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SAFETY GUIDELINES AND PROCEDURES FOR BIOSCIENCE-BASED INDUSTRY AND OTHER APPLIED MICROBIOLOGY*

Prepared by

the UNIDO secretariat

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SUMMARY

General Objective

The purpose of the UNIDO/WHO/UNEP working group on safety measures for biotechnology research and industry is to establish a process through which the potential risks arising from this rapidly evolving technology can be assessed and appropriate safety measures designed. While doing so it is emphasized that biotechnology, with its advanced techniques of genetic engineering, holds great promise for all nations of the world, particularly the developing countries. For this reason, safety measures should be consistent with the degree of anticipated risk and not be made as to hinder needed developments.

Specific Objectives

1. Consider whether genetically engineered organisms pose added risks to researchers, workers and public.

2. Consider whether immuno-suppressed persons are at added risk if performing biotechnology R+D or working for bioscience-based industry.

3. Consider whether new, unique substances produced via biotechnology will pose added risks to workers or public.

4. Consider whether there are risks associated with the growing of cell lines and hybridomas for the production of monoclonal antibodies.

5. Consider whether bio-wastes disposal pose any particular risks.

6. Consider whether to consider the issue of deliberately releasing genetically engineered microorganisms into the environment.

7. In view of the foregoing, consider existing risk assessment schemes and determine their suitability to assessing risks associated with biotechnology R+D and with bioscience-based industry.

8. Consider existing rules and regulations pertaining to pertinent industries in order to evaluate whether these are adequate to manage bioscience-based industry.

9. Suggest improvements as necessary if the existing body of rules and regulations is deemed insufficient or inadequate.

10. In case entirely new guidelines and/or procedures need to be desinged in order to manage bioscience-based industry, formulate general recommendations as to their contents.

11. Consider whether biotechnology R+D and applications pose any special problems to or in developing countries that should be dealt with apart from concerns related to developed countries.

12. Consider how the recommendations being made by the UNIDO/WHO/UNEP working group will be legitimized and given wide-ranging support.

13. Consider the future role of the ICGEB in formulating safety procedures, guidelines and to monitor national rules and regulations.

I. Introduction

UNIDO has since its inception been involved in several aspects of applied microbiology. However, after 1981 this type of activity has been significantly expanded as the organization initiated a series of measures, the objective of which was, and remains, to make certain the fruits likely to emanate from advanced biotechnology R+D, including genetic engineering, would be shared by developing countries. The most important initiative being undertaken is to establish and make operational the International Centre for Genetic Engineering and Biotechnology (ICGEB) in two components located in New Delhi, India and Trieste, Italy. As of this writing, 36 countries belong to the ICGEB and several more will undoubtedly join in the near future. Further, operational activities will begin in provisional ICGEB facilities as early as the beginning of 1986.

During the preparatory work for the ICGEB, the matter of safe laboratory practices, especially as they pertain to research on genetically engineered microorganisms, became a matter of concern to UNIDO. As several countries offered to host the ICCEB and/or its affiliated centres, it became clear that national legislation which were aimed at ensuring safe laboratory practices varied from almost no control to control measures akin to U.S. or U.K. guidelines. As the time grows ever shorter before research begins at both ICGEB and at its affiliates, the matter of drawing up and applying adequate and uniform safety rules and practices throughout the ICGEB system takes on an air of urgency. Futher, since research at the ICGEB and its affiliates is to be of an applied nature, and since products and processes will ensue as soon as practicable, there is also a need to consider safety rules and practices as they may be applicable to bioscience-based industry (and to industry which will utilize the advanced biotechnology techniques).

While UNIDO has by definition an interest in safety practices as they relate to industry, it is also aware of the concerns the World Health Organization (WHO) has in this area as they relate to health and safety. Particular note has been made of the publication Laboratory Biosafety Manual (1) with its guidelines pertaining to laboratory practices, transfer and shipping of specimens, guide to biosafety equipment, etc., and the report by WHO's Regional Office for Europe

"Health Impact of Biotechnology" (2). Overlapping interests between the two organizations led to the establishment of continous communications between UNIDO and WHO's programme Safety Measures in Microbiology. Eventually, it was decided between the two to constitute a working group and begin a systematic study on whether a set of rules and practices could and should be elaborated, the applications of which could be recommended to all countries.

