GMO/LMO- Risk Assessment and Risk Management

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Short history of biosafety regulation

Some terms used in risk assessment

Risk Assessment in the Cartagena Protocol

Risk Assessment procedures and some examples

Risk Management - procedures and terminology

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History

- **Gordon research conference on nucleic acids in the USA in 1973 - Worries by scientists regarding newly developed methodology of replicating bacterial plasmids with e.g. introduced virus genes and possible adverse effects of the ongoing recombinant DNA (rDNA) research activities.**

- **Identification of adequate methods to prevent spreading of rDNA molecules due to lack of knowledge and uncertainties in predicting possible negative effects.**

- **US National Academy of Sciences asked Dr. Paul Berg to head a Committee on recombinant DNA molecules. In 1974, the "Berg Committee" published their famous letter in Science and Nature (Berg *et al.* 1974).**

- **The Berg Committee requested the National Institutes of Health in the USA to consider the establishment of an advisory committee. They also requested scientists working in this field not to conduct certain experiments on bacterial plasmids and rDNA molecules involving antibiotic resistance, bacterial toxins, cancer and tumour development.**

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The Berg Committee wanted an advisory committee to be in charge of:

i) overseeing an experimental program to evaluate the potential biological and ecological hazards of certain types of rDNA molecules;

ii) develop procedures which would minimize the spread of such molecules within human and other populations; and

iii) devising guidelines to be followed by investigators working with potentially hazardous rDNA molecules.

As a result of the recommendations from the Berg committee and the concerns raised by scientists working in this field, the "International Congress on Recombinant DNA molecules" was organised in February 1975 at the Asilomar Conference Centre in California (Berg *et a1*. 1975).

The Asilomar Conference made a statement that was approved by its Executive Committee and the Governing Board of the National Research Council acting on behalf of the United States National Academy of Sciences.

Due to the recommendations and discussions from the Gordon research conference, the Berg committee and the Asilomar conference, the first NIH guideline on rDNA was developed and entered into force in 1976 . The intended application of the NIH guideline was for scientific research on bacteria and rDNA molecules in containment.

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OECD

In 1983, OECD member countries established an *Ad hoc* Group of governmental experts on "Safety and Regulations in Biotechnology". Their mandate was to:

Review country positions as to the safety in use of genetically engineered organisms at the industrial, agricultural and environmental levels, against the background of existing or planned legislation and regulations for the handling of micro-organisms;

Identify what criteria have been or may be adopted for the monitoring or authorisation for production and use of genetically engineered organisms in: industry, agriculture and the environment. Explore possible ways and means for monitoring future production and use of rDNA organisms in: industry, agriculture and the environment.

OECD published in 1986 the report from the *Ad Hoc* Committee, "Recombinant DNA Safety Considerations", the so-called "Blue Book" (OECD, 1986).

The "Blue Book", became in many respects the basis for Biosafety regulations of GMOs and gene technology in the western world.

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Definitions

Case by Case:

Regulatory principle - separate management of specific GMO applications from other GMO applications that authorities receive. Connected to risk assessment procedures.

The rational is that each GMO transformation event may differ, and therefore should have a separate particular evaluation by the authorities (and the applicant), in order to evaluate all possible hazards and risks of that specific GMO.

Step by step

Part of the development of GMOs in order to prevent possible hazards to be realised. Knowledge gained through this stepwise procedure is an important basis for collecting information needed in risk assessments and application of specific GMOs.

The step-by-step is used in research and development stages, it includes that a GMO: Should be characterised and carefully observed whereby safety and performance date are collected at each research stage from e.g. laboratory, microcosms, glasshouse, before small and larger field testing is conducted.

If a hazard or negative potential is identified, the organism can be brought back to a higher confinement level for safety reasons, or the experiment can be terminated.

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Cartagena Protocol; Article 15

RISK ASSESSMENT

1. **Risk assessments undertaken pursuant to this Protocol shall be carried out in a scientifically sound manner, in accordance with Annex III and taking into account recognized risk assessment techniques. Such risk assessments shall be based, at a minimum, on information provided in accordance with Article 8 and other available scientific evidence in order to identify and evaluate the possible adverse effects of living modified organisms on the conservation and sustainable use of biological diversity, taking also into account risks to human health.**

2. **The Party of import shall ensure that risk assessments are carried out for decisions taken under Article 10. It may require the exporter to carry out the risk assessment.**

3. **The cost of risk assessment shall be borne by the notifier if the Party of import so requires.**

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Annex III

RISK ASSESSMENT

Objective

1. The objective of risk assessment, under this Protocol, is to identify and evaluate the potential adverse effects of living modified organisms on the conservation and sustainable use of biological diversity in the likely potential receiving environment, taking also into account risks to human health.

