COMMISSION OF THE EUROPEAN COMMUNITIES

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PROPOSAL FOR A COUNCIL DIRECTIVE

establishing safety measures against the conjectural risks
risks associated with recombinant DNA work

(submitted to the Council by the Commission)

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REASONS FOR PROPOSAL

The aims of this preamble are to introduce the essential features of recombinant DNA work in the general background of modern developments in biotechnology and to present the considerations which have led the Commission to prepare the project of a directive compelling the Member States to adopt general precautions against hazards possibly associated to certain forms of recombinant DNA work.

Recombinant DNA work and its importance for Research and Development

Modern techniques and most particularly the use of recently discovered enzymes, called restriction enzymes, now allow the arrangement of genetic material in combinations which at the moment do not exist under natural conditions. The general method involves the isolation of DNA from a donor organism, its fragmentation by restriction enzymes into groups of one or more genes, the coupling of selected fragments to a vector (usually a virus or a constituent of the cell to be used as host) and its introduction in a host-cell which may be propagated to form populations of identical cells called clones.

Provided that the genetic material transferred in this manner replicates and expresses itself in its new surroundings, there are theoretically no limits to the range of organisms with new properties which may be produced through the use of recombinant DNA technology. In practice, however, the cloning and expression of foreign DNA into widely unrelated host-organisms are extremely difficult to achieve and, in some cases, probably impossible. Yet, DNA sequences coding for human placental lactogen and human growth hormone have been cloned in the bacteria Escherichia coli (a natural resident of the human digestive tract) and in at least two instances (expression in E. coli of a chemically synthetized gene for the hormone somatostatin and of the yeast structural

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gene for the enzyme imidazole-glycerophosphate dehydratase) has it been shown that the expression problem could be overcome.

It is obvious, in view of these prospects and of these results, that recombinant DNA technology opens up new avenues for fundamental and applied work which will certainly lead to an enormous improvement in our knowledge of genetic structures and genetic functions and which, in the long run, could completely revolutionize certain production methods in agriculture and industry. While growth hormone and insulin represent well know examples of products which could be elaborated at industrial level by manipulated bacteria, several other substances (calcitonin, prolactin, neurotransmitters, antibodies ...) may also be produced in the same manner by the pharmaceutical industries. In the medical sciences, one may conceive that the repairing of genetic defects in man will one day become feasible with the help of recombinant DNA work. In agriculture, through appropriate genetic transfers in isolated protoplasts regenerated afterwards into entire plants, modified crop species could be obtained which would combine the characteristics of unrelated species and present novel properties with regard to nitrogen uptake, disease resistance and a wide range of different quality factors. Such progresses are not yet in sight but are within our reach as long term objectives. Countries with modern technologies, such as the USA and Japan, have fully realized the importance of research in this area and in all related fields of applied molecular biology.

Risks associated to recombinant DNA work

While it is difficult to predict what a competent microbiologist could achieve if he undertook to improve systematically, through genetic manipulations, the virulence of important plant pathogens or to incorporate in *E. coli* the DNA from highly pathogenic organisms like *Bacillus anthracis* or *Clostridium botulinum*, it appears that, except for such deliberate attempts to endanger man and his environment, the risk associated to recombinant DNA work is at the moment conjectural and, to a very large extent, controllable.

- Conjectural nature of the associated risks

There is, in theory, a risk that living organisms, and particularly microorganisms residing in man or in species important to man, acquire upon

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receipt of foreign DNA properties which render them dangerous and harmfull. As a matter of fact, any transfer of genetic information which confers simultaneously to the host-organism a selective advantage and a modification of characters will to some extent affect our environment. The effects may be almost negligible or beneficial if the new characters are nearly neutral or useful to man; they may be devastating, either at short or long term, if they promote new factors (pathogenicity, induction or propagation of cancers, modification of environmental equilibrium, rupture of food chains ...) which man and the surroundings he has domesticated are unable to tolerate.

