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AD HOC TECHNICAL EXPERT GROUP ON RISK ASSESSMENT AND RISK MANAGEMENT UNDER THE CARTAGENA PROTOCOL ON BIOSAFETY
Bonn, Germany, 2-6 June 2014
Item 3.2 of the provisional agenda*

REVISED TRAINING MANUAL ON RISK ASSESSMENT OF LIVING MODIFIED ORGANISMS

1. In its decision BS-VI/12, the Conference of the Parties serving as the meeting of the Parties to the Protocol (COP-MOP) mandated the Online Forum on Risk Assessment and Risk Management and the Ad Hoc Technical Expert Group (AHTEG) on Risk Assessment and Risk Management to "[c]oordinate, in collaboration with the Secretariat, the development of a package that aligns the Guidance on Risk Assessment of Living Modified Organisms (e.g. the Roadmap) with the training manual 'Risk Assessment of Living Modified Organisms' in a coherent and complementary manner, for further consideration of the Parties, with the clear understanding that the Guidance is still being tested".

2. The Online Forum and the AHTEG held several rounds of discussion with a view to improving the coherence between the Roadmap and the "Manual on Risk Assessment of Living Modified Organisms" (i.e. the Manual).[1]

3. Taking into account the fact that the testing of the Guidance, which comprises the Roadmap, was still in progress and the fact that the COP-MOP may wish to establish a process for its improvement, the alignment between the contents of the Roadmap and the Manual was limited to revising and restructuring the Manual alone while keeping the Roadmap untouched throughout the process.

4. The resulting revised Manual is being made available as an information document for the face-to-face meeting of the AHTEG to be held in Bonn, Germany from 2 to 6 June 2014.

* UNEP/CBD/BS/AHTEG-RA&RM/5/1.
1 Available at http://bch.cbd.int/onlineconferences/forum_ra/discussion.shtml.

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Training Manual on Risk Assessment of Living Modified Organisms in the context of the Cartagena Protocol on Biosafety

Convention on Biological Diversity

UNEP

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Module 1:

Overview of Biosafety and the Cartagena Protocol on Biosafety

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Using this module

This module contains introductory sections explaining basic concepts in biosafety and an introduction to the Cartagena Protocol on Biosafety and other international biosafety-related bodies and organizations. The section on the Cartagena Protocol on Biosafety explains its history, scope and objective, and provides an overview of its relevant articles and provisions.

This module also includes a section on other international bodies involved in risk assessment in the context of biosafety, such as the Food and Agriculture Organization of the United Nations (FAO), the Codex Alimentarius, the International Plant Protection Convention (IPPC), the World Organisation for Animal Health (OIE), the World Trade Organization (WTO), the Organisation for Economic Cooperation and Development (OECD), as well as bilateral and multilateral agreements.

Introduction to biosafety and the Cartagena Protocol on Biosafety

History of the Protocol

The United Nations Conference on Environment and Development (also known as the “Earth Summit”), held in Rio de Janeiro in 1992 marks a significant achievement in the overall policy of the United Nations on the environment. Several documents resulting from that meeting constitute the basis of the international law on biosafety, such as Agenda 21, the Rio Declaration on Environment and Development and the United Nations Convention on Biological Diversity.

Agenda 21 is a comprehensive programme for action in social and economic areas and for conserving and managing the natural resources. Its chapter 16 addresses the “Environmentally sound management of biotechnology” (see box below) by recognising that modern biotechnology can make a significant contribution to enhancing food security, health and environmental protection, and outlining the need for international agreement on principles to be applied to risk assessment and management and set out the implementation of safety mechanisms on regional, national, and international levels.

Agenda 21, chapter 16, paragraph 29

“There is a need for further development of internationally agreed principles on risk assessment and management of all aspects of biotechnology, which should build upon those developed at the national level. Only when adequate and transparent safety and border-control procedures are in place will the community at large be able to derive maximum benefit from, and be in a much better position to accept the potential benefits and risks of, biotechnology.”

Source: UNCED (1992a).

The Rio Declaration on Environment and Development is a series of principles defining the rights and responsibilities of States. Principle 15 allows countries to take precautionary action to prevent environmental degradation where there are threats, but no conclusive evidence, of serious or irreversible damage (see box below).

Principle 15 of the Rio Declaration on Environment and Development

"In order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation."

Source: UNCED (1992b).

The Convention on Biological Diversity (CBD) was inspired by the global community's growing commitment to sustainable development. It represents a dramatic step forward in the conservation of biological diversity, the sustainable use of its components, and the fair and equitable sharing of benefits arising from the use of genetic resources. The CBD addresses access to biotechnology and the sharing of its benefits in articles 16 ("Access to and Transfer of Technology") and 19 ("Handling of Biotechnology and Distribution of its Benefits"). The issue of safety in biotechnology is addressed in articles 8(g) and 19(3) of the CBD.

More specifically, in Article 8(g), Parties to the CBD are called upon to establish or maintain means to regulate, manage or control the risks associated with the use and release of living modified organisms (LMOs) resulting from biotechnology which are likely to have adverse impacts on the conservation and sustainable use of biological diversity. In Article 19(3) the Parties are called upon to consider the need for and modalities of a protocol for the safe transfer, handling and use of LMOs resulting from biotechnology that may have adverse effect on the conservation and sustainable use of biological diversity.

Article 8(g). In-situ Conservation of the Convention on Biological Diversity

"Each Contracting Party shall, as far as possible and as appropriate:

Establish or maintain means to regulate, manage or control the risks associated with the use and release of living modified organisms resulting from biotechnology which are likely to have adverse environmental impacts that could affect the conservation and sustainable use of biological diversity, taking also into account the risks to human health".

Source: Convention on Biological Diversity (1992).

Article 19(3). Handling of Biotechnology and Distribution of its Benefits of the Convention on Biological Diversity

"The Parties shall consider the need for and modalities of a protocol setting out appropriate procedures, including, in particular, advance informed agreement, in the field of the safe transfer, handling and use of any living modified organism resulting from biotechnology that may have adverse effect on the conservation and sustainable use of biological diversity."

Source: Convention on Biological Diversity (1992).

Taking into account the provisions above, the Conference of the Parties to the Convention on Biological Diversity decided, at its second meeting, to develop a protocol on biosafety, specifically focusing on the transboundary movement of LMOs that may have adverse effects on the conservation and sustainable use of biological diversity taking into account human health.

As a preliminary tool to serve as interim guidance for biosafety, a set of International Technical Guidelines for Safety in Biotechnology was drafted by UNEP and adopted by the Global Consultation of Government-designated Experts in Cairo, Egypt in December 1995.

In 1996, the Conference of the Parties for the Convention on Biological Diversity established an Open-ended *Ad Hoc* Working Group on Biosafety to develop a draft protocol. This Working Group met six times between 1996 and 1999 and, at the conclusion of its last meeting, a draft protocol was submitted for consideration by the Conference of the Parties at an extraordinary meeting in February 1999, in Cartagena, Colombia. The Conference of the Parties was not able to finalize its work in Cartagena. As a result, the Conference of the Parties suspended its first extraordinary meeting and agreed to reconvene as soon as possible.

The Conference of the Parties reconvened and adopted the Cartagena Protocol on Biosafety on 29 January 2000 in Montreal, Canada. The Protocol entered into force on 11 September 2003 upon ratification by the fiftieth Party. As of September 2011, 161 Parties had acceded/ratified the Protocol.

What is Biosafety?

In its broad sense, the term biosafety refers to the protection of human health and the environment from potential harm due to biological agents.

Under the Convention on Biological Diversity (CBD), and more specifically under the Cartagena Protocol on Biosafety (hereinafter "the Protocol")[2], the term biosafety essentially refers to safety procedures aimed at regulating, managing or controlling the risks associated with the use and release of LMOs resulting from biotechnology which are likely to have adverse environmental impacts that could affect the conservation and sustainable use of biological diversity, taking also into account risks to human health. Biosafety comprises multidisciplinary scientific fields including, but not limited to biology, ecology, microbiology, molecular biology, animal and plant pathology, entomology, agriculture and medicine as well as legal and socio-economic considerations, and public awareness.

What are living modified organisms?

According to the Cartagena Protocol on Biosafety:[3]

a) "Living modified organism" means any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology;

b) "Modern biotechnology" means the application of:

   i. *in vitro* nucleic acid techniques, including recombinant deoxyribonucleic acid (DNA) and direct injection of nucleic acid into cells or organelles; or

   ii. fusion of cells beyond the taxonomic family;

   that overcome natural physiological reproductive or recombination barriers and that are not techniques used in traditional breeding and selection.

2 The text of the Cartagena Protocol on Biosafety is available at http://bch.cbd.int/protocol/text/ .

3 Article 3, paragraphs (g) and (i).

An LMO is therefore an organism that contains a novel combination of genetic material and results from (i) *in vitro* modification of nucleic acid (DNA or RNA) molecules; or (ii) cell fusion between organisms of different taxonomic families. In either case, for an organism to be considered an LMO, the techniques used in its development should be ones “that overcome natural physiological reproductive or recombination barriers and that are not techniques used in traditional breeding and selection”.

Modern biotechnology techniques include, but are not limited to, *in vitro* DNA and RNA techniques for the modification of genetic material (e.g. by insertion, modification or deletion of genes or other nucleic acid sequences) in all types of organisms, such as plants, animals, microbes and viruses.

Objective and scope of the Protocol

The objective of the Protocol is “to contribute to ensuring an adequate level of protection in the field of the safe transfer, handling and use of living modified organisms resulting from modern biotechnology that may have adverse effects on the conservation and sustainable use of biological diversity, taking also into account risks to human health, and specifically focusing on transboundary movements”.

The Protocol establishes rules and procedures for the safe handling, transfer, and use of LMOs. The Protocol focuses on the transboundary movement of LMOs destined for introduction into the environment and those intended for use directly as food, feed or for processing. The protocol seeks to protect biological diversity, taking into account human health, from the potential risks posed by living modified organisms resulting from modern biotechnology (UNEP, 2006).

All LMOs that may have adverse effects to biodiversity or human health are within the scope of the Protocol. Nevertheless, some types of LMOs may be excluded from some provisions, as indicated below:

Scope of the Cartagena Protocol on Biosafety

► ***LMOs subject to the provisions of the Protocol***

All LMOs [that] may have adverse effects on the conservation and sustainable use of biological diversity, taking also into account risks to human health (Article 4).

► ***LMOs excluded from the Protocol’s provisions on transboundary movements***

LMOs that are pharmaceuticals for humans that are addressed by other international organizations or agreements (Article 5).

Source: IUCN (2003).

Living modified organisms for intentional introduction into the environment - Advanced Informed Agreement (AIA)

The Advanced Informed Agreement (AIA) defines mandatory procedures to be applied to the first transboundary movement of an LMO for intentional introduction into the environment. LMOs intended for direct use as food, feed, or for processing are subject to a different procedure, as outlined in the next section.