Use of risk assessment

2. Risk assessment is, inter alia, used by competent authorities to make informed decisions regarding living modified organisms.

General principles

3. Risk assessment should be carried out in a scientifically sound and transparent manner, and can take into account expert advice of, and guidelines developed by, relevant international organizations.

4. Lack of scientific knowledge or scientific consensus should not necessarily be interpreted as indicating a particular level of risk, an absence of risk, or an acceptable risk.

5. Risks associated with living modified organisms or products thereof, namely, processed materials that are of living modified organism origin, containing detectable novel combinations of replicable genetic material obtained through the use of modern biotechnology, should be considered in the context of the risks posed by the non-modified recipients or parental organisms in the likely potential receiving environment.

6. Risk assessment should be carried out on a case-by-case basis. The required information may vary in nature and level of detail from case to case, depending on the living modified organism concerned, its intended use and the likely potential receiving environment.

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Annex III Continue:

Methodology

7. The process of risk assessment may on the one hand give rise to a need for further information about specific subjects, which may be identified and requested during the assessment process, while on the other hand information on other subjects may not be relevant in some instances.

8. To fulfil its objective, risk assessment entails, as appropriate, the following steps: An identification of any novel genotypic and phenotypic characteristics associated with the living modified organism that may have adverse effects on biological diversity in the likely potential receiving environment, taking also into account risks to human health;

   (b) An evaluation of the likelihood of these adverse effects being realized, taking into account the level and kind of exposure of the likely potential receiving environment to the living modified organism;

   (c) An evaluation of the consequences should these adverse effects be realized;

   (d) An estimation of the overall risk posed by the living modified organism based on the evaluation of the likelihood and consequences of the identified adverse effects being realized;

   (e) A recommendation as to whether or not the risks are acceptable or manageable, including, where necessary, identification of strategies to manage these risks; and

   (f) Where there is uncertainty regarding the level of risk, it may be addressed by requesting further information on the specific issues of concern or by implementing appropriate risk management strategies and/or monitoring the living modified organism in the receiving environment.

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Annex III continue:

Points to consider

9. Depending on the case, risk assessment takes into account the relevant technical and scientific details regarding the characteristics of the following subjects:

(a) Recipient organism or parental organisms. The biological characteristics of the recipient organism or parental organisms, including information on taxonomic status, common name, origin, centres of origin and centres of genetic diversity, if known, and a description of the habitat where the organisms may persist or proliferate;

(b) Donor organism or organisms. Taxonomic status and common name, source, and the relevant biological characteristics of the donor organisms;

(c) Vector. Characteristics of the vector, including its identity, if any, and its source or origin, and its host range;

(d) Insert or inserts and/or characteristics of modification. Genetic characteristics of the inserted nucleic acid and the function it specifies, and/or characteristics of the modification introduced;

(e) Living modified organism. Identity of the living modified organism, and the differences between the biological characteristics of the living modified organism and those of the recipient organism or parental organisms;

(f) Detection and identification of the living modified organism. Suggested detection and identification methods and their specificity, sensitivity and reliability;

(g) Information relating to the intended use. Information relating to the intended use of the living modified organism, including new or changed use compared to the recipient organism or parental organisms; and

(h) Receiving environment. Information on the location, geographical, climatic and ecological characteristics, including relevant information on biological diversity and centres of origin of the likely potential receiving environment.

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There is no definition of "Scientifically sound manner" in the protocol and no internationally agreed understanding of the term. This may give rise to disagreements between states. **(IUCN Environmental and Policy Law paper No. 46 – A guide to the Cartagena Protocol on Biosafety)**

The phrase implies that a Risk Assessment should be conducted in a systematic way and undertaken with inputs from people with appropriate qualification and experiences in relevant fields.