More recently, UNIDO became acquainted with the interest that the United Nations Environment Programme (UNEP) has in the topics of bio-wastes disposal and the deliberate release of genetically engineered organisms into the environment. In view of the obvious overlap of interests, UNEP was informed of the planned UNIDO/WHO working group and asked if it would be interested to partake in its activities. The response was positive and, after consultations with WHO, it was decided between the three to quickly constitute a UNIDO/WHO/UNEP working group to consider all facets of microbiological safety pertaining to research institutions and industry.

In view of the foregoing, the UNIDO staff in this document presents its ideas on the subject, stressing those which apply to industry and industrialization. Accordingly, this paper begins with a section on risk and risk assessment, continues with some thoughts on risks that could be associated with applied microbiology, then concludes with a few suggestions for activities to be undertaken by the UNIDO/WHO/UNEP working group.

II. Risk and Risk Assessment

Risk, as it is here understood, is a measure of the probability of sustaining injury or death in the course of, or because of, research activity or activities pertaining to bioscience-based industry. Risk assessment is the attempt to determine as exactly as possible how high or low this probability is of being realized. Risk assessment schemes can be based on data used by the chemical and pharmaceutical industries to develop such concepts as "no observed effect levels", "acceptable daily intake", "permissible exposure limits", and LD_{50} (lethal level for 50 per cent of the exposed population).

Of direct pertinence to microbiological research and industrial activity is the classification system developed by WHO to classify microorganisms in one of four risk groups, with Risk Group I consisting of microorganisms believed unlikely to cause human disease or animal disease of veterinary importance, while Risk Group IV includes pathogens "...that usually produces serious human animal diseases and may be readily transmitted from one individual to another, directly or indirectly" (3). Once the microorganism(s) for use either in a research project or for industrial purposes has been classified, it should be possible to define the conditions under which work with that organism would proceed. However, shortcomings of this scheme as it relates to the concerns of the UNIDO/WHO/UNEP working group may include, (1) disease agents which affect plants are not included, and (2) a genetically engineered microorganism may not easily fit into a risk group, at least until after it has been studied closely.

Guidelines now being drafted by the World Bank for identifying, analyzing and controlling dangerous industrial installations (3) will also be of interest to the working group. It is expected that a two level system will be developed: the first consists of industrial plants that employ hazardous substances above a certain threshold level and that will therefore be obliged to notify the World Bank, while the second level consist of "full safety cases" - i.e. plants that use hazardous substances in such quantities or which are so dangerous that full safety use assessments have to be performed. According to one account, the objectives of the "full safety cases" are: "to identify the nature and scale of the use of dangerous substances at the installation; to give an account of the arrangements for safe operation and for control of serious deviations that could lead to an accident; to identify the type, relative likelihood and broad consequences of mishaps that might occur; and to demonstrate that the developer has appreciated the major hazard potential of the company's activities and has considered whether the controls are adequate" (4).

Though the World Bank guidelines are being drawn up primarily for chemical industrial plants, they would appear to also be at least partially useful for bioscience-based industry, taking into consideration that microorganisms used in and by industry present different problems than do chemicals.

Aside from the WHO classification system and the as yet unseen World Bank guidelines, traditional risk assessment schemes may not be so useful when regarding the bioscience-based industry since they may present the following shortcomings:

- Historial statistical data indicative of causal relationships between exposure to a substance and injury does not exist in bioscience-based industry when considering genetic engineering techniques.

- Accidents which expose workers to a substance (or radiation) have many times served the useful purpose of providing reliable data pertaining to conditions of exposure and their effects. Available information indicates that accidents in the bioscience-based industry have so far proven benign. However, it is difficult to incorporate negative data in risk assessments.

- The conditions of exposure (level, frequency, duration and route) that are tested in animal models are different from the conditions of actual human exposure (themselves poorly defined even in established industry). The situation in regard to genetically engineered organisms and the substances they produce is that virtually no data is available from either animal models or from experimentally induced injuries.

- No data is available to the bioscience-based industry from epidemiological investigations of chronic exposure or injury, and very little such data can be expected in the next 5-10 years.