In practice, however, this risk has not yet been verified. On the contrary, most of the experiments and model scenarios (see for instance CURTISS R. Ann. Rev. Microbiol. 30 : 507-533, 1976 and report of the U.S. - EMBO Workshop held in Ascot, England, January 27-29, 1978) constructed for assessment purposes do point out that organisms bearing recombinant DNA are perhaps unlikely, for various reasons dealing with the low adaptive fitness of manipulated cells and the general requirements for transcription and infection, to generate biohazards greater than those associated to conventional research with pathogens. In addition, it may be suggested from the fact that the reproductive barriers and isolating mechanisms operating in nature are error-prone and overlapping that there is perhaps no such thing, under natural conditions, as an absolute barrier to gene exchange between any two organisms. Thence man and his environment, since they survived the continuous flow of genetic information between species, may possibly be considered as relatively tolerant to any new form of recombinant DNA.

- Possibilities for control

Particularly because the scientists engaged in recombinant DNA work were the first to point out (Asilomar Conference, 1973) the dangers possibly associated to their activities, research in this area has continuously been connected to the development of containment devices and of monitoring systems. As a result of this, methods, crippled host strains and facilities have been created which greatly reduce the chance that an organism bearing recombinant DNA escapes the laboratory (physical containment) or survives to conditions prevailing outside the laboratory (biological containment).

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While the forms of containment available, and particularly those pertaining to biological containment, certainly need to be improved and sophisticated, they already provide, when used correctly, a very strong protection against the risk that man and his environment are contaminated by recombinant DNA.

Guidelines and national safety measures

The development of recombinant DNA techniques has caused intense public and scientific debate in many countries which involved such issue as the definition of the field covered by recombinant DNA work, the classification of this work in categories of risks and in levels of containment, the necessity for state control, the type of control (voluntary or statutory) to be involved and the protection of intellectual property.

In the USA, the National Institute of Health (NIH) released very detailed guidelines providing an accurate classification of research activities in categories of risks and of assigned containment levels. At the moment only the laboratories sponsored by the NIH are compelled to follow these guidelines which are presently under revision and will probably be made less stringent. Guidelines somewhat similar to those of the NIH have been prepared or are in preparation, outside the Community, in all countries with advanced technologies but, as yet, no compulsory order have been issued on the matter in these countries.

Within the European Community, the United Kingdom has rendered compulsory advance notification of genetic manipulation work by all those who intend to carry out such work on the national territory. A code of practice, which differs from that of the NIH on essential points dealing with classification procedures and containment methods, is at the moment operated under a voluntary basis but with the understanding that the inspectors of the Health and Safety executive have extensive powers to enforce duties as well as precautions recommended by the British Advisory Group. The other Member States have also prepared or adopted guidelines to research with recombinant DNA which in some cases adhere to either the British or the American system and in others represent a compromise between the two sets of guidelines.

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In France, The Netherlands, Denmark and Belgium, the National Advisory Committees have been assigned the task to register the work at hand and to review research proposals. While a declaration of agreement has been drafted in France under which governmental, academic and industrial laboratories will submit to review and approval any project for recombinant DNA work, only two Member States (The Federal Republic of Germany and The Netherlands) have, in addition to the United Kingdom, clearly indicated an intention to introduce regulations on recombinant DNA research. In the Federal Republic of Germany, the compulsory orders will first be restricted to research financed by national funds; at a later stage, they will be extended to activities supported by the "Länder" and by private sources.

The elaboration or adoption of guidelines in the Member States and in other European countries has been greatly facilitated by the critical reviews and recommendations which were issued by the ad-hoc committee on recombinant DNA research of the European Science Foundation and by the Standing Committee of E.M.B.O. on recombinant DNA.

Necessity for national legislations based on Community standards

It is the view of the Commission that six different sets of considerations strongly underline the necessity for national laws on the matter :

- Harmony between Member States

Although it is not desirable, in view of the differences between the various containment facilities available in Europe, that identical guidelines are adopted and followed by all Member States, it is nevertheless essential, to avoid large variations in research potentialities, that certain basic

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principles of safety are accepted and adhered to by the Community of Member States. The present situation in which some Member States have adopted legislation on recombinant DNA work or are planning to do so while others haven't as yet defined any formal policy on the matter is, in this respect, unacceptable to the eyes of the Commission because it will lead to the development of differing conditions of safety, work and success between Member States and, subsequently, to the concentration of research activities at the most permissive sites. Such an expansion of divergences will not arise if national legislations, harmonized in part around a core of Community principles, are adopted in each Member State and provide the necessary tools for the permanent implementation of safety measures comparable in essence throughout the entire Community.