Examples of the types of scientific expertise and information for undertaking risk assessments relating to LMOs:

Risk assessment requires a range of expertise which should be reflected in the competence and experience of those carrying out the assessment in a scientifically sound manner. The different fields of expertise needed for scientifically sound risk assessment may include, as appropriate:

* Nucleic acid technology
* Molecular genetics
* Population genetics
* Marine biology
* Ecology
* Taxonomy
* Microbiology
* Plant biology/botany
* Veterinary science
* Agronomy
* Forestry
* Pathology
* Epidemiology
* Process technology
* Entomology
* Toxicology
* Zoology
* Biochemistry
* Virology

(UNEP, International Technical guideline for Safety in Biotechnology)

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The Protocol does not explain the term "possible adverse effects".

The possible adverse effects of LMOs that are to be identified and evaluated are those that might affect the conservation and sustainable use of biological diversity, taking also into account risks to human health.

Based on the wording of Article 15, and on the methodology for risk assessment set out in Annex III, it would appear that all such possible adverse effects are to be identified.

The evaluation of each possible adverse effect that has been identified then includes an assessment of the probability or likelihood of that adverse effect occurring, and of its consequences should it occur (Risk assessment = Probability x Consequence).

Possible adverse effects to be considered may include both short-term and cumulative, long-term effects, as well as direct, indirect and delayed effects (e.g. as in the EU Directives).

(IUCN Environmental and Policy Law paper No. 46 – A guide to the Cartagena Protocol on Biosafety; http://www.iucn.org/themes/law/pdfdocuments/Biosafety-guide.pdf)

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Taking into account recognized risk assessment techniques?

Cartagena Protocol; Article 14. Risk Assessment: ¨…Such risk assessments shall be based, at a minimum, on information provided in accordance with Article 8 and other available scientific evidence… Article 8: The notification shall contain, at a minimum, the information specified in Annex I.

Annex I

INFORMATION REQUIRED IN NOTIFICATIONS UNDER ARTICLES 8, 10 AND 13

(c) Name and identity of the living modified organism, as well as the domestic classification, if any, of the biosafety level of the living modified organism in the State of export.

(e) Taxonomic status, common name, point of collection or acquisition, and characteristics of recipient organism or parental organisms related to biosafety.

(f) Centres of origin and centres of genetic diversity, if known, of the recipient organism and/or the parental organisms and a description of the habitats where the organisms may persist or proliferate.

(h) Description of the nucleic acid or the modification introduced, the technique used, and the resulting characteristics of the living modified organism.

(i) Intended use of the living modified organism or products thereof, namely, processed materials that are of living modified organism origin, containing detectable novel combinations of replicable genetic material obtained through the use of modern biotechnology.

(j) Quantity or volume of the living modified organism to be transferred.

(k) A previous and existing risk assessment report consistent with Annex III.

(l) Suggested methods for the safe handling, storage, transport and use, including packaging, labelling, documentation, disposal and contingency procedures, where appropriate.

(m)Regulatory status of the living modified organism within the State of export (for example, whether it is prohibited in the State of export, whether there are other restrictions, or whether it has been approved for general release) and, if the living modified organism is banned in the State of export, the reason or reasons for the ban.

(n) Result and purpose of any notification by the exporter to other States regarding the living modified organism to be transferred.

(o) A declaration that the above-mentioned information is factually correct.

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Recognized risk assessment techniques?

- Both OECD and EU have made guidelines on appropriate and accepted risk assessment techniques. One major problem is that it is differences in the acceptance of hazard identification, knowledge gaps and therefore also the out coming results from the risk assessment.
- All risk assessments includes analysis of knowledge gaps of importance to identify potential risks and hazards. It includes e.g. pinpointing and identification of risks and hazards from the studies conducted by the applicant (notifier) and the literature they provide in order to prove for the authorities (and the society) that their LMO/GMO is safe and a good product.
- The discourse in the "scientific world of risk analysis" is often linked to whether tested hypothesis, including methods and the out coming results, are presenting acceptable answer to risk relevant questions. "Ownership" to the definition of what is important and acceptable, - is therefore important **(*nice to know* and *need to know*, may differ depending on what is "defined" to be important).**
- The results and the methods used are very often interpreted differently, dependent on the "experts" scientific background, or research area, including personal opinions. The differences in understanding and weighting of results and uncertainties often ends in completely different recommendations to the authorities and decision makers.
- The Authorities may therefore use the precautionary principle (or approach) as a basis for their decision due to the uncertainties identified in the risk assessment.