In view of these shortcomings (and from others that cannot here be described) it may be that the UNIDO/WHO/UNEP working group will have to formulate new procedures for risk assessment in reference to biotechnology, including genetic engineering, and the industries which will employ it.

III. Conjectural Risks Associated with Applied Biotechnology

Following is a preliminary listing of research and industrial activities involving biotechnology, including genetic engineering, that may pose risks. Throughout it must be kept in mind that laboratory personnel and workers are the ones who are the most at risk.

1. Risks associated with the construction and propagation of new organisms.

The conjectural hazards of constructing and manipulating new microorganism were extensively debated during the recombinant DNA (rDNA) controversy and as a result a sizeable body of evidence was built up demonstrating the low or non-existent risk of rDNA research. Nevertheless, as a result of voiced public concerns and because it was thought prudent safety procedures to manage perceived risky research were developed and implemented to guarantee the safety of laboratory personnel and public. While recognizing that an essential difference exists between research and industrial practices (in research the objective is to examine whether or not transformation takes place while in industrial processes the genetically engineered organisms resulting from research are used), this existing body of evidence may be used by the UNIDO/WHO/UNEP group to lay an objective foundation for the consideration of the large-scale production of genetically engineered organisms. However, it is doubtful whether information from this source may be applicable to the consideration of genetically manipulated plants and animals. Since plants are already being genetically engineered, it will be necessary to rather quickly come to grips with regulatory issues pertaining to the growing of genetically engineered plants, both in greenhouses and in fields.

2. Risks associated with the use of unique strains for industrial production.

It is axiomatic among infectious disease specialists that the larger the number of disease-causing organisms an individual is exposed to, the greater the likelihood of him contracting the disease. One may

wonder if an analogous situation could arise as bioscience-based firms use extremely large numbers of unique organisms in industrial processes and bioscience workers, in case of mishaps, become exposed to them. Further, the question of immuno-surpressed persons has not been adequately addressed. These persons (an ever-increasing number including, for example, diabetics and those being treated with antibiotics or anti-cancer drugs) often are attacked by organisms innocuous to normal persons. Will these persons face increased risks when exposed to genetically engineered organisms?

Industrial practices differ from research in that they do not take place in standardized cabinets or in small volumes. It is probable that industrial equipment much like that used in the present fermentation industry will be used to process genetically engineered organisms. If so, it will probably be prudent to examine whether this equipment is adequate from a safety viewpoint when genetically engineered organisms are processed in very large volumes.

3. Risks associated with the products obtained from the new strains.

The question may be asked whether products now being made available through biotechnological means of manufacture, that have not previously existed, will pose new hazards to workers and the public. It is doubtful whether specific measures for the physical containment of genetically engineered organisms will have to vary from those now used in, for example, the pharmaceutical industry. Similarly, existing regulations governing the safety testing and labelling of new drugs and food additives will probably be sufficient to regulate similar substances produced through new biotechnology. Yet, the question remains if there is likely to be any additional risks associated with new products. Perhaps additional hazards could appear as a result of unique substances, produced for the first time, proving to be powerful allergens or auto-immunogens, with bioscience workers the most likely to be intially threatened.

4. Risks associated with the propagation of hybridomas.

At the time of this writing, apparently no one has sounded any warnings about risks associated with growing hybridomas in industrial quantities. Nevertheless, it may be worthwhile for the UNIDO/WHO/UNEP working group to investigate this area in order to assess if in the future, risky processes or products may be developed.

5. Risks associated with the disposal of bio-wastes.

Some bioscience industrial practices will produce no dangerous wastes, for example, those during which the cells are ruptured to recover the desired protein. Other practices may pose problems with disposal of wastes, in particular those using bacteria and yeast that secrete the desired substances into the substrate and are thus still viable at the end of their useful life. The UNIDO/WHO/UNEP group may wish to consider the formulation of safety criteria for bio-wastes disposal including setting standards for permissible concentrations of chemicals, proof of non-viableness of organisms to be disposed of and other variables.