- The exemplary value of legislation on recombinant DNA technology

Genetic manipulations only form a small part of the attempts which man is now making for assuming the responsibility for life on this planet and for transforming his approach to the domestication of lower forms. Several new methods have now been developed which allow the immobilization on carriers, for industrial use, of enzymes and of cells, the production of new synthetic compounds, the mass-production of proteins in fermentation batches and, in a general manner, a complete modification of the relationship between man and nature. In the long term, the applications of molecular biology to agriculture and industry will unavoidably transform life in society and will induce significant and, possibly, irreversible changes to our environment. To request that the techniques which are to bring these changes are subjected, from the start, to statutory control and to legislation does not constitute an aggression to progress but, on the contrary, a recognition of the need to adapt society to new scientific developments.

Recombinant DNA work, even though the risk it represents is conjectural, well analysed in the Member States and possibly not greater than the dangers associated to conventional research with pathogens, constitutes, in this connexion, a choice material for establishing compatibilities between legislation and the development of modern technologies and for preparing a first basis to the dispositions which will undoubtedly have to be taken in the future to protect man against his own achievements. Provided that the legislation adopted is tolerant, flexible, and associated to a stimulation of research through funding, the opportunity should not be missed.

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- Gravity of the hazards

The classification of a risk as conjectural does not imply that the risk under consideration is benign. While scenarios representing the planet colonized by a new class of organisms combining the requirements and features of bacteria and mammals are of course purely fictitious the expansion of myxomatosis in Europe or the destruction of a tobacco field by black shank illustrate the gravity of the dangers which may be associated to the sudden spread of microorganisms with properties adapted to their environment. It is, as a matter of fact, in prevision of such conjectural dangers that various forms of physical containment and certified strains of bacteria unable to survive outside laboratory conditions are being produced throughout the Western world. If the gravity of the risk involved is such as to require the elaboration of these expensive protection devices it certainly justifies the preparation of orders intended to insure that they effectively serve their purpose and are used to protect against the risk which they are supposed to contain.

- Expansion of recombinant DNA work

Scientific progress in the field is occuring so rapidly that a number of experiments involving the production and use of recombinant DNA can now be executed on a routine basis and constitute classical approaches to certain investigations in molecular genetics. What appeared to be, a few years ago, a very sophisticated technique accessible to a small number of highly specialized institutes is being commonly used, in many laboratories, for specifying genes and their products. In addition, several centers devoted to applied research, and among them many laboratories operated by private industries, have become aware of the potentialities of recombinant DNA techniques for genetic engineering purposes and have launched, or are contemplating to launch, important research actions centred upon the production and use of recombinant DNA. Thus the risk, if there is one, which is associated to recombinant DNA is increasing with time in proportion with the total number of sites where such work is carried out.

- Transnational nature of the risk

The fact that the biological material subjected to recombinant DNA work usually includes viruses and bacteria which, assuming their escape from the laboratory, are not subjected to the barrier of national borders reduces to a certain extent the liberty of individual nations to define and to follow independent policies in the field of genetic manipulations. Agreement must be reached within communities of neighbouring countries on the general objectives and scale of the protection systems which are to be established and guarantees must be given to the respect of these agreements. Such agreements and such guarantees can best be generated through legal dispositions, taken in each country, which are based upon a core of principles adopted in common.

- Research in laboratories from private enterprises

While it is possible to conceive, in the absence of national legislations regulating work with recombinant DNA, that the governmental funding agencies maintain a certain level of control over the research activities of universities and national institutes, it is far more difficult to envisage, in the absence of legal dispositions, a system compelling the laboratories from private industries to adhere to the terms of national guidelines on recombinant DNA. There is, in other words, in a country where such guidelines are followed on a voluntary basis, a risk that different laboratories working at identical levels of risks do not observe the same rules to safeguards and to containment. Whereas it is obvious that a situation of this type is unacceptable it is also equally obvious, in view of the importance of recombinant DNA technology for the promotion of European bio-industries, that a legislation on recombinant DNA work must not endanger intellectual property rights and that special attempts will have to be made by the legislator to restrict to a minimum the disclosure by industries of confidential scientific information.