The AIA procedure begins with the Party of export or the exporter notifying the Party of import of the proposed transboundary movement of an LMO for intentional introduction into the environment. The notification must contain at a minimum the information specified in Annex I of the Protocol including, among other things, contact details of the exporter and importer, name and identity of the LMO and its intended use, as well as a risk assessment report consistent with Annex III of the Protocol.

The Party of import has 90 days to acknowledge the receipt of the notification, and 270 days to communicate its decision to the notifier and the Biosafety Clearing-House (BCH).[4] In its decision, the Party of import may approve[5] or prohibit the import of the LMO, request further information or extend the decision period for a defined amount of time. If the Party of import does not communicate its decision within 270 days, it should not be understood that consent was given.

Application of the Advanced Informed Agreement (AIA) procedure

► ***LMOs subject to AIA provisions***

LMOs intended for intentional introduction into the environment (Article 7(1)).

► ***LMOs excluded from the Protocol's AIA provisions***

- LMOs in transit (Article 6(1)).
- LMOs destined for contained use in the Party of import (Article 6(2)).
- LMOs intended for direct use as food or feed, or for processing (LMO-FFPs) (Article 7(2)).
- LMOs identified by the meeting of the Parties to the Protocol as being not likely to have adverse impacts (Article 7(4)).

Source: IUCN (2003).

Living modified organisms for direct use as food, feed, or for processing (LMO-FFPs)

According to Article 11 of the Protocol, a Party that makes a final decision regarding domestic use, including placing on the market, of an LMO that may be subject to transboundary movement for direct use as food or feed, or for processing shall submit to the BCH the information specified in Annex II of the Protocol, within fifteen days. This information includes, among other things, the name and identity of the LMO and its approved uses, as well as a risk assessment report consistent with Annex III of the Protocol (see Article 11(1)).

Competent National Authorities

Each Party should designate one or more competent national authorities (CNAs) who will perform the administrative functions required by the Protocol and are authorized to take decisions on the LMOs for which they are designated (see Module 2).

4 Unless article 10, paragraph 2(b) applies.

5 A decision that approves the use of an LMO may be done with or without conditions. If there are conditions, the decision must set out the reasons for the conditions.

Risk Assessment (Article 15 and Annex III)

Article 15 of the Protocol sets out the provisions for Parties to conduct risk assessments of LMOs. It requires that risk assessments be carried out in a scientifically sound manner in accordance to Annex III and taking into account recognized risk assessment techniques.

While the Party considering permitting the import of an LMO is responsible for ensuring that a risk assessment is carried out, it has the right to require the exporter to do the work or to bear its cost. This is particularly important for many developing countries (SCBD, 2003).

The Protocol, therefore, empowers governments to decide whether or not to accept imports of LMOs on the basis of risk assessments. These assessments aim to identify and evaluate the potential adverse effects that an LMO may have on the conservation and sustainable use of biodiversity in the receiving environments.

Annex III sets out the general principles and methodology for the risk assessment process.

The general principles for conducting a risk assessment under the Protocol are that (i) it must be carried out in a scientifically sound and transparent manner and on a case-by-case basis, (ii) 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, and (iii) risks of LMOs should be considered in the context of the risks posed by the non-modified recipients or parental organisms in the likely potential receiving environment.

Individual Parties use these general principles to guide the development and implementation of their own national risk assessment process (see Module 2).

The following are considerations regarding some of the general principles for risk assessment:

Scientific soundness **–** The Cartagena Protocol explicitly states that risk assessments should be carried out in a scientifically sound manner. The principle of scientific soundness entails that risk assessments are to be undertaken in a systematic way on the basis of verifiable and reproducible information by, for example, reporting on methods and data in sufficient detail to enable others to repeat the steps of the risk assessment independently. Some countries have integrated this principle into their own procedures with specific suggestions about what type of information is appropriate for use in a risk assessment. In many cases, different sources and criteria for scientifically sound information have been set, ranging from scientific literature, studies presented by the notifier and expert opinions, etc. Consultations among scientific experts may also be considered as an appropriate means for gathering such information.

Transparency **–** Annex III states that risk assessments should be conducted in a transparent manner. Most countries with National Biosafety Frameworks (NBFs) have procedures in place to ensure the transparency of risk assessments. The CNAs often show what transparency mechanism is in place to handle notifications and how the mechanism is applied in each case. The level of transparency, however, may range from public notification to broad public involvement.

Some countries, for instance, make the necessary requirements for conducting risk assessments available online and, if an approval is granted for release of an LMO into the environment, a public notification is usually issued by posting the release online (see also provisions of Article 23 on "Public Participation" and the section below on "Stakeholder participation").

Example 1 – Need for transparency

"Transparency is needed in all parts of risk assessments, including:

1) the objective and scope
2) the source, nature and quality of the data, detailed methods, explicit assumptions, variabilities, identified uncertainties and their significance for the outcome
3) the output and conclusions

A transparent risk assessment should be clear, understandable and reproducible. It may help the clarity of the text if particularly complex technical descriptions are annexed to the assessment. [...]

Transparency in risk assessment contributes to:

• meeting the legitimate needs of stakeholders to understand the basis for risk assessment;
• allowing an informed debate on scientific issues;
• providing a framework in which consumers can have confidence;"

Source: EFSA (2009).

***Case-by-case* –** Annex III states that risk assessments should be carried out on a case-by-case basis, i.e. a commonly accepted approach where each LMO is considered relative to the environment in which the release is to occur and to the intended use of the LMO. The required information may vary in nature and level of detail from case-to-case, depending on the LMO concerned, its intended use and the likely potential receiving environment.

The legal frameworks of some countries may also specify other elements to be taken into consideration in each "case".

Example 2 – The case-by-case basis is fundamental to risk assessment of LMOs

A case-by-case approach is one where each release of an LMO is considered relative to the environment in which the release is to occur, and/or to the intended use of the LMO in question. A risk assessment performed for a particular LMO intended to be introduced to one environment may not be sufficient when assessing the possible adverse effects that may arise if that LMO is to be released under different environmental conditions, or into different receiving environments. A risk assessment performed for a particular use of a particular LMO may not be sufficient when assessing the possible adverse effects that may arise if that LMO is to be used in different ways. Because of this, it is important for each case to be addressed separately, taking into account specific information on the LMO concerned, its intended use, and its potential receiving environment.

Source: IUCN (2003).

Considerations on how to apply these two general principles when conducting a risk assessment are discussed in Module 3.

Annex III also contains a number of steps for conducting the risk assessment as well as points to consider on the technical and scientific details regarding, for example, the characteristics of the genetic modification, biological characteristics of the LMO, differences between the LMO and its recipient organism, its intended use, the likely receiving environment, amongst other things.

Module 3 of this training manual explains each step of the risk assessment process according to Annex III of the Protocol.

The Biosafety Clearing-House

The Biosafety Clearing-House (BCH; http://bch.cbd.int) is a mechanism set up under the Cartagena Protocol on Biosafety to facilitate the exchange of information on LMOs and assist countries that are Parties to the Protocol to better comply with their obligations.

The BCH provides open and easy access to a variety of scientific, technical, environmental, legal and capacity building information provided in all 6 languages of the UN.

The BCH contains the information that must be provided by Parties to the Protocol, such as decisions on release or import of LMOs, risk assessments, competent national authorities, and national laws.

Governments that are not Parties to the Protocol are also encouraged to contribute information to the BCH, and in fact a large number of the decisions regarding LMOs have been registered in the BCH by non-Party governments.

The records of decisions, risk assessments, LMOs, donor and recipient organisms, and DNA sequences are cross-referenced in a way that facilitates data retrieval. For instance, while looking at an LMO record, all the records for the risk assessment that reference that specific LMO can be easily accessed and retrieved.

The BCH also contains other relevant information and resources, including information on national contacts, capacity-building, a roster of government-nominated biosafety experts, and links to other websites, publications and databases through the Biosafety Information Resource Centre (BIRC).

Other provisions under the Protocol

In addition to the provisions above, the Protocol also requires the Parties to the Protocol, consistent with their international obligations, to consult the public during the decision-making process regarding LMOs (Article 23); make the results of such decisions available to the public (Article 23) and allow the decision-making process to take into account socio-economic considerations arising from the impact of the LMOs on the conservation and sustainable use of biodiversity (Article 26).

Other International Biosafety-related Bodies

Several other international bodies and organizations carry out activities that are relevant to the trade and environmental aspects of LMOs. A brief overview of these bodies is provided below.

International Plant Protection Convention

The International Plant Protection Convention (IPPC; www.ippc.int) is a multilateral treaty for international cooperation in plant protection. It aims to protect plant health while facilitating international trade. The IPPC applies to cultivated plants, natural flora and plant products and includes both direct and indirect damage by pests (including weeds). The IPPC was adopted by the Conference of the FAO in 1951. There are currently 173 contracting Parties to the IPPC.

The governing body of the IPPC is the Commission on Phytosanitary Measures (CPM). The CPM has adopted a number of International Standards for Phytosanitary Measures (ISPMs) that provide guidance to countries and assist contracting Parties in meeting the aims of the convention. The IPPC is recognized by the World Trade Organization as the relevant international standard setting body for plant health. Application of ISPMs is not mandatory; however under the WTO-SPS Agreement (see below) phytosanitary measures based on international standards do not need additional scientific or technical justification.

ISPM No. 11 (IPPC, 2004) describes the factors to consider when conducting a pest risk analysis (PRA) to determine if a pest is a quarantine pest. The main text of the standard (indicated with “S2” throughout the text) and particularly Annex 3 of this ISPM includes guidance on conducting PRA on LMOs.

In order to increase member countries' capacity to conduct pest risk analysis, the IPPC has developed a training course and training materials.[6]

Codex Alimentarius Commission

The Codex Alimentarius Commission (CAC; www.codexalimentarius.net) is a subsidiary body of the FAO and the World Health Organization (WHO) established in 1961-63 to protect the health of consumers and ensure fair practices in food trade. It currently has 166 members.

Codex Alimentarius, which means "food code", is a compilation of standards, codes of practice, guidelines and recommendations on food safety prepared by the Commission. In the area of foods derived from biotechnology, the Codex provides guidance on human health risk analysis in its “Principles for the Risk Analysis of Foods Derived from Modern Biotechnology” (CODEX, 2003) and in its “Working Principles for Risk Analysis for Food Safety for Application by Governments” (CODEX, 2007).

6 The IPPC training materials are available at https://www.ippc.int/index.php?id=186208 .

Food and Agriculture Organization

The Food and Agriculture Organization (FAO; www.fao.org) of the United Nations also carries out activities on biosafety and biosecurity. Among these, the FAO Working Group on Biosafety is responsible for two of FAO's Priority Areas for Interdisciplinary Action (PAIAs), namely "Biosecurity for Agriculture" and "Food Production and Biotechnology Applications in Agriculture, Fisheries and Forestry".

World Organisation for Animal Health

The World Organisation for Animal Health (OIE; www.oie.int) is an international intergovernmental organization founded in 1924 for improving animal health worldwide. As of June 2010, the OIE had 176 member countries.