6. Risks associated with the deliberate release of genetically engineered microorganisms into the environment.

The question of the large-scale release of genetically engineered organisms into the environment may also have to be dealt with. Already persmission has been sought to spray a huge number of genetically engineered organisms on plants to prevent frost damage. In the near future similar requests will be made to perform field trials in order to enhance oil recovery, to recover metals and minerals from different low-quality sources, and to fight insects and weeds. Will unique genetically engineered organisms stay in the niches they are designed for, or is there a possibility one (or more) of them could spread, causing unanticipated damage? In view of the contentious nature of this issue, care will have to be taken how the working group will attempt to deal with it.

In concluding this section, a special mention will be made of one of the conclusions made in the aforementioned WHO report, namely that the "...conjectural risks of the application of recombinant DNA and other techniques to biotechnology can be assessed and managed with current risk assessment strategies and control methods"(5). If this is the case, these available methods would still have to be altered or adjusted to take into account the unique characteristics given to biotechnology due to the discovery and application of genetic engineering techniques. In particular, the lack of data on long-term effects (as pointed out above) makes for an incomplete risk assessment. Therefore, it may be adviceable to try to formulate a "new" risk assessment scheme that could be considered "organic" in that it will become incrementally improved with time as new data becomes available and is taken into account. At first it may be that the scheme will be based largely on empirical observations and the subjective opinions by researchers, technologists, and other industrial practitioners. However, with the passage of time and as data accumulates from both directed research and industrial operations, the scheme will become more and more based on objective criteria.

Once a risk assessment scheme has been formulated and put into practice, it should be possible to characterize the nature and magnitude of the risks associated with the practices of bioscience-based industry and to calculate the degree of confidence associated with the analysis. These will provide the basis for attempting risk management; i.e., concrete attempts by UNIDO/WHO/UNEP working group to formulate control measures applicable to the bioscience-based industry. Initially, the working group may consider two components of risk management. First, whether or not the assessed risk is important. The magnitude of importance will probably have to be determined not only on the calculated probability of the risk but also on the degree of confidence one can place on the data underlying the risk assessment. Second, if the decision is made that the assessed risk, or risks, is sufficiently important to worry about, then the working group will have to decide how and to what extent measures are required to sufficiently manage the risk(s).

IV. Safety Measures Related to Biotechnology R+D and to Bioscience-based Industry

The history of industrialization shows that when some industries have been poorly or not at all regulated, society and the environment have suffered. The experiences with the chemical (including pesticide) industry are particularly illuminative. In view of the historic necessity of regulating some industry, it is reasonable to investigate whether bioscience-based industry should be managed by society. If so, the main questions which face the UNIDO/WHO/UNEP working group are: (1) whether existing rules and guidelines are adequate in themselves to regulate biotechnology R+D and the new bioscience-based industry; (2) whether these rules and guidelines are deficient but may be used as a base upon which to formulate improved guidelines and procedures; or (3) whether a completely new set of guidelines and procedures will have to be formulated since the modern bioscience-based industry has unique characteristics and therefore poses unique problems. A subsidiary question, when considering these main questions, is whether research and industrial activities that is being, or is likely to be, undertaken in developing countries pose any special problems that require special answers.

1. Adequacy of existing rules and guidelines.

The working group may wish to regard existing national rules and guidelines and assess whether any or all of them are adequate to manage research and industry. Given the limited resources that will probably be available to the working group, it will be impossible to more than sample national laws in this area. It is likely that an OECD study presently underway (6) will adequately cover the applicable laws and rules in developed countries. As to developing countries, a suggestion may be made to use the information provided by countries which have nominated national institutions for affiliation with the ICGEB. A reasonable request can be made to these governments to provide information pertaining to the safety practices of R+D institutions and the laws and rules which govern their management in order to make certain the candidate institution will fulfil minimal criteria of safety. If the

working group's mandate is of a lengthy duration, it may consider to formulate a mechanism for monitoring national laws and rules as they evolve with the advance of biotechnology and its applications.

2. Improvements of existing rules and guidelines.

After a sample of national laws and rules has been appraised, it should be possible to identify shortcomings pertaining to biotechnology R+D and industry. Shortcomings may range from being inconsequential to serious gaps. But the important part will be to find out whether there are generic shortcomings and, if so, whether there are possibilities for recommending palliative corrective measures applicable to most of them.

