Values also enter by partly fixing a weighting on the factors being balanced. How important is the environment, high technology, or economic progress?

This leads to the second issue facing international regulation in biotechnology: While disagreements over these values can certainly occur locally, the range of the disagreement is greater when we consider decisionmakers coming from different cultures or countries. For example, one country might value a

particular species of animal more highly than its neighboring countries do because of the role that animal plays in its history, folklore, myths, etc. Plainly, that country will have sharp disagreements with its neighbors concerning the appropriate trade-offs and levels of safety if these animals are at significant risk.

Trade-off solutions are also obviously a function of the available information and its interpretation. This suggests two ways people could disagree on a trade-off solution even though they agree on values. (1) There could be a disagreement because one party does not have all the relevant data available. In a sense this is a trivial disagreement since it can be resolved, at least theoretically, by making available all the relevant data. (2) Even if all the relevant data is available, there could be a disagreement in interpreting the data. After all, experts do disagree in the assessment of technological risks.

These two types of disagreements can clearly arise in the international arena. The first type of disagreement -- disagreements arising because not all parties are aware of the relevant data -- can be an especially important problem for developing nations that lack the appropriate expertise in identifying and collecting the information. Nevertheless, while this may be an important practical problem, the situation is quite clear theoretically: all parties have a responsibility to ensure that all the relevant information is made available. The second type of disagreement -- disagreements arising because the

experts disagree -- can be an important problem especially if the opposing experts happen to fall into different cultures. For example, consider a case where the experts of nation A are mainly ecologists and the experts of nation B are mainly evolutionary biologists. Even as a theoretical matter, the resolution of this type of disagreement is not at all clear.

Prospects for International Regulation

Most developed countries have been developing biotechnology regulations internally. There have been a number of attempts on an international level to reach agreement on a framework for product evaluation and on requirements for field testing. Developing countries may be able to benefit from these efforts, but in each case one must make certain that the particular country's or region's needs are being met. These needs will affect the type and stringency of the regulatory framework. This requires considering the economic, cultural and social aspects of the particular country as well as the scientific issues such as the specifics of the product and how it might affect the ecological balance. International cooperation is essential not only because many of the products will be marketed on a global scale but also because viable organisms released to the environment will not respect political boundaries.

International cooperation in environmental issues has been accepted as necessary in a number of areas. UNEP, IUCN and WWF have recently signed a memorandum establishing a monitoring center to be called the World Conservation Monitoring Center, and

each of the three partners have pledged financial support. Similarly the FAO published in 1986 an international code of conduct on the distribution and use of pesticides which not only describes the shared responsibilities but also discusses the need for a cooperative effort and for generally accepted practices. Nevertheless, concerns have been raised about the status of regulations in developing countries [10].

As demonstrated by the difficulties encountered in field testing a recombinant Rinderpest vaccine in Africa, progress in generating products which have the potential to boost the standard of living and aid agriculture is markedly slowed in the absence of clear regulatory pathways. Thus, the lack of an internal regulatory framework within developing countries and the lack of agreements between developing countries may well result in an even slower development and application of biotechnology products.

With these thoughts in mind, one can ask if the regulatory procedures of the US, the regulatory procedures of any developed country, or the agreements between developed countries are satisfactory models for developing countries. The well-documented problems within the US concerning coordinating the individual agencies and the eight unauthorized releases points out the difficulties within one country. Even within national boundaries differences of public opinion can occur to produce resistance to field tests and products: tests in different parts of the US have encountered different reactions. While the OECD

guidelines may be accepted this year, they are the result of a series of meeting that began in 1983. This delay points to the problems associated with gaining international agreement for guidelines.

Nevertheless, there have been many public meetings, debates within expert panels, government reports, presentations at meetings of scientific societies, and publications in scholarly journals. There is thus an extensive knowledge base which should include many if not all of the important issues concerning safety and environmental biotechnology. The time, effort, and cost of reaching the current plateau in biotechnology regulation need not be duplicated by developing countries.

The large differences between developing countries in geography, training of regulatory officials, presence of a regulatory infrastructure, cultural background, and available expertise in required disciplines points to future difficulties in developing appropriate regulatory procedures.

However, the documents of the OECD, the guidelines generated by the developed countries, and the proposed scientific rationales for evaluating the safety of biotechnology products produced by scientific societies and organizations [11,12,13,14,15] form a valuable starting point in meeting some of these difficulties. These materials, further refined as a result of international or regional meetings, could lead to a general and basic document describing both principles and procedures (Basic Principles and Procedures Document) for

estimating potential ecological effects of engineered organisms on a national and regional basis. The document should be sufficiently comprehensive to enable a country to identify principles and to select procedures so that it could conduct a risk assessment which would be sensitive to its cultural, social and economic values. While the document could not contain binding requirements, the principles of assessing risk and of estimating benefits would be clearly defined. The only requirement on sovereign states is that they conduct the risk-benefit process in a manner appropriate to their country and region.

A second important value of the document would be to demystify the science underlying biotechnology. The process of producing risk assessment principles would require a thorough review of the debates, conclusions, guidelines, and safety research on a world-wide scale. Thus, experts in biotechnology as well as involved government officials could become familiar with the safety issues. It could also provide a basis for public education.

Developing countries could greatly benefit from the activities of the developed countries by taking advantage of electronic access to ecologically oriented data banks [16,17] and by using artificial intelligence systems. Both of these tools are being developed to aid the evaluation of safety regarding the marketing and releasing of genetically engineered products. These tools would help resolve another issue -- the lack of a

large cadre of well-trained scientists in many developing countries. Expert panels can be formed to evaluate individual proposals. However, these panels require a pool of expertise which is unavailable in most countries. This shortage of trained personnel is affecting the US regulatory process, leading to a reliance on government staff scientists and on ad hoc communication with experts. The need for a large panel would be diminished if the principles involved and the data needed were clearly identified at an early stage in the assessment. A BPPD would have the effect of limiting the breadth of the expert panel. If the data needed are clearly defined in advance, one could select experts from closely related fields and rely on them to develop information in the fields required by the case at hand.

The development and utilization of a BPPD, along with the identification and linking of the appropriate electronic data bases, would have an effect on another important aspect of the utilization of biotechnology products. Public resistance to field tests and product utilization is directly related to the amount of information available to the public and how it is presented. Compliance by investigators is directly related to the amount of information available to them that justifies the need for the regulations and indicates how best to comply. Establishing a mechanism for conducting workshops aimed at informing the public and the regulated community about the risk assessment process would have a positive effect on compliance.

The existence of a data bank would provide access to authoritative sources and ensure completeness of the data acquisition effort. This information could be used for public education as well as for decision making.

Thus, the BPPD would have a positive effect on the development of internal and regional biotechnology regulations, it would provide a basis for public education and involvement, and it might decrease the requirement for specific experts. The international scope of the process needed to develop the document would take full advantage of all of the regulatory debate that has taken place thus far. The result could be a document acceptable by all participants because it has a sound scientific base and public support.

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