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A Community directive on recombinant DNA work

The problems raised by genetic manipulations and the possible need for a Community directive compelling each Member State to adopt certain measures of protection and of control against conjectural risks have been discussed several times by the Committee on Medical and Public Health Research (C.R.M.) and by ad hoc expert groups in the presence of representatives of E.S.F. and EMBO.

Following this period of consultation, the Commission prepared the attached project for a Council directive regulating work on recombinant DNA. This project takes simultaneously into account the necessary requirements for safety and the need for flexibility and adaptation to local circumstances. While stipulating that recombinant DNA considered to be associated to conjectural hazards cannot be performed if it is not first registered and authorized by the National Authority, the proposed directive leaves entire liberty to this National Authority in each Member State to establish the categorization and containment levels which it deems most appropriate. Special provision is taken for work tabulated as low risk and attempts are made to reduce at a minimum the amount of scientific information which is to be disclosed for registration and authorization purposes. Finally, full reference is made in the text of the directive to the fact that the terms of the present orders will have to be reviewed regularly at short intervals and revised, when necessary, at the light of new developments and scientific progresses. In addition, the Commission will study the special case, covered at the moment by the terms of the present directive, which concerns the use of recombinant DNA material for large scale industrial production; if necessary additional directives adapted to such case will be proposed by the Commission.

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Original : English

CONJECTURAL HAZARDS OF RECOMBINANT DNA WORK

Council Directive

The Council of the European Communities,

Having regard to the Treaty establishing the European Economic Community, and in particular Article 235 thereof,

Having regard to the proposal from the Commission,

Having regard to the opinion of the European Parliament,

Whereas Article 2 of the Treaty assigns to the Commission the task, among others, to promote throughout the Community a harmonious development of economic activities, a continuous and balanced expansion and an increase in stability ;

Whereas the development of basic and applied biological research is of a kind to contribute with efficiency towards the achievement of these objectives ;

Whereas this development implies, in several sectors, that recombinant DNA work be performed on certain organisms ;

Whereas recombinant DNA work performed on certain organims, and particularly on microorganisms resident in man, or in certain animal and plant species used in agriculture, may present conjectural hazards to man, to his food resources and to his environment in general ;

Whereas measures of protection settled by the authorities against such conjectural hazards must be combined with the development of recombinant DNA work;

Whereas this development involves epidemiological and hence international conjectural hazards ;

Whereas the disparities between the provisions in force or in preparation in the different Member States for establishing measures of protection against the conjectural hazards of recombinant DNA work may give rise to differing conditions of safety, work and success affecting directly the scientific and technological competitiveness of the laboratories concerned in the Member States;

Whereas action by the Community in the matter is therefore necessary to the realization of the objectives of the Treaty;

Whereas it is necessary to take into account the complexity of the problem posed by the conjectural hazards of certain types of recombinant DNA work, the rapid evolution in the understanding of this problem, the extent of the research sector concerned and the importance that must be attached to the consideration of local circumstances when assessing the hazards involved in performing scientific work ;

Whereas protocols are prepared for experiments in recombinant DNA work and it is necessary to minimize the dissemination of the substance of those protocols and research projects based on the production and use of recombinant DNA in order to safeguard scientific and industrial secrecy and to protect intellectual property ;

Whereas the Treaty has not provided the necessary powers for this purpose;

HAS ADOPTED THIS DIRECTIVE :

Article 1

1.1 This directive concerns the conjectural hazards associated with recombinant DNA work.

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1.2 For the purpose of this directive, the following terms have the meaning hereby assigned to them :

a) Recombinant DNA work : the formation of new combinations of heritable material by the insertion of nucleic acid molecules produced, by whatever means, outside the cell, into any virus, bacterial plasmid or other vector system so as to allow their incorporation into a host organism in which they do not naturally occur but in which they are capable of continued propagation.

b) Recombinant DNA materials : the product of recombinant DNA work consisting of organisms, including viruses and viroids, containing recombinant DNA molecules.

c) Laboratory : the site where one or more persons are engaged or planning to become engaged in recombinant DNA work and/or where one or more persons have introduced or are planning to introduce recombinant DNA materials.