The objectives of the OIE are to: (a) guarantee the transparency of animal disease status world-wide; (b) collect, analyze and disseminate veterinary scientific information, (c) provide expertise and promote international solidarity for the control of animal diseases; and (d) guarantee the sanitary safety of world trade by developing sanitary rules for international trade in animals and animal products.

Within the mandates of the OIE, the principal aim of import risk analysis is to provide importing countries with an objective and defensible method of assessing the disease risks associated with the importation of animals, animal products, animal genetic material, feedstuffs, biological products and pathological material.

Organisation for Economic Cooperation and Development

The Organisation for Economic Cooperation and Development (OECD; www.oecd.org) provides a setting where governments compare policy experiences, seek answers to common problems, identify good practice and coordinate domestic and international policies.

With regard to risk assessment, the OECD has published the "Recombinant DNA Safety Considerations" (OECD, 1986) and consensus documents, which focus on the biology of the recipient organisms or introduced traits and are useful in background preparation for an LMO risk assessment.[7]

World Trade Organization

The World Trade Organization (WTO; www.wto.org) is an international organization responsible for establishing the rules of trade between nations. It has a number of agreements that affect the trade of LMOs. One such agreement is the international treaty of "Agreement on the Application of Sanitary and Phytosanitary Measures", also known as the SPS Agreement.

The SPS Agreement concerns the application of sanitary and phytosanitary measures for food safety and animal and plant health regulations and may apply to LMOs. Article 5 of the SPS Agreement is of interest in the context of this training material since it addresses risk assessment and the determination of the

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7 Available at http://www.oecd.org/science/biotrack/consensusdocumentsfortheworkonthesafetyofnovelfoodsandfeeds.htm.

appropriate level of sanitary or phytosanitary protection. Article 3 of the SPS Agreement recognizes the standards, guidelines and recommendations set by IPPC, OIE and Codex Alimentarius Commission.

Other WTO agreements, such as the Technical Barriers to Trade (TBT) Agreement, Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPs) and the General Agreement on Tariffs and Trade (GATT) may also apply to LMOs.

Bilateral, regional and multilateral agreements

In addition to international treaties and standards, countries may engage in bilateral, regional and multilateral agreements, such as free-trade agreements (FTAs), provided they are consistent with the objective of the Protocol and do not result in a lower level of protection than that provided for by the Protocol. Such agreements could also be used to undertake shared responsibilities in assessing risks to facilitate decisions on LMOs.[8]

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8 According WTO (at http://www.wto.org/english/tratop_e/region_e/region_e.htm), the overall number of Regional Trade Agreements (RTAs) in force has been increasingly steadily, a trend likely to be strengthened by the many RTAs currently under negotiations. Of these RTAs, Free Trade Agreements (FTAs) and partial scope agreements account for 90%, while customs unions account for 10 %. The Regional Trade Agreements Information System (RTA-IS), at http://rtais.wto.org/UI/PublicMaintainRTAHome.aspx, contains information on those agreements that have either been notified, or for which an early announcement has been made, to the WTO.

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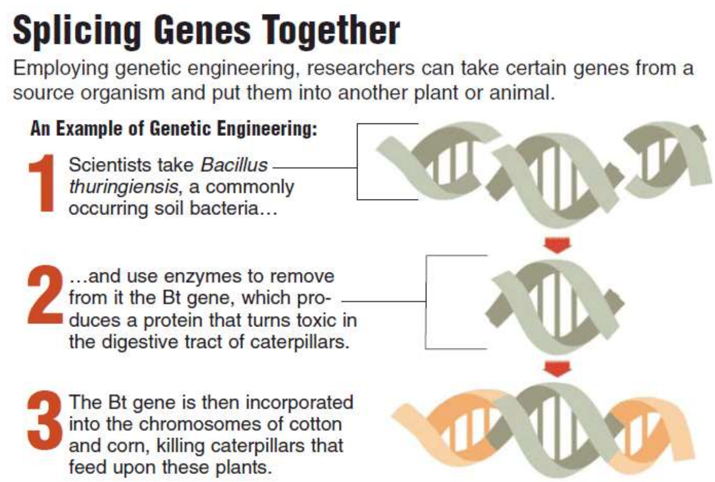
Annex - Techniques used in modern biotechnology

Overview of techniques used in modern biotechnology

LMOs are most commonly developed through the use of *in vitro* nucleic acid techniques by inserting, deleting or modifying a gene or DNA/RNA sequence in a recipient or parental organism.

The terms genetic modification, genetic engineering, recombinant DNA and DNA manipulation are terms that apply to the direct modification of an organism's genes. The terms genetically modified organism (GMO) as well as genetically engineered or transgenic organism are often used interchangeably with LMO. The Cartagena Protocol emphasizes the "living" nature of the organism, and some of its provisions also apply to processed materials that originate from LMOs and contain detectable novel combinations of replicable genetic material obtained through the use of modern biotechnology.

Figure 1* – In vitro *nucleic acid techniques



Source: North Carolina State University (website).

LMOs can also be produced through cell fusion where cells from two different organisms that do not belong to the same taxonomic family are fused resulting in an organism containing the genetic information from both parental cells. The resulting LMO may contain the complete genomes of the parental organisms or parts of their genomes. Cell fusion can be applied to bacterial, fungal, plant or animal cells, using a variety of techniques to promote fusion.

Commonly used methods for genetic modification of plants

Production of LMOs through genetic modification is a multistage process that can be achieved through a variety of methodologies. Methods that are commonly used in the development of LM plants can be summarized as follows:[9]

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9 Adapted from IUCN (2003).

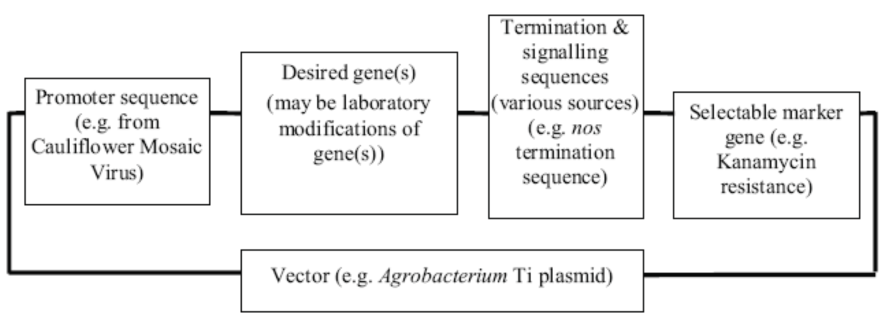
- Once a gene of interest has been identified and isolated from a donor organism, it is manipulated in the laboratory such that it can be inserted effectively into the intended recipient organism. The manipulation may, for example, include changes to the sequence of nucleotides so as to enhance or modulate the expression of the gene once it is introduced into the intended recipient organism.

- One or more genes of interest, as well as other nucleotide sequences needed for the proper functioning of the gene(s) of interest, may then be built in an orderly sequence into a "transformation cassette",[10] as shown in figure 2. The transformation cassette typically includes a "promoter sequence" and "termination sequence" which are necessary to ensure that the gene is expressed correctly in the recipient organism. Different promoter sequences control gene expression in different ways; some allow the continuous expression of the gene (these promoters are known as "constitutive"), while others switch the expression of the gene on or off in different tissues, organs and/or developmental stages of the organism or in reaction to other external influences. Some promoters may be highly specific to the point that they regulate gene expression only in a few cells of the organism and during short, specific developmental stages.

- A "marker gene" is often incorporated into the transformation cassette to help identify and/or select cells or individuals in which the transformation cassette(s) was successfully introduced. Marker genes may, in some cases, be removed from the LMOs at a later stage. identify or select cells or organisms.

- Finally, the transformation cassette may be incorporated into a larger DNA molecule to be used as vector.[11] The purpose of the vector is to assist the transfer of the transformation cassette into the recipient organism.

Figure 2 – Scheme of a transformation cassette and vector



Note: Transformation cassettes currently used may include multiple elements – for example, several promoter sequences and desired genes.

Source: IUCN (2003).

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10 A transformation cassette comprises a group of DNA sequences (e.g., parts of a vector and one or more of the following: a promoter, the coding sequence of a gene, a terminator, other regulatory sequences), which are physically linked and often originated from different donor organisms. The transformation cassette is integrated into the genome of a recipient organism through methods of modern biotechnology to produce an LMO. A transformation cassette may also be called "expression cassette" (mainly when a specific expression pattern is aimed at), "DNA cassette" or "gene construct".

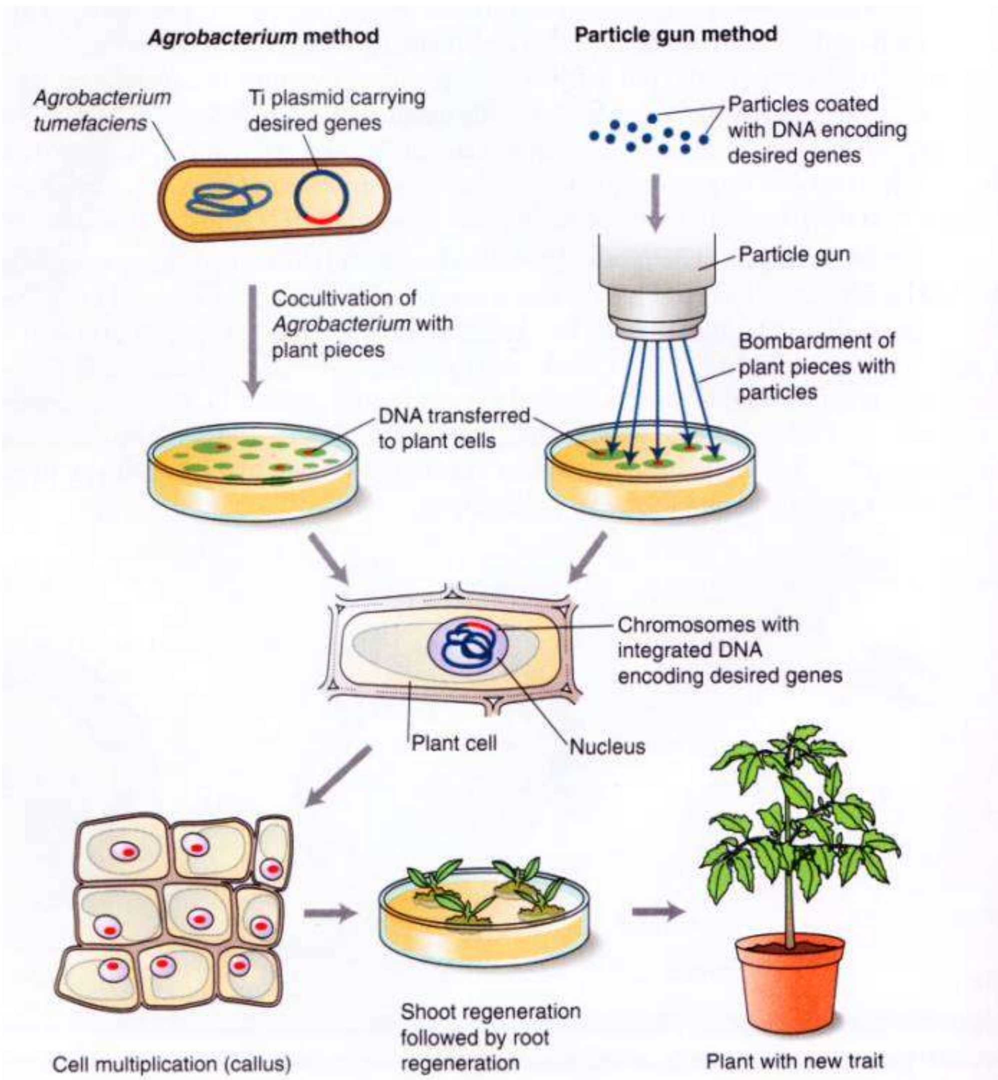
11 In the context of genetic modification, a vector is an organism (e.g., virus) or a DNA molecule (e.g., plasmid, nucleic acid cassettes) used to assist the transfer of genetic material from a donor organism to a recipient organism.