3. Creating a new set of rules and procedures.

If existing management measures are found completely inappropriate or deficient, new measures may have to be formulated and applied. This task would obviously be beyond the possibility of the working group to take on. In this case, the group could consider making a recommendation for the creation of new measures by competent authorities and, additionally, could suggest general guidelines on how they should be constructed.

Whatever approach is taken for designing improved or new safety measures, account has to be taken of the dynamism of biotechnology. Since the field is evolving so rapidly and since all new developments cannot be predicted, it is important that measures be flexible and amenable to change. A useful lesson of flexibility may be the gradual relaxation of the NIH guidelines (and the other national measures based on them) that has taken place as new data became available demonstrating the safety of recombinant DNA.

V. Concluding Thoughts

It is probable that most rules which now exist pertaining to applied microbiology are those which have been formulated either to regulate existing industries, particularly those related to pharmaceuticals and chemicals, or to protect the environment. In

addition, as a result of the public concern over rDNA research in the late 1970s, many nations elaborated guidelines regulating such research (the UK and US in 1976 and Japan in 1979).

After approximately nine years of existing with and taking account of rDNA rules and regulations, their value (or lack of) is still being discussed. A sizeable group of scientists believe that rDNA research poses no hazards to society and that the rules which came into existence were hurriedly contrived to appease a vocal few who managed to sensationalize their views. These rules, in the thinking of these scientists, serve no good purpose but only tend to hinder legitimate research and researchers. Conversely, there are those who believe that the existing rules do not go far enough, that they were promulgated by scientists themselves who were only intent on protecting their interests and the public be damned.

The reason why this wide divergence of views on rDNA rules is here mentioned is that it alludes to the question whether there is an overriding necessity for promulgating additional safety guidelines and procedures for the bioscience-based industry. Since there are likely to be both those who will decry the need for such guidelines and those who may wish to see the adoption of very stringent rules and regulations, this question has to be considered in depth by the UNIDO/WHO/UNEP working group and if the decision is to go ahead, it will have to be based on sound reasoning.

A point that should be made is regarding the legitimization of the safety guidelines and procedures that may be formulated by the UNIDO/WHO/UNEP working group. Though biotechnology has been part of human endeavours for thousands of years the recent rDNA controversy and sensationalist stories in the popular press about eugenics have caused the public to equate biotechnology with rDNA, eugenics and, less precisely, "tinkering with genes" or "fooling around with mother nature". For these reasons, it may be worthwhile for the group to consider some type of a public information programme which would have as its aim the informing of scientists, decision-makers and the general public of the measures which it has taken and how they relate to guaranteeing the safety of bio-industrial practices. In order to give a

sense of authority to the measures taken, it is important that eminent scientists and non-scientists take part in the workings of the UNIDO/WHO/UNEP group and subsequently, are mobilized in a supporting campaign to have the resulting safety guidelines and procedures widely understood and accepted.

Lastly, the group may wish to consider whether the ICGEB could take on one or more functions in regards to either risk assessment or the elaboration of safety management measures, or both. Since its membership is global and since it is, by the definition of its Statutes, to be a research centre of high excellence, it could be the legitimizing authority to the work of the group. Eventually, it may be appropriate for the ICGEB to take over the mandate from the UNIDO/WHO/UNEP working group and perpetuate its work. Simultaneously, it could assume the tasks of continiously monitoring national laws and regulations related to biotechnology safety and to collect and collate information on long-term effects, if any appear in the laboratories or industries.

Footnotes and Bibliography

1. WHO, Laboratory Biosafety Manual, (Geneva: WHO, 1983).

2. "Health Impact of Biotechnology", Report on a WHO Working Group, Dublin, 19 November 1982, in Swiss Biotech, vol. 2, No. 5, 1984, pp. 7 - 32.

3. "New Code on Plant Hazards in Third World", European Chemical News, 18 March 1985, p. 19.

4. Ibid.

5. "Health Impact of Biotechnology", op.cit., p.8.

6. OECD has been performing a study on conjectural risks and regulations associated with biotechnology since 1984. The report is, as of this writing, expected to be released in the fall of 1985.

Additional Sources

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