Article 2

1 Each Member State shall take appropriate steps to ensure that no activities involving recombinant DNA work or the acquisition and use of recombinant DNA materials may be performed on its territory without prior notification to the appropriate national authorities and, except for activities falling in categories of low risk, without prior authorization from these authorities.

2 To this effect, each Member State shall subdivide in classes, according to their nature and the conjectural hazards that they involve, the various types of recombinant DNA work.
This distribution in classes shall be based upon the source and degree of purity of the DNA molecule, the vector-host system utilized and the manipulative procedures proposed. The classes of recombinant DNA work thus established shall then be grouped into categories defined on the basis of the particular safety and supervisory measures that must be adopted in order to prevent man or his environment from incurring any hazard that the Member State may deem excessive. The safety and supervisory measures assigned to the various classes of recombinant DNA work shall include the implementation of sound laboratory practice

(if necessary through proper training of safety officers, research workers and technicians) and the use of physical and biological means of containment.

3 Notification of the intention to undertake recombinant DNA work or to acquire recombinant DNA materials shall be lodged by the requesting laboratory with the national authority. The notification shall be accompanied by :

- the portion of the experimental protocol which is required for the evaluation of safety at the site where the proposed activities are to be carried out and, in the case of the acquisition of recombinant DNA materials, by the description of these materials and of shipping conditions;

- the list of the protective and supervisory measures to be applied throughout the duration of the experimental work and during storage, propagation and handling of recombinant DNA materials;

- the description of the general education in recombinant DNA research and of the training received by the members of the staff who will participate to the proposed activities or will be responsible for supervision, monitoring or safety.

4 The national authority shall assess or have assessed, according to the criteria it deems most suitable, the conjectural hazards associated to the proposed activities. It may require from the applicant further information for the evaluation of conjectural risks and safety conditions and, wherever such investigation seems necessary, it shall make a detailed on-site examination of the conditions of protection and safeguards.

Article 3

1 On the basis of the information available, the national authority shall take one of the following decisions :

- to authorize the proposed activities under the conditions described by the applicant;

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- to authorize the proposed activities on certain conditions ;

- to prohibit the proposed activities.

2 The decision of the national authority shall be notified in writing to the laboratory concerned within a period not exceeding ninety days from the date of receipt of the original application for authorization.

3 The national authority shall ensure, by the methods it deems most effective and appropriate, that only the activities that it has authorized are carried out on the national territory. The national authority shall ensure that the protective and supervisory measures referred to in Article 2(3), second indent, and the conditions referred to in Article 3 (1), second indent, are strictly adhered to. Member States shall provide for appropriate sanctions against any breach of these rules.

4 The national authority has the power to revoke any authorization it has given.

5 If the Member State amends the definition of any of the categories of recombinant DNA work requiring special safety measures, or if these measures are amended, the national authority shall ensure that any new requirement shall be immediately fulfilled by the laboratories in possession of recombinant DNA materials or performing recombinant DNA work on the national territory. The national authority shall revoke any authorization which does not comply with the new requirement and, in this case, shall order the suspension of activities in hand ; resumption of these activities shall be conditional upon the issue of a new authorization which may be established only after examination of the protective and supervisory measures adopted by the laboratory concerned.

Article 4

1 Member States shall bring into force the provisions needed in order to comply with this directive within one year of its notification. They shall forthwith inform the Commission of the European Communities thereof.

2 Member States shall ensure that the text of the measures which they adopt in the field covered by this Directive is communicated to the Commission. Each text shall be published by the Commission.

3 Member States shall transmit to the Commission the details of the categorization system which they have adopted and shall immediately inform the Commission of any modification made to this system. The Commission will publish the details of these categorization systems as well as any amendment made to them by Member States.

4 Member States shall submit to the Commission, at the end of each calendar year, the list of authorizations delivered during the year and a general report of their experience and problems encountered with the regulation of recombinant DNA work.

Article 5

1 Because of the unceasing progress of knowledge and techniques in the field of basic and applied biology, this Directive and its continued applicability to production activities of industries shall be throughly reviewed, and revised if necessary, at regular intervals not exceeding two years.

Article 6

1 This Directive is addressed to the Member States.

Done at

For the Council

The President