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Risk Assessment in the Context of EC Directives on Genetically Modified Organisms

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This introductory paper focuses on three general questions:

1. **What are GMOs according to EC directives?**
2. **Why risk assessment?**
3. **How risk assessment?**

1. What are genetically modified organisms (GMOs)?

The definition of a GMO used in EC directives is:

"a GMO means an organism in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination."

In order to understand this definition, it is useful to place it in the context of a human activity that has been carried out for thousands of years: selective breeding.

Ever since man started to produce his own food, he tried to modify plants, animals and micro-organisms in such a way that they could better serve his purposes. This activity was employed for many different purposes, for example in order to get better and more producing live stock, to get better and more producing plants for food production, and to get better equiped micro-organisms for the production of beer or cheese. If we compare the original species of plants and animals with the results of centuries of breeding and selection, we can see that the results of this activity of man are impressive. For example, over hundreds of years man increased the weight of a maize ear thirty times; and over the milk production by cows was increased from less than half a litre of milk a day to thirty litres daily. However, there is a natural barrier which sets limits to conventional breeding: plants can only cross with certain related plants and animals can only cross with certain related animals. Dogs do not cross with sheep, and tulips do not cross with oak trees.

An important step forward in the understanding of the mechanisms and limitations of breeding was delivered by the work of scientists such as Gregor Mendel in the last century, and Watson and Crick in this century. Through the work of these scientists, it became clear that breeding depends on the exchange of genetic information, called DNA.

With the development of an understanding of genetics, a new science developed, molecular biology. The first time this term was used was in 1938. With the use of this new technology, scientists attempted to overcome the limitations in breeding set by natural barriers.

In the early 70s, the first results were reported.

By using the "recombinant DNA" technique, it was possible to "cut and glue" pieces of DNA of one organism, and with the use of a vector, to place it in another organism. Although many technical problems have to be solved, with the use of the recombinant DNA technique, it is in principle possible to bring genetic material of any organism into any other organism. Not only

from any plant into any other plant, or from any animal into any other animal. With this new technique, genetic information of micro-organisms can be introduced in plants, genetic information of human beings can be introduced in micro-organisms (for example to produce insulin), and so forth. In principle, there are no limitations. Since the first recombinant DNA application, several other techniques are developed with which it also is possible to make new combinations of genetic material which are not likely to be produced in nature.

Some of those techniques are:

- protoplast fusion, or hybridisation: with this technique cells are "fused" after their cell wall is removed;
- micro-injection; with a microscopic small pipet DNA is injected into the nucleus of a cell;
- DNA particle gun method: tungsten bullets coated with DNA are "simply" shot through cells, leaving the DNA in the cell behind;
- organel transplantation: where for instance the nucleus of one cell is transplanted into another cell.

These are only examples. Other techniques have been developed, and will be developed.

2. Why risk assessment?

The introduction of these new molecular technologies initiated an international discussion on the safety in biotechnology. In 1974 one of the pioneers of this new technology, Paul Berg, expressed his view on the potential risks of recombinant DNA applications in the famous "Berg letter", leading to a self-imposed moratorium on certain experiments. Following the Berg letter and the Asilomar convention, much international attention has been given to the question of safety in biotechnology. This attention resulted in hundreds of documents, research programmes, guidelines and regulations. This resulted, among others, in two EC Directives on genetically modified organisms: the EC Directive 90/219/EEC on the contained use of genetically modified micro-organisms, and Directive 90/220/EEC on the release of genetically modified organisms. These directives lay down a system for harmonization of risk assessment and risk management with regard to the safety for human health and the environment.

Before discussing the general outlines of the risk assessment laid down in those two directives, let us first focus on a fundamental question: why risk assessment?

Are GMOs inherently dangerous?

No. The technique of genetic modification is neutral, and the resulting organisms (GMOs) are neither inherently dangerous nor inherently safe.

So, why risk assessment?

The rationale for risk assessment is "accountability beforehand". This is a matter of common sense, nothing more and nothing less.

This conference, where risk assessment in the area of chemicals is an important issue, offers a good opportunity to place the rationale for risk assessment of GMOs in a broader context. Formerly, all chemical substances could be placed on the market without further ado. This meant that a chemical substance was only taken off the market when harm had been done. Pesticides being a case in point.