The transformation cassettes are integrated into the genome of the recipient organism through a process known as transformation, as outlined in figure 3. This can be carried out through different methods such as infection using *Agrobacterium*, particle bombardment or microinjection.

Transformed cells are then selected, e.g. with the help of a marker gene, and regenerated into complete LMOs. The subsequent step is the further selection of the modified organisms that contain the desired transgene(s)[12] or modification, and express the desired characteristics. Through selection, many experimental LMOs are discarded and only a few events may reach the stage of commercialization.

In the case of LM plants, cross-breeding to introduce the transgene(s) into other recipient varieties is also common.

Figure 3 – Genetic modification of plants



Source: **Mirkov (2003).**

12 A nucleic acid sequence in an LMO that results from the application of modern biotechnology as described in Article 3 (i) (a) of the Protocol.

Examples of commercialized LMOs

In 1978, the first commercialized LMO was produced with the creation of an *Escherichia coli* strain (a bacteria) that produces the human protein, insulin. In 1996, the first genetically modified seeds were planted in the United States for commercial use.[13]

To date, the most broadly commercialized LMOs introduced into the environment are agricultural crops. According to the International Service for the Acquisition of Agri-biotech Applications (ISAAA), the worldwide area cultivated with LM crops has been growing steadily since 1996, and in 2009, the cultivation of LM crops accounted for 170 million hectares (James, 2012). Soy, maize, cotton, and rapeseed that are resistant to herbicides and/or able to produce pesticidal proteins account for the majority of LM crops being currently commercialized (see LMO Registry in the Biosafety-Clearing House at http://bch.cbd.int/database/lmo-registry).

In 2009, a goat that produces an anticoagulant drug for humans was the first LM animal to be approved for commercial production.[14] Zebra fish containing fluorescent protein genes are another example of LM animals on the market. Moreover, a number of LM vaccines for humans and animals have been commercialized.

To date, there are no examples of the commercialization of LMOs resulting from cell fusion.

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13 FLAVR SAVR™ Tomato by Calgene Inc.

14 http://www.gtc-bio.com/atryn-antithrombin-recombinant.

Module 2:

Preparatory Work – Understanding the context in which a risk assessment will be carried out

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Contents of this module

Introduction
National context
- National protection goals and assessment endpoints
- National Biosafety Framework
- Competent National Authorities
- Practices and principles
- Other national and international obligations

Expert advice and the roles of the risk assessor(s)
- Scientific advisory body
- Responsibilities of the risk assessor(s)
- Roster of Experts on Biosafety
- Stakeholder participation

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Using this module

This module aims at assisting risk assessors in setting the stage for a risk assessment to be carried out in a scientifically sound and transparent manner, and on a case-by-case basis. While Module 1 addressed the broader context of biosafety, Module 2 addresses the context of specific risks assessments.

It highlights the importance of understanding how national policies and international obligations provide overarching guidance for the process. A risk assessor should be familiar with national regulatory and administrative frameworks, including national risk assessment practices, general principles and various obligations, since they establish the legal context for any risk assessment conducted by a national authority.

This module describes the relationship between national policies that establish protection goals, regulatory requirements and risk assessment processes that would be compliant with the Cartagena Protocol on Biosafety. It also provides elements to facilitate the understanding of the mandate of risk assessors and the multidisciplinary nature of the risk assessment process.

Introduction

Prior to receiving an LMO notification, risk assessors[15] may need to familiarise themselves with issues such as environmental protection goals, regulatory requirements and compliance of a national framework with the Protocol to gain an understanding of the general framework within which the risk assessment must be carried out to comply with international obligations, national laws and administrative procedures.

The biosafety framework of each country may address administrative matters by establishing mechanisms for (i) the selection of risk assessors and/or establishment of advisory bodies; (ii) handling confidential information (Article 21); (iii) public awareness and participation (Article 23); and (iv) if and how socio-economic considerations should be taken into account in the decision-making process (Article 26), amongst other things. The following sections of this module provide an overview on how some issues might be considered by risk assessors prior to undertaking a risk assessment.

National context

National protection goals and assessment endpoints

Countries are sovereign in setting their own goals such as the protection of the environment, biodiversity or the health of their citizens. In so doing, they often adopt environmental and public health strategies as part of their national policy and legislation. These strategies, in turn, are often derived from, or compliant with, broader internationally agreed instruments.

15 For the purposes of this training material, the term "risk assessor" refers to an individual mandated by a Competent National Authority (CNA) to conduct and manage the risk assessment process.

Environmental and health policies and laws often define sets of "protection goals", which are defined and valued environmental outcomes that guide the formulation of strategies for the management of activities that may affect the environment. Some protection goals are defined broadly (e.g. conservation of biodiversity) while others are more specific (e.g. protection of a threatened or endangered species). The context for all (environmental) risk assessments is set by the relevant protection goals, regardless of whether they are broad or specific.

Example 3: Protection goals – Aichi Biodiversity Targets

► Strategic Goal A: Address the underlying causes of biodiversity loss by mainstreaming biodiversity across government and society

► Strategic Goal B: Reduce the direct pressures on biodiversity and promote sustainable use

► Strategic Goal C: To improve the status of biodiversity by safeguarding ecosystems, species and genetic diversity

► Strategic Goal D: Enhance the benefits to all from biodiversity and ecosystem services

► Strategic Goal E: Enhance implementation through participatory planning, knowledge management and capacity building

Source: Convention on Biological Diversity (website)

Example 4 – Biodiversity protection goal in the European Union

"To halt the loss of biodiversity and the degradation of ecosystem services in the EU by 2020, restore them in so far as feasible, while stepping up the EU contribution to averting global biodiversity loss."

Source: Council of the European Union (2010).

In addition to the protection goals, national legislations sometimes also define "assessment endpoints". An assessment endpoint is an explicit expression of the environmental value that is to be protected, operationally defined as an entity (such as salmon or honeybees, soil quality) and its attributes (such as their abundance, distribution or mortality).

Ecological assessment endpoints, for instance, are most easily expressed in terms of impacts on a valued species (e.g. survival and reproduction of the yellow fin tuna). Any component, from virtually any level of biological organization or structural form that is recognized as an entity that needs to be protected, can be considered an assessment endpoint.

Example 5 – Assessment endpoints

"An assessment endpoint is an explicit expression of the environmental value to be protected, operationally defined as an ecological entity and its attributes."

Source: US Environmental Protection Agency (1998).

Once a risk assessment has been triggered, the risk assessor(s) will need to identify the relevant protection goals and assessment endpoints when these are available. The risk assessor(s) then determines which assessment endpoints are meaningful to the specific case at hand to ensure that the protection goals will be adequately covered. For example, the regulatory framework of a country may identify "agricultural biodiversity" as one of its protection goals and the risk assessor(s) may be asked to consider, as an assessment endpoint, the abundance of a valued species, for example an insect pollinator, in the environment where the LMO may be released.

Selecting endpoints is among the most critical aspects when preparing a conceptual model for the risk assessment as it contributes to setting the stage for the risk assessment and the remaining steps of the processIn conclusion, before undertaking a risk assessment of an LMO, risk assessors and other biosafety officers should understand national protection goals and the importance of deciding upon relevant assessment endpoints in order to plan a risk assessment. Issues related to protection goals and relevant assessment endpoints are outlined in more detail in Module 3 under "Planning phase".

National Biosafety Framework

Many countries address biosafety related issues through a large process that includes the development and implementation of a National Biosafety Framework (NBF). An NBF consists of a combination of policy, legal, administrative and technical instruments that are set in place to address the safety of the environment and human health in relation to modern biotechnology.

In most cases, the administration of biosafety responsibilities is either shared by several government departments (e.g. environment, agriculture, health, science) or centralized and managed by one office which is responsible for the coordination of biosafety issues over a number of government departments.

The choice of framework most often reflects existing regulatory structures and the resources available at the national level for implementing the biosafety regulations.

There has been a significant increase in the number of countries that possess NBFs. A global initiative funded by the Global Environment Facility (GEF) and its implementing agencies helped this process by providing administrative and technical assistance to countries for developing and implementing their NBFs in accordance with their obligations under the Cartagena Protocol.

Countries' requirements and priorities resulted in the development of national biosafety policies in a variety of forms. Some choose to develop a stand-alone policy on biosafety, whilst others formulated combined policies on biotechnology and biosafety. Some policies are part of wider policies on biodiversity conservation and environmental protection, trade related issues, biosecurity and quarantine, or established within the overall context of sustainable development or Agenda 21 (UNCED, 1992).

As of May 2012, through the GEF funded initiatives, 121 developing countries have completed the development phase of their National Biosafety Frameworks and made them available online.[16]

Competent National Authorities

While the NBFs consist of policy, legal, administrative and technical instruments, the institutional responsibility for decision-making and for risk assessments of LMOs usually falls to the Competent National Authorities (CNAs). According to the Cartagena Protocol, each Party is to designate one or more CNAs to perform the administrative functions required by the Protocol.

Additionally, according to the Protocol, Parties are obliged to clearly indicate, though the Biosafety Clearing-House (BCH), any existing laws, regulations or guidelines for implementation of the Protocol, as well as the names and addresses of its CNA(s). [17]

The NBFs usually set out competencies and procedures depending on the LMO (e.g. the type of LMO or its intended use). As such, risk assessments may be assigned to different CNAs within the same country.

Example 6 – Competent National Authorities in Mexico

In Mexico, for instance, depending on the LMO and its intended use, one or more of its CNAs (Ministry of Health, Ministry of Agriculture, Livestock, Rural Development, Fisheries and Food, and Ministry of Environment and Natural Resources) may be responsible for the risk assessment.

Source: Biosafety Clearing-House.

The options chosen by countries for the institutional setup of CNAs in each NBF include (i) a single CNA receiving and processing all requests regarding LMOs, or (ii) more than one CNA, each with different responsibilities and with either a single or multiple routes for the submission of applications regarding LMOs.

In cases when a Party designates more than one CNA, information on their respective responsibilities should be clearly stated and made available to the BCH. This information may include, for instance, which CNA is responsible for which type of LMO.