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EU Directive 2001/18 (Official Journal of the European Communities 17.4.2001)

A. Objective

The objective of an Environmental Risk Assessment (e.r.a.). is, on a case by case basis, to identify and evaluate potential adverse effects of the GMO, either direct and indirect, immediate or delayed, on human health and the environment which the deliberate release or the placing on the market of GMOs may have. The e.r.a. should be conducted with a view to identifying if there is a need for risk management and if so, the most appropriate methods to be used.

B. General Principles

In accordance with the precautionary principle, the following general principles should be followed when performing the e.r.a.:

- identified characteristics of the GMO and its use which have the potential to cause adverse effects should be compared to those presented by the non-modified organism from which it is derived and its use under corresponding situations;
- the e.r.a. should be carried out in a scientifically sound and transparent manner based on available scientific and technical data;
- the e.r.a. should be carried out on a case by case basis, meaning that the required information may vary depending on the type of the GMOs concerned, their intended use and the potential receiving environment, taking into account, i.a., GMOs already in the environment;
- if new information on the GMO and its effects on human health or the environment becomes available, the e.r.a. may need to be readdressed in order to:
  - -determine whether the risk has changed;
  - -determine whether there is a need for amending the risk management accordingly.

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Maize 1507 Application

(Applicant: Pioneer Hi-Bred International Inc. Non of the information was confidential)

What has been commented by Competent Authorities in Europe under Directive 2001/18 (Case from 2003). Some of the topics is listed below:

- The organization of the notification
- Case specific monitoring and general surveillance plan
- Detection and identification methods / protocol
- Molecular characterisation
- Stability and expression of the insert
- Toxicology and allergenicity
- Impact on non-target organisms
- Altered weed management
- Traceability and Labelling
- Co-existence and unavoidable mixing with conventional maize

The "<u>need for further information list</u>" is very long, and relates to all the mention issues above.

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Prp	Prp^{SC}
4,4	4,4
4	4
7,2	7,2
1,6	1,6
9,2	9,2
18	18
4,4	4,4
3,6	3,6
4,8	4,8
4	4
4,8	4,8
2,8	2,8
6,8	6,8
6	6
5,2	5,2
3,6	3,6
4,4	4,4

Compare composition of proteins?

Prions: Structure and not only composition!

The central dogma has fallen with HUGO; not one gene – one gene product any more. The complexity of gene regulation and proteins has increased with new knowledge.

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Risk Management

- Is often understood as management strategies, mechanisms and measures put in place in order to control risks identified in the risk assessment; and/or
- preventing risks and hazards to be realized linked to different activities conducted while developing, releasing, or using LMOs/GMOs.

Cartagena Protocol; Article 16. Risk Management:

2. Measures based on risk assessment shall be imposed to the extent necessary to prevent adverse effects of the living modified organism…

Contained Use of LMOs/GMOs is a risk management strategy in order to prevent unanticipated and/or anticipated hazards to be realized. Generally because we expect and accept that the organisms and the modifications in question can be hazardous when released, and therefore want to keep it strict under control (e.g. categorization systems on physical containment strength in laboratory classification, L1, L2, etc, depending on the GMOs potential for making harm if released).

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For the release of LMOs that are plants, risk management measures that are commonly applied include the following:

- Isolation distances or “buffer zones” (to the next field of the same crop and to other hybridization partners to minimize pollen transfer);
- Border rows with non-transgenic plants (to catch pollen);
- After release treatment: inactivation of remaining plants and seeds, specific soil treatment after harvest (e.g. measures for early germination in order to destroy volunteers);
- After release control (e.g. removal of volunteers in the next year/s); and
- Partial or full restrictions preventing planting in specified areas (e.g. to prevent horizontal gene flow).

(IUCN Environmental and Policy Law paper No. 46 – A guide to the Cartagena Protocol on Biosafety)

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Cartagena Protocol; Article 16. Risk Management

4. **Without prejudice to paragraph 2 above, each Party shall endeavour to ensure that any living modified organism, whether imported or locally developed, has undergone an appropriate period of observation that is commensurate with its life-cycle or generation time before it is put to its intended use.**

The "life-cycle" or generation time will depend on the LMO concerned.

In the case of trees or long-lived animals, a life-cycle could be measured in years or even centuries. The generation time – the time taken from germination or birth for the organism to produce progeny/offspring – will however generally be shorter than the period of their life-cycle.