Nowadays in the EC, and I am speaking of the period from 1981 onwards, a new chemical substance can only be brought onto the market if it has been established beforehand whether or not harmful effects are to be expected. The procedure would seem to be perfectly logical, but it has taken years and involved a great deal of environmental damage before we reached this stage.

We have learnt our lesson from what has happened with new chemicals. With the use of the new molecular techniques, (totally) new combinations of genetic traits can be made with which there is relatively little or no experience. Analogous to new chemicals, this unfamiliarity or uncertainty is the rationale for specific attention. The preventive approach.

In addition, it should be emphasized that risk assessment does not imply that risk exists, but simply that it is necessary to establish, by some means or another, whether a risk exists.

Summarizing: the rationale for risk assessment is "accountability beforehand".
The community at large can only benefit maximally from the potentials of this new technology if it is developed and applied judiciously, in order to avoid to the extent possible negative side effects that have diminished the potentials of many new technologies in the past.

This concept has been recognized and laid down in the Agenda 21 Programme "Environmentally sound management of biotechnology" of the United Nations Conference of Environment and Development. Agenda 21 was signed by most countries in Rio in June this year.

3. How risk assessment?

In the European Community, the EC Directives mentioned before lay down a general outline for risk assessment. This general outline is presented in the form of "points to consider".

Whether or not a certain application of a GMOs, may involve a risk, depends on **the characteristics of the GMO** involved and the **way it is applied.**

Taking the last item first: the way in which a GMO is applied will influence the potential for risk. In a very general way, a distinction can be made in "contained use" of GMOs and "released into the environment".

This distinction can be recognized in the two EC Directives: one directive deals with the contained use and the other deals with the release into the environment. Contained use is described as those applications where certain physical, or physical and biological, barriers are used to limit the contact of the GMOs with the environment. Examples of contained use are: applications in laboratories, research greenhouses and process installations. A release into the environment is defined as every application which is not contained use.

With regard to the potential for risk for human health or the environment, it is obvious that there is a difference between the use of organisms in laboratories under strict conditions, and for example a large scale release in the environment.

In the first case, the risk assessment may rely primarily on the level of containment (e.g. is the building sufficiently "closed"?). Fifteen years of experience with contained use provided us with a detailed categorization of containment levels and safety procedures.

For releases into the environment, the characteristics of the GMO are the key issue. Here, experience and knowledge is relatively limited.

The question of describing the characteristics of the GMO, is more complicated.

To start with, we should recognize that there are two fundamental questions to be answered:

1) Does the GMO itself, because of the modification, pose a risk to human health and the environment?
2) Can the genetic material of the GMO be transferred to other organisms, which – as a result – can pose a risk to human health or the environment?

Let us take again the second question first. It should be recognized that it is very well possible that a gene does not constitute a safety concern in the organism in which it is introduced, but that there may be a safety concern if that gene is transferred to other organisms. For example, the introduction of antibiotic resistance in a soil bacteria does not a priori make that particular bacteria harmful for human health. However, if that antibiotic resistance is transferred to a bacteria which is pathogenic to man, there is a safety concern, because it may have the effect that patients infected with the (resistant) bacteria can not be treated with that antibiotic.

Turning to the first question "does the GMO itself pose a risk to human health and the environment", it should be recognized that much of the methods used to answer this question are still very much of a qualitative nature.

The characteristics of a certain GMO have to be known, in order to decide whether the GMO itself poses a risk to human health and the environment.

The characteristics of the GMO can be derived from:

- The characteristics of the original organism, also called the host of parental organism(s). For example, it may be relevant to know whether we are dealing with a sterile culture crop plant which is not able to survive outside agricultural setting, or with a plant which can hybridize with wild relatives and which has weedy characteristics.
- The characteristics of the vector, the carrier, may be relevant, if that vector has harmful DNA or RNA sequences.
- The characteristics of the introduced genetic material and the related traits.