In most of the draft NBFs, developed by countries assisted by the UN Environment Programme (UNEP) as a GEF implementing agency, the responsibility of risk assessment has been assigned to the CNA(s) or the overall biosafety body, with or without advice from either an *ad hoc* scientific advisory body, or an established advisory committee.

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16 See http://www.unep.org/biosafety/National%20Biosafety%20frameworks.aspx. A large number of the adopted or draft NBFs are also available on the BCH under the 'Laws and Regulations' section.

17 Laws, regulations and guidelines, as well as CNAs' contact details and other national information requested by the Cartagena Protocol can be accessed through the menu "Country Profiles" available in the BCH at http://bch.cbd.int .

Example 7 – Competent National Authority(ies) and National Biosafety Frameworks

While the competent national authority (or authorities) is responsible for carrying out administrative functions under the Protocol vis-à-vis other Parties, the decision-making process under a Party's national biosafety framework for reaching a decision on the proposed import of an LMO is likely to involve a wide range of national authorities. The national biosafety framework should set out the domestic level procedure, including any necessary consultations, by which any decision on a proposed import will be taken.

Source: IUCN (2003).

National Biosafety Frameworks, when established, define the conditions that trigger the need for a risk assessment. Without prejudice to any right of a country to subject all living modified organisms to a risk assessment, under the Cartagena Protocol two specific cases require mandatory risk assessments prior to making a decision: a) the first intentional transboundary movement of a living modified organism for intentional introduction into the environment of the Party of import, and b) a final decision regarding the domestic use of a living modified organism, including its placement on the market, that may be subject to transboundary movement for direct use as food or feed, or for processing.

Upon receiving a request that triggers a risk assessment, the CNA takes several actions as part of a process to ensure that a scientifically sound risk assessment is carried out by risk assessors. These may include the following:

(a) Reviewing the LMO notification for completeness against a pre-determined list of information;[18]
(b) Specifying the terms of reference of the risk assessment and the information expected in the final report;
(c) Identifying one or more risk assessors who will conduct and manage the risk assessment.

Example 8 – Institutional responsibilities for risk assessment

Albania – the National Biosafety Committee makes decisions, being advised by Scientific Commission of the National Biosafety Committee. The scientific committee shall consist of seven members. The members of the scientific committee will be experts from the field of microbiology, genetics, medicine, biochemistry and molecular biology, pharmacy, agriculture, veterinary science, biotechnology and safety at work.

Caribbean – The CNA is assisted in its work by a Scientific Advisory Committee, which is responsible for conducting risk assessment. In Grenada and the Bahamas, risk assessment is done by the national biosafety coordinating body. In addition to the Scientific Advisory Committee, St. Lucia's National

18 In case of a notification for transboundary movement to countries that are Parties to the Cartagena Protocol this list shall contain at a minimum the information specified in Annex I (in case of an application for the intentional introduction into the environment) or in Annex II (in case of a decision regarding LMOs intended for direct use as food or feed, or for processing).

Competent Authority is supported in its work by a legislated entity called the Biosafety Unit. Staffing of the Unit is also legally constituted and is comprised of the following: biosafety coordinator, information technology specialist, biosafety appraisal officer, public education specialist, administrative secretary and inspectors.

Gambia – An inter-sectoral National Biosafety Technical Working Group will be established with primary responsibility for risk assessment; decision making will be through the National Biosafety Technical Committee.

Tajikistan – Risk assessment will be (the responsibility of) an Expert Board under the National Biodiversity and Biosafety Center (NBBC). It will consist of experts from research institutions of Academy of Science, Tajik Academy of Agricultural Science and Ministry for Healthcare. All these subdivisions have a relevant capacity, technical equipment and work experience.

Tonga – The Director for Department of Environment (the NCA) can specify the means by which scientifically-based risk assessments are to be carried out, and appoint appropriate bodies to undertake risk assessments.

Source: UNEP (2006).

Practices and principles

The risk assessment process includes practices and principles that may differ between countries. As seen in Module 1, Annex III of the Protocol lists the general principles for risk assessment. Individual Parties use these general principles to guide the development and implementation of their own national risk assessment process. As such, the general principles for risk assessment may be incorporated into the country's laws, or be included in guidelines adopted by the country.

Example 9 – Risk assessment practices in various countries

In **Argentina**, once an LM plant has been sufficiently field-tested, the applicant may request that the crop be 'flexibilized,' that is, be approved for unconfined (usually large-scale) planting for certain specified uses. These are: (1) for regulatory purposes – to provide material for analytical, toxicological and other required tests; (2) for export; (3) for off-season seed increase – not to be sold in the country; (4) for tests to be later presented (after approval for commercialization is granted) in support of new variety registration; or (5) for pre-commercial multiplication pending variety registration.

In **Canada** the risk assessment audits for plants with novel traits (PNTs, which includes LMOs) are undertaken in offices of the Plant Biosafety Office of the Canadian Food Inspection Agency (CFIA; http://www.inspection.gc.ca/english/plaveg/bio/pbobbve.shtml).

In **Mexico**, a group of scientists, together with authorities from the Ministry of Agriculture, analyse the applicant's risk assessment on the basis of national legislation. This group may request help from other experts to decide on an application. When the Ministry of Agriculture has become familiar with an LM crop, it may allow the applicant to increase the area planted for the crop, but the applicant will have to continue to present the risk assessment as was done for the first application. Any biosafety measures for a semi-commercial release would also have to be maintained.

In **New Zealand**, responsibility for risk assessment lies with the applicant based on the criteria in the legislation. Forms and guides assist applicants understand the intent of the legislative criteria. The Environmental Protection Authority (EPA), formely "Evironmental Risk Management Authority", evaluates the information provided and if required can seek further expert information or reports as appropriate. Low risk activities that conform to the requirements of the regulatory regime are not publicly notified. Some activities are discretionary for public notification while there are others for which there is a mandatory requirement for public notification (see the EPA website http://www.epa.govt.nz/).

In the **Philippines** the National Committee on Biosafety for the Philippines audits the risk assessment on LMO activities and calls on the expertise of the Scientific and Technical Review Panel to provide an independent safety audit and recommendations.

In **South Africa**, as a general guideline, if scientific reviewers consider a repeat activity of assessed risk to be one that does not differ from an earlier approved activity in terms of the nature of the LMO (host and modified DNA), the applicant, the release environment, the size of the release and the confinement conditions, they will consider a fast track procedure for approval.

In the **United Kingdom**, the UK Advisory Committee on Releases to the Environment (ACRE) reviews the safety of LMO activities at the request of Ministers and makes recommendations on whether activities should proceed and what minimum risk management conditions are needed to minimise harm to the environment and human health (see http://www.defra.gov.uk/acre/about/).

In the **United States**, the U.S. Department of Agriculture's (USDA) Animal and Plant Health Inspection Service (APHIS; http://www.aphis.usda.gov) identifies specific activities where notification only is needed before an activity commences. The regulators review all of these notifications and can request full risk assessment review if they believe the activity differs sufficiently from the familiar to warrant this additional regulation. Risk assessments are audited within APHIS, the Environmental Protection Agency (EPA; http://www.epa.gov) and the Food and Drug Administration (FDA; http://www.fda.gov) depending on the nature of the LMO and its use.

Source: UNEP-GEF (2005).

Other national and international obligations

A country may have national laws and international obligations, such as trade agreements, that are not directly related to biosafety or to the environment but may influence how the risk assessor(s) will proceed once a risk assessment of an LMO is triggered. Such obligations may, for instance, affect establishing the scope of the risk assessment (see Module 3).

For examples of relevant international treaties and agreements see Module 1.

Expert advice and the role of the risk assessor(s)

Scientific advisory body

In some countries the necessary expertise required to carry out risk assessments of LMOs resides in the regulatory agencies and the risk assessments are carried out internally. In such cases, these agencies typically have the option of requesting additional expert input if deemed necessary.

On the other hand, the regulatory frameworks of many other countries call for the establishment of scientific expert panels on an *ad hoc* basis once a risk assessment has been triggered. In such cases, a CNA assesses what expertise is needed for each specific case and pools together an external team of risk assessors consisting of experts in the relevant scientific fields. Such an advisory body may contain a pool of experts at the national, regional or international levels, who can be called upon to assist the mandated risk assessor(s) when a need arises. A scientific advisory body allows the CNA to quickly engage the appropriate expertise for a particular risk assessment. In cases when a CNA establishes a team or panel of risk assessors, it typically designates one of the risk assessors to coordinate the risk assessment process.

Example 10 – How scientists are involved in the risk assessment process

National institutions responsible for a biosafety framework may include, for instance, a scientific advisory body that carries out or reviews a risk assessment and recommends what, if any, risk management measures may be needed to protect the environment and human health.

In **Belarus**, experts who will conduct risk assessment will be chosen from a roster of experts that will be adopted by Government. In every case experts will be selected separately.

In **Mexico**, the Ministry of Agriculture, one of the CNAs for Biosafety, consults a group of scientists for advice on each request. The Inter-Secretarial Commission on Biosafety of Genetically Modified Organisms (CIBIOGEM, http://www.cibiogem.gob.mx) also has a database of 350 experts in different disciplines from whom they can seek advice.

In **New Zealand**, in addition to the in house expertise of EPA, an expert science panel of eminent researchers has been established and a roster of experts including overseas experts is maintained and is used as appropriate.

In **South Africa**, the regulatory office has a database of over 60 scientists and experts used in risk assessment. However, not all of these experts are needed for every review. The reviewers all sign a confidentiality agreement with the regulators.

Source: UNEP-GEF (2005).

Responsibilities of the risk assessor(s)

National frameworks establish different types of responsibilities for the risk assessors. These responsibilities are usually specified in the terms of reference for the risk assessment and may include, for example:

- Review of the information provided in the LMO dossier, and in particular the information in the risk assessment provided by the applicant, if available;
- Identify any other relevant scientific information on the subject at hand, including previous risk assessments or new information that has come to light;
- Consider information gaps and scientific uncertainties and possible ways to address them;
- Conduct the risk assessment and prepare a report.

These actions are performed in a process that can be iterative. For example, it is possible that while the risk assessment is being conducted, a new piece of scientific information comes to light and reveals some information gaps that had not been previously identified. In such a case, it may be necessary to identify and engage additional sources of scientific expertise that should be included in the initial risk assessment panel or scientific advisory body.

In reviewing the LMO dossier or at any subsequent steps of the risk assessment, the CNA(s) or the risk assessor(s) may decide that further documentation is needed and may choose to request it from the applicant or to conduct or commission their own testing.

The risk assessor(s) in charge of leading the process is often responsible for the coordination of the expert panel or risk assessment team. Additionally they report the findings and disseminate relevant documents among other parties involved, including other stakeholders (see below), as appropriate, to ensure that information is shared properly and in a timely manner.