Information obtained through "long term" observation of LMOs; identifying possible environmental interactions and hazards, taking also into consideration possible health effects, may therefore be a prerequisite for risk assessments and risk management strategies under the Protocol.

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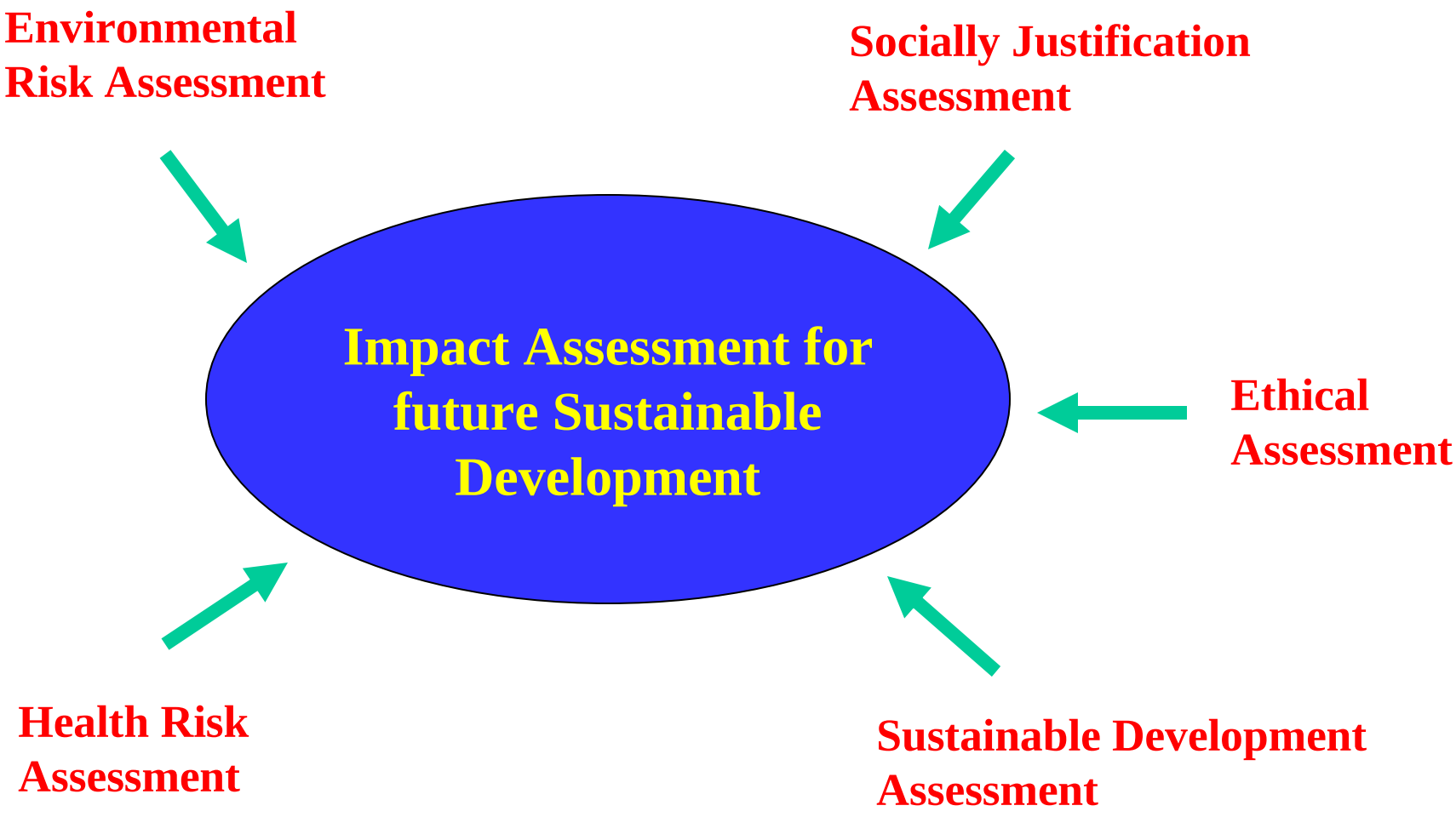
The Norwegian Gene Technology Act:

Section 11: Impact assessment

Applications for approval of deliberate release pursuant to section 10 shall contain an impact assessment setting out the risk of detrimental effects on health and the environment **and other consequences of the release.**

The Aim and Intention of the Norwegian Gene Technology Act



Thank You for Your Attention

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