In addition to these elements, empiric data on the GMO, derived from earlier developmental stages or testing, are relevant. In this context, it should be recognized here that organisms are developed and evaluated in a "step wise fashion", through an appropriate continuum, for example from the laboratory stage, through stages of field testing, to final (e.g. commercial) application. Progression through these developmental stages entails in general a reduction of containment, whilst size is often gradually increased.

Examples of some issues in the risk assessment of GMOs

Some examples may illustrate the complexity of this area of risk assessment.

As an example, the main issues will be presented of the risk assessment regarding the introduction into the environment of genetically modified potatoes in the Netherlands. Potatoes are chosen as an example, because potatoes do not cross with the wild flora in the Netherlands.

This keeps the examples surveyable. In the Netherlands, several genetically modified potatoes have been subject to risk assessment for an introduction into the environment.

Acknowledging that the characteristics of potatoes and the proposed releases were well described, the risk assessment focused on the introduced new genes and the traits related to this introduced genetic material.

The new traits introduced in the potatoes were:
- virus resistance
- herbicide resistance
- insect resistance
- bacteria resistance
- fungi resistance
- antibiotic resistance
- non selectable markers
- change in starch composition
- diminished bruise sensitivity
- Erwinia (soil disease) resistance

The main issues related to these new genetic traits in these potatoes were very diverse: recombinations of viral material leading to viruses with a new host range, toxicological effects, development of resistance against certain biological pest control agents, effect on non-target or beneficial organisms, frost sensitivity, increased "weediness", and so forth. In the accompanying table, the safety concerns related to the introduced new genes and traits are summarized.

This table summarizes the main safety issues that were considered during the risk assessment procedure. This does not imply that after the risk assessment, these issues were reason for concern. For a good understanding of this table, it should be recognized that consideration of some of those issues depend on the scale of the application. For example, if there is uncertainty about potential impacts on beneficial soil organisms, the conclusion may be that such uncertainty is acceptable on a small scale, but not on a large scale. Here again, we should remember the "step wise" development and evaluation of organisms.

This example should make clear that this area of risk assessment is still very much in the qualitative stage. This does not imply that the risk assessment methods can not supply decision makers with sufficient information to take decisions in individual cases of releases.

However, in order to move forward to more quantitative assessments, more attention should be given to (long term) monitoring and to potential long term ecological effects.

4. Conclusions

Turning to the objective of this Conference, several conclusions can be made:
- The community at large can only benefit maximally from the potentials of a new technology if it is developed and applied judiciously, in order to avoid to the extent possible negative side effects that have diminished the potentials of many new technologies in the past.
- GMOs are neither inherently risky nor inherently safe. However, with the use of the new molecular techniques, new combinations of genetic traits can be made with which there

is relatively little or no experience. This unfamiliarity or uncertainty is the rationale for specific attention.
- Unlike the chemical and nuclear industry with recognized quantitative methods for risk assessment, assessment of environmental risk of the introduction of organisms is still very much qualitative;
- However, fifteen years of experience with contained use provided us with a detailed categorization of assessment procedures and containment levels;
- Risk assessment for releases into the environment is still in its early stages of development. Nevertheless, this area of risk assessment is rapidly evolving and already provides decision makers with sufficient data to take decisions in individual cases;
- Two major areas for further work in this area are:
  1) improve (long term) monitoring methods and standards;
  2) stronger focus on potential long term ecological impacts.

Examples

Trait * Insert	Safety Considerations
Virus Resist. * PUX/PLRU	– Recombinations → Viruses with a new host range?
Herbicide Resist. * Basta	– Toxicological considerations – Increased herbicide use
Insect Resist. * CRYI(A)/BT	– Resistance against BT – Effect on non target insects
Bacteria Resist. * Apeadicine IB * Cecropine B	– Effect on beneficial soil micro-organisms
Fungi Resist. * Osmotine II	– Effect on beneficial soil micro-organisms
Antibiotic Resist. * NPT II, HPT, CAT	
Non Select. Mark. * GUS (-Int)	
Starch Composit. * A.S. cDNA	– Frost sensitivity
Diminished Bruise * A.S. cDNA	– Alkaloid Compounds
S. Brevidens Fus. * Erwinia Resist	– Alkaloid Compounds – Volunteers