Parties to the Protocol shall ensure that they have procedures to protect confidential information as per Article 21 of the Protocol and in accordance with national legislation. As such, the risk assessor(s) is also required to respect any confidential business information indicated by the CNA taking into account that, according to the Protocol, the following information cannot be considered confidential: a) the name and address of the notifier; b) a general description of the living modified organism(s); c) a summary of the risk assessment highlighting the effects of the LMO on the conservation and sustainable use of biological diversity, taking also into account risks to human health; and d) any methods and plans for an emergency response.

Once a scientific risk assessment is completed, the risk assessor(s) prepares a risk assessment report in accordance with the terms of reference established by the CNA. The report should be sufficiently detailed to provide the necessary scientific information to the decision makers (see Module 3).

Roster of Experts on Biosafety

To facilitate countries' access to relevant expertise when needed, the Parties to the Cartagena Protocol on Biosafety established the "Roster of Experts on Biosafety". The aim of this Roster is to "provide advice and other support, as appropriate and upon request, to developing country Parties and Parties with economies in transition, to conduct risk assessment, make informed decisions, develop national human resources and promote institutional strengthening, associated with the transboundary movements of living modified organisms".

Information on individuals listed in the Roster of Experts on Biosafety is accessible through the BCH at http://bch.cbd.int/database/experts. As of March 2014, the Roster of Experts on Biosafety contained 159 experts from 45 countries.

Stakeholder participation

In the context of risk assessments of LMOs, stakeholders are all those with an interest or stake in biosafety, i.e. in the safe transfer, handling and use of LMOs in the country (UNEP-GEF, 2003).

While there is no direct mention to stakeholder participation in Article 15 on Risk Assessment of the Protocol, Article 23 requires that Parties consult the public in the decision-making process regarding an LMO.

Determining the extent to which the public and other stakeholders may be involved in the decision-making process is the prerogative of each regulatory framework. Some countries have a mechanism that enables public participation during the risk assessment and/or decision-making process. For example, one of the CNAs in New Zealand, the Environmental Protection Agency (EPA,www.epa.govt.nz), opens LMO notifications to public consultation on its website.

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Module 3:

Conducting the Risk Assessment

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Using this module

This module provides an overview of the risk assessment methodology. It is structured into five sections. The first section provides an overview of the general methodology for environmental risk assessment and reviews some of the terms used. The second section elaborates on issues that are overarching to the entire risk assessment process, such as the quality and relevance of information needed and considerations of uncertainty. The third section explains some common actions that are undertaken when setting the context and scope of the risk assessment. The fourth section discusses the specifics of the process of conducting the risk assessment, and follows the methodology and steps in Annex III of the Protocol along with a short description on how risk assessors may proceed in each of these steps. Under Step 1 of this section, an overview of the elements that form the basis of conducting a scientifically sound risk assessment, on a case-by-case basis, is provided. For each of these elements, this section also includes the “Points to consider” as outlined in Annex III of the Protocol, along with a short rationale as to how this information may be useful. The fifth and final section of this module outlines how to communicate the findings and conclusions of the risk assessment process, and recommendations as to whether or not the risks are acceptable or manageable.

It is noted that this module does not replace Annex III, but it aims to assist risk assessors in the practical use of the concepts contained therein. Any methodology or terminology that is used in this module but not included in Annex III or in the Protocol does not reflect a particular regulatory approach to risk assessment of LMOs, but rather draws from a variety of academic and regulatory experiences. As in the other modules, examples from various approaches to risk assessment are provided in the boxes.

Although many of the principles included in this module are applicable to a wide range of LMOs, this module focuses primarily on risk assessment of LM plants produced through the application of *in vitro* nucleic acid techniques, due to the experience available.

Introduction

Risk assessments are intended to calculate or estimate the risk to a given target organism, system, or (sub)population, including the identification of uncertainties, following exposure to a particular agent, taking into account the inherent characteristics of the agent of concern as well as the characteristics of the specific target system (WHO, 2004). In the context of biosafety, risk assessment can be defined as the process of estimating risks that may be associated with an LMO on the basis of what adverse effects may be caused, how likely the adverse effects are to occur, and the consequences should they occur.

The risk assessment process involves a critical review of available data for the purpose of identifying and possibly quantifying the risks resulting from, for example, natural events (flooding, extreme weather events, etc.), technology, agricultural practices, processes, products, agents (chemical, biological, radiological, etc.) and any activity that may pose threats to ecosystems, animals and/or people.

The objective of a risk assessment under the Cartagena 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” (Annex III).

The results of risk assessments of living modified organisms (LMOs) are typically used by decision-makers to make informed decisions regarding the approval, with or without conditions (e.g. requirements for risk management and monitoring strategies), or prohibition of a certain use of the LMO.

This module provides an introduction to risk assessment and considerations that may assist risk assessors in conducting risk assessments of LMOs that are consistent with Article 15 and Annex III of the Protocol. [19]

Overview of the risk assessment methodology

In order to understand what is meant by risk assessment it is important to be familiar with the concepts of ***risk*** and ***hazard***, and how these terms differ. The term “risk” does not have a single unambiguous definition but it is often defined as “the probability of harm”. This is broadly understood as the likelihood that a harmful consequence will occur as the result of an action or condition.

Figure 4 – Assessing risks

Source: http://www.scienceinthebox.com/en_UK/safety/riskassessment_en.html .

19 Taking into consideration the experience available, the focus of this training module will be LMOs produced through the application of *in vitro* nucleic acid techniques (i.e. produced through genetic transformation) and not on LMOs produced through cell fusion beyond the taxonomic family (see Article 3 of the Protocol).

Risk is often assessed through the combined evaluation of hazard and exposure.

- "*Hazard*", in the context of LMO risk assessment, is defined as the potential of an organism to cause harm to human health and/or the environment (UNEP, 1995).
- "*Exposure"* means the contact between a hazard and a receptor. Contact takes place at an exposure surface over an exposure period (WHO, 2004). In the risk assessment of LMOs, "exposure" can be understood as the route and level of contact between the likely potential receiving environment and the LMO or its products.

The exposure pathway from the hazard to the receptor and the possible exposure scenarios[20] form important additional elements in understanding risk. Ascribing the probability and consequences of exposure of a receptor to the hazard characterizes the risk. All these elements must be evaluated to form an effective and useful risk assessment for specific scenarios (UNEP Division of Technology, Industry and Economics).

A simple example can be used to distinguish hazard from risk: acids may be corrosive or irritant (i.e. a hazard) to human beings. The same acid is a risk to human health only if humans are exposed to it without protection. Thus, the degree of harm caused by the exposure will depend on the specific exposure scenario. If a human only comes into contact with the acid after it has been heavily diluted, the risk of harm will be minimal but the hazardous property of the chemical will remain unchanged (EEA, 1998).

Example 11 – What is risk? What is Risk Assessment?

Risk: the combination of the magnitude of the consequences of a hazard, if it occurs, and the likelihood that the consequences will occur.

Risk assessment: the measures to estimate what harm might be caused, how likely it would be to occur and the scale of the estimated damage.

Source: UNEP (1995).

Risk assessment of LMOs can be divided into four main phases (WHO, 2004):

(a) *Hazard identification* – The identification of the type and nature of adverse effects that an LMO could cause to an organism, system, or (sub)population.
(b) *Hazard characterization* – The qualitative and/or quantitative evaluation of the nature of the adverse effects associated with an LMO.
(c) *Exposure assessment* – Evaluation of the exposure of the environment, including organisms, to an LMO or products thereof.
(d) *Risk characterization* – The qualitative and/or quantitative estimation, including attendant uncertainties, of the overall risk.

If risks are identified during the *risk characterization* step above, risk management strategies may be identified which may effectively prevent, control or mitigate the consequences of the adverse effects. As

20 *"Exposure scenario"* is a set of conditions or assumptions about sources, exposure pathways, amounts or concentrations of agent(s)involved, and exposed organism, system, or (sub)population (i.e., numbers, characteristics, habits) used to aid in the evaluation and quantification of exposure(s) in a given situation.

such, the risk assessment process often includes an additional step to identify a range of possible risk management strategies that could reduce the level of risk.

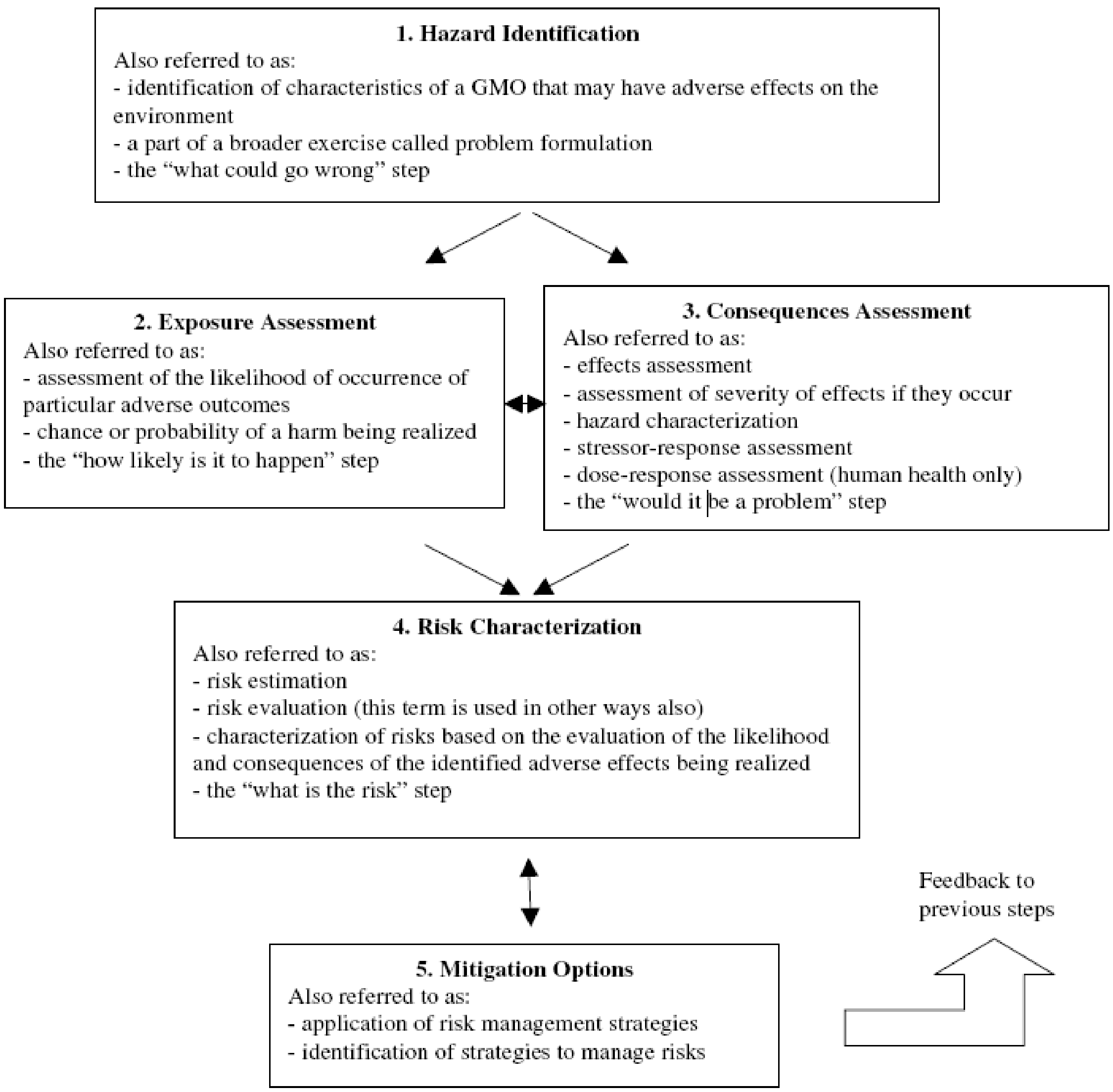
It is worth noting, however, that it is only during the decision-making process that a choice is made as to whether an identified risk is acceptable and whether or not risk management strategies are to be implemented (see more details on the identification of risk management strategies under step 5).

As a whole the risk assessment process can be highly iterative; meaning that one or several steps may need to be re-evaluated when, for instance, new information becomes available in an attempt to increase the level of certainty.

The methodologies for risk assessment of LMOs have evolved over the past few decades. At a conceptual level, the methodologies have been adapted from the existing paradigms for environmental risk assessment developed for chemicals and other types of environmental stressors (Hill, 2005). As a result, the terminology used within each methodology may vary.

Familiarity with the different terms used in risk assessment enables a more direct comparison between the terminology used in Annex III and different risk assessment frameworks. It will also facilitate the interpretation of results from different risk assessments, for instance, for the same LMO.

Figure 5 – Variation in terminology used to describe methodological components common to many risk assessment frameworks



Source: Hill (2005)

Overarching issues

Risk assessors need to identify the information needed to conduct a risk assessment and understand how it will be used. Using and interpreting existing information, as well as identifying information gaps and understanding how to deal with scientific uncertainty are important factors during the risk assessment.

Quality and relevance of information

Considerations of the quality and relevance of information available for the risk assessment are important throughout the risk assessment process. Relevant information may be derived from a variety of sources such as existing scientific literature, experience and outcomes from previous risk assessments, in particular for the same or similar LMOs introduced in similar receiving environments, as well as new experimental data such as laboratory experiments (e.g. early tier toxicology testing), confined field experiments or other scientific observations. The relevance and level of detail of the information needed may vary from case to case depending on the nature of the modification of the LMO, on its intended use, and on the scale and duration of the environmental introduction.

Scientifically sound methodologies should be determined and documented for testing any identified risk scenario. When assessment methods are well described, risk assessors and subsequent reviewers are better equipped to determine whether the information used was adequate and sufficient for characterizing the risk.

Example 12 – Data acquisition, verification, and monitoring

"The importance of the data acquisition, verification, and monitoring process in the development of accurate risk assessments has been emphasized. Models, no matter how sophisticated, are simply attempts to understand processes and codify relationships. Only the reiteration of the predictive (risk assessment) and experimental (data acquisition, verification, and monitoring) process can bring models close to being a true picture of reality."

Source: UNEP/IPCS (1994).

Identification and consideration of uncertainty

Uncertainty is an inherent and integral element of scientific analysis, and its consideration is undertaken throughout the whole risk assessment process. The risk assessment methodology as set out by the Cartagena Protocol states that "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".[21]

Although uncertainty may, in some cases, be addressed by requesting additional information, the necessary information may not always be available or new uncertainties may arise as a result of the provision of additional experimental data. The golden rule during the risk assessment of an LMO is to request additional information that is relevant to the overall evaluation of risk and will facilitate the decision making. Thus, it is important to consider and analyze, in a systematic way, the various forms of uncertainty (e.g. types and sources) that can arise at each step of the risk assessment process.

Uncertainties may arise from: (i) lack of information, (ii) incomplete knowledge, and (iii) biological or experimental variability, for example, due to inherent heterogeneity in the population being studied or to variations in the analytical assays. Uncertainty resulting from lack of information includes, for example, information that is missing and data that is imprecise or inaccurate (e.g., due to study designs, model systems and analytical methods used to generate, evaluate and analyse the information) (SCBD, 2012).

21 Paragraph 8(f) of Annex III.

If the level of uncertainty changes during the risk assessment process (e.g. by provision of new information), an iteration of parts or the entire risk assessment process may be needed.

It is important to note that while scientific uncertainty is considered during the risk assessment process and the results of uncertainty considerations may be reported it is, ultimately, the responsibility of the decision-makers to decide how to use the information in conjunction with the principals of the precautionary approach when making a decision on an LMO.

Example 13 – Scientific uncertainty

"There is no internationally agreed definition of 'scientific uncertainty', nor are there internationally agreed general rules or guidelines to determine its occurrence. Those matters are thus dealt with – sometimes differently – in each international instrument incorporating precautionary measures."

Source: IUCN (2003).

Planning phase

Establishing the context and scope

When the regulatory process of a country triggers the need for a risk assessment, it usually results in a request from the competent authority to the risk assessor(s). This request includes the scope of the risk assessment to be carried out as well as some important elements that will set the context of the risk assessment. In a typical case-by-case scenario, in accordance with the Cartagena Protocol, these elements will include at a minimum: the LMO(s), its(their) specific use(s) and, in cases of introduction into the environment, the likely potential receiving environment(s) where the LMO may be released and establish itself. As such, the case-by-case approach does not allow an existing risk assessment to be applied "as is" to different LMOs, uses or receiving environments. Nevertheless, a risk assessment carried out on a case-by-case basis most often takes into account relevant knowledge and experience gained in previous risk assessments.

In practice, if a risk assessor is faced with a request by the Competent National Authorities (CNA) to conduct or review a risk assessment that does not follow the case-by-case principle, the risk assessor recommends to the CNA that a new risk assessment be carried out with a scope that is specific to the case under consideration (i.e. the LMO, its specific use and the likely potential receiving environment).

Protection goals for the conservation and sustainable use of biodiversity, may be defined in national, regional and international policies. In setting the context of a risk assessment, these goals may be relevant to the identification and selection of appropriate assessment endpoints and to determining which methodology will be used in the risk assessment process. Understanding the contribution of national, regional and regulatory policies in setting the context of the risk assessment is part of the preparatory work for a risk assessment as seen in Module 2.

After consideration of the protection goals, the risk assessment of a particular LMO proceeds to establishing the scope in order to define the extent and the limits of the risk assessment process. This phase usually consists of at least three main actions: (i) selecting relevant assessment endpoints or representative species on which to assess potential adverse effects; (ii) establishing baseline information; and (iii) when possible, establishing the appropriate comparator(s).

Although these actions are described here as separate activities, in practical terms, this is an iterative process where the risk assessors will usually draw on the results of each action to inform the subsequent actions until all their elements have been considered sufficiently enough to enable the risk assessment to proceed.

Selecting relevant assessment endpoints or representative species

The purpose of an assessment endpoint or of representative species is to provide a measure that will indicate whether or not the LMO may cause an adverse impact on a protection goal. In order to be useful, the selected assessment endpoints or characteristics of the representative species should be specific and measureable.

Assessment endpoints or species representative of important ecological functions[22] or roles should be selected on a case-by-case basis. The complexity of ecosystems and the large number of potential candidates add to the challenges in selecting the appropriate assessment endpoints in ecological systems. Some important criteria for the selection of assessment endpoints to be used in the risk assessment of LMOs may include, for example: (i) their relevance to the protection goals; (ii) a well-defined ecological function; (iii) accessibility to measurement; and (iv) level of potential exposure to the LMO.

Identifying assessment endpoints or representative species that are relevant within the context of the likely potential receiving environment allows the risk assessor(s) to focus on interactions that are likely to occur. Moreover, risk scenarios may be also formulated to include assessment endpoints or representative species that are not present in the likely potential receiving environment but may, nevertheless, be indirectly exposed to the LMOs. This could occur, for example, if a third species, which is sexually compatible with the LMO and the representative species, has a distribution area that overlaps with the distribution areas of the former two providing an indirect exposure pathway between them.

Example 14 – Common problems in selecting assessment endpoints

- Endpoint is a goal (e.g., maintain and restore endemic populations);
- Endpoint is vague (e.g., estuarine integrity instead of abundance and distribution of a species);
- Ecological entity may not be as sensitive to the stressor;
- Ecological entity is not exposed to the stressor (e.g., using insectivorous birds for avian risk of pesticide application to seeds);
- Ecological entities are irrelevant to the assessment (e.g., lake fish in salmon stream);
- Importance of a species or attributes of an ecosystem are not fully considered;
- Attribute is not sufficiently sensitive for detecting important effects (e.g., survival compared with recruitment for endangered species).

Source: US Environnemental Protection Agency (1998).

22 "Ecological function" is the role of an organism in ecological processes. The relevance of specific ecological functions in the risk assessment will depend on the protection goals. For example, organisms may be part of the decomposer network playing an important role in nutrient cycling in soils, or may be important as a pollen source for pollinators and pollen feeders.

Example 15 – Questions asked when selecting representative species for assessing effects of Bt plants on non-target organisms

- Which variant of the Bt protein are we dealing with?
- Where is it expressed (in the leaves, pollen or only in the roots)?
- Is it produced in the plant throughout its life or only during particular growth phases?
- Which insects come into contact with the Bt protein?
- Is this contact direct and long-term or only occasional?
- Which insects ingest the Bt protein through their prey?

Source: GMO Safety (website).

Establishing the baseline

In risk assessment, the baseline is a description or a measurement of existing conditions of an environment, or its attributes or components without the LMO under consideration and taking into account different practices in use (e.g., agricultural practices). The baseline description or measurement may provide quantitative (e.g., number of organisms, variability of abundance) and/or qualitative information about the receiving environment as a reference for estimating effects of the LMO or its use including, if applicable, information on the assessment endpoints. Baselines can refer to, for instance, a particular environment or health conditions of a population.

Baselines are established with the aim of having descriptive and/or measurable information on any element of the likely potential receiving environment that is considered relevant in assessing the impacts from the introduction of the LMO, including considerations on possible impacts on human health.

In practice, if relevant assessment endpoints or representative species are selected, the baseline data will consist of data that establishes the conditions of these endpoints or species before the introduction of the LMO in question.

The choice of comparators

As seen above, a comparative approach is one of the general principles of risk assessment as set out in Annex III to the Protocol, where risks associated with the LMO "should be considered in the context of the risks posed by the non-modified recipients or parental organisms in the likely potential receiving environment".

Using a comparator, i.e. non-modified recipients or parental organisms of the LMOs used as an element to establish the basis for a comparative assessment in accordance with Annex III, helps a risk assessor to identify the novel characteristics of the LMO and assess if the LMO presents a greater, lesser or equivalent risk compared to the non-modified recipient organism that is used in a similar way and in the same environment.

The ideal comparator is the closest non-modified genotype to the LMO, i.e. (near-)isogenic lines.[23] However, (near-)isogenic lines are not always available and the choice of appropriate comparators may be guided by policies or guidelines adopted by the country undertaking the risk assessment (e.g. EFSA, 2011). Moreover, depending on the context, the step of the risk assessment and question being asked, a risk assessor may also choose to consider similar or related non-modified genotypes as useful comparators. Related management practices and experience with similar non-modified organisms may also be helpful. For example, when considering the risk assessment for an insect resistant LM crop, a risk assessor may wish to consider, amongst other things, the available experience with pest control practices applied to non-modified organisms of the same species (e.g. use of spores from *Bacillus thuringiensis* as pesticides).

In some circumstances, choosing an appropriate comparator(s) can be a challenge. This may happen, for example, in the case of LM crops that are tolerant to abiotic stress if the non-modified recipient or parental organisms are not capable of growing in the receiving environment. In extreme situations, when a suitable comparator cannot be grown under the same conditions and in the same or similar receiving environment as the LMO, it may be necessary to treat the LMO as a novel species in that environment (i.e. introduced species). This means that the characterization of the LMO (see below) will focus not only in the novel genotypic and phenotypic characteristics[24] resulting from the genetic modification, but rather on the characterization of an entire new genotype in the particular receiving environment.

Conducting the risk assessment

Conducting the risk assessment involves synthesizing what is known about the LMO, its intended use and the likely potential receiving environment to establish the likelihood and consequences of potential adverse effects to biodiversity, taking into account human health, that result from the introduction of an LMO.

Neither the Protocol nor this Manual makes a distinction between the various types of introductions into the environment, such as releases for experimental purposes or releases for commercial purposes. However, the nature and level of detail of the information needed to conduct the risk assessment will vary depending on the intended use of the LMO (e.g. type of release), the LMO itself and the likely potential receiving environment.

The following sections will address the steps of the risk assessment methodology described in paragraph 8 of Annex III to the Protocol. These steps describe a structured and integrated process whereby the results of one step are relevant to subsequent steps. Additionally, the risk assessment process may need to be conducted in an iterative manner, whereby certain steps may be repeated or re-examined to increase or re-evaluate the reliability of the risk assessment. If during the process, new information arises that could change the outcome of a step, the risk assessment may need to be re-examined accordingly.

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23 “Isogenic lines” are two or more lines differing from each other genetically at one *locus* only; “near-isogenic” lines are two or more lines differing from each other genetically at several *loci*.

24 “Genotypic characteristics” are those relating to “genotype” as all or part of the genetic constitution of an organism. “Phenotypic characteristics” are those relating to “phenotype” as the observable physical or biochemical characteristics of an organism, as determined by both genetic and environmental factors.

Step 1: Identification of any novel genotypic and phenotypic characteristics associated with the LMO that may have adverse effects

The first step of the risk assessment is "an identification of any novel genotypic and phenotypic characteristics associated with the LMO that may have adverse effects on biological diversity in the likely potential receiving environment, taking into account risks to human health".[25]

What constitutes an "adverse effect" (also referred to as "damage" or "harm") will depend on the context and scope of the risk assessment taking into account, as appropriate, the specific protection goals as seen above.

Example 16 – Potential adverse effects

"Harm [potential adverse effect] reflects an undesirable condition involving damage or injury. This includes change in the morphology, physiology, growth, development, reproduction or life span of an organism or group of organisms that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress or an increase in susceptibility to other influences. The perception of harm can vary between people. It can also change over time and differ according to other factors such as variations in the vulnerability of individuals or type of land use. For example, a cold medication may be considered harmful if it causes severe side-effects. However, if a cancer drug causes the same type of side-effects, it may not be considered harmful. Similarly, a plant producing large amounts of biomass in a pasture may be considered desirable whereas the same plant may be considered harmful (weedy) in a nature conservation area as it may end up displacing a native species. In addition, one harmful outcome can sometimes give rise to further downstream harms. For example, increased harms from weeds, pests or pathogens can lead to loss of biodiversity."

Source: OGTR (2013).

Example 17 – Potential risks

With every new emerging technology, there are potential risks. These include:

- ► The danger of unintentionally introducing allergens and other anti-nutrition factors in foods;
- ► The likelihood of transgenes escaping from cultivated GM crops into wild relatives;
- ► The potential for pests to evolve resistance to the toxins produced by GM crops;
- ► The risk of these toxins affecting non-target organisms.

Source: GMAC Singapore (website).

25 Paragraph 8(a) of Annex III.

Example 18 – Potential adverse effects from weediness in plants

► Competitive exclusion of other plants;
► Reduction in yield/biomass of other plants;
► Reduction in quality of products/services;
► Restriction of physical movement (e.g. of water, people, animals);
► Harm to human and/or animal health;
► Altered ecosystem processes (e.g. levels of nitrogen fixation, water supply and use, soil sedimentation or erosion and salt accumulation).

Source: FAO (2011a).

Example 19 – Topics of concern

According to the International Centre for Genetic Engineering and Biotechnology (ICGEB), the main issues of concern derived from the deliberate introduction of LM crops (and their derived products) into the environment or onto the market are classified as:

Risks for animal and human health – Toxicity & food/feed quality/safety; allergies; pathogen drug resistance (antibiotic resistance), impact of selectable marker;

Risks for the environment – Persistency of gene or transgene (volunteers, increased fitness of LM crop, invasiveness) or of transgene products (accumulative effects); susceptibility of non-target organisms; change in use of chemicals in agriculture; unpredictable gene expression or transgene instability (gene silencing); environmentally-induced (abiotic) changes in transgene expression; ecological fitness; changes to biodiversity (interference of tri-trophic interactions); impact on soil fertility/soil degradation of organic material;

Gene transfer – Through pollen or seed dispersal & horizontal gene transfer (transgene or promoter dispersion); transfer of foreign gene to micro-organisms (DNA uptake) or generation of new live viruses by recombination (transcapsidation, complementation, etc.);

Risks for agriculture – Resistance/tolerance of target organisms; weeds or superweeds; alteration of nutritional value (attractiveness of the organism to pests); change in cost of agriculture; pest/weed management; unpredictable variation in active product availability; loss of familiarity/changes in agricultural practice."

Source: ICGEB (website).

The genotypic and phenotypic characterization of an LMO provides the basis for identifying differences, both intended and unintended, between the LMO and its recipient or parental organism(s). Molecular analyses may be performed to characterize the products of the modified genetic elements, as well as of other genes that may have been affected by the modification. Data on specific expression patterns may be relevant for risk assessment in order to determine exposure, and may also include data confirming the absence of gene products, such as RNA and proteins, different from those originally intended. For example, in the case where the gene product (i.e. the RNA or protein that results from the expression of a gene) is intended to function only in a specific tissue, data may be used to confirm its specificity in that tissue and demonstrate its absence in other tissues.

Other phenotypic data are often presented to indicate that the LMO is behaving as anticipated. This could include data on reproductive characteristics, alterations in susceptibility to pests and diseases or tolerance to abiotic stressors, etc.

Once the potential adverse effects have been identified, the risk assessment proceeds to estimating the likelihood and consequences of these effects. To this end, developing risk scenarios may in some cases provide a useful tool.

A risk scenario may be defined as a sequence of events with an associated probability and consequence. In the context of risk assessment of LMOs, a risk scenario may be explained as a scientifically supportable chain of events through which the LMO might have an adverse effect on an assessment endpoint.

Example 20 – A Risk scenario

"The possibility that growing Bt corn may kill ladybird beetles due to ingestion of the Bt protein when preying on insects feeding on the GM corn, thereby reducing the abundance of coccinellids in the agroecosystem and increasing the incidence of pests."

Source: Hokanson and Quemada (2009).

A well-defined risk scenario should be scientifically plausible and allow the assessor to identify information that is necessary for the assessment of risks.

Although some risk scenarios may appear as obvious (e.g. potential for insect resistant plants to affect insect herbivore populations), it is always useful to identify the risk scenarios fully. Clear and well-defined risk scenarios can also contribute to the transparency of a risk assessment because they allow others to consider whether or not the subsequent steps of the risk assessment have been adequately performed and facilitate the consideration of possible strategies to manage the identified risks.

A common challenge in generating a well-defined risk scenario is to choose representative species that would be exposed to the LMO. This is why an exposure assessment should be considered when selecting assessment endpoints.

When establishing risk scenarios several considerations may be taken into account. These may include: (i) gene flow followed by introgression of the transgene in species of interest; (ii) toxicity to non-target organisms; (iii) allergenicity; (iv) multi-trophic interactions and indirect effects; and (v) resistance development. The following paragraphs explain some of these considerations in more detail:

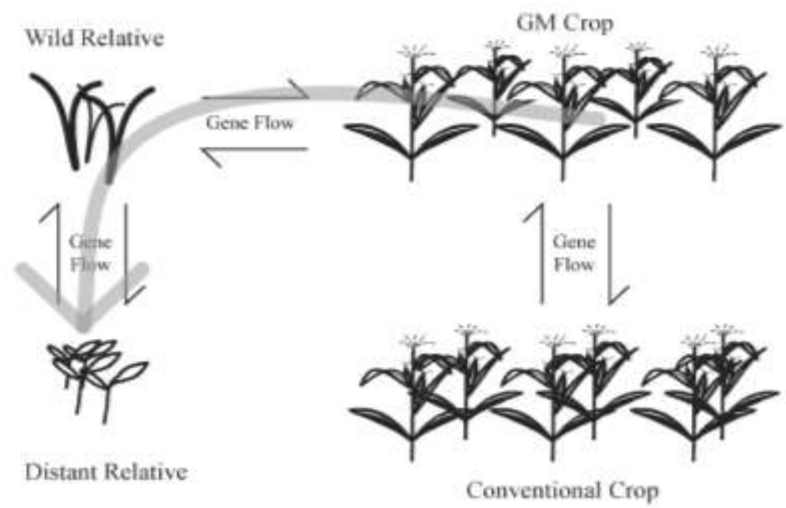
Gene flow followed by introgression of the transgene in species of interest – "Gene flow" is the transfer of genetic material from one organism to another by vertical or horizontal gene transfer;[26] or the movement of an organism from one environment to another. In the case of plants, vertical gene flow may occur even between organisms that are located far apart since pollen can be carried across large distances by the wind or insects, for instance. "Introgression" is the movement of a gene or genetic element from one species into the gene pool of another species or population, which may result in a stable incorporation or some fertile offspring.

26 "Vertical gene transfer" refers to the transfer of genetic material from one organism to its offspring via asexual, parasexual or sexual reproduction. Also referred to as "vertical gene flow". "Horizontal gene transfer" refers to the transfer of genetic material from one organism to another through means other than inheritance from parent to offspring (i.e., vertical).

Gene flow followed by introgression from an LMO to non-modified organisms may or may not be considered an adverse effect depending on the protection goals.

The potential for gene flow is first evaluated by investigating if sexually compatible species are present in the likely potential receiving environment. If sexually compatible species are present, there is a possibility of gene flow from the LMO to these species. Whether or not the modified genetic elements can potentially introgress into the population of the sexually compatible species will be largely determined by the biology of the recipient organism and of the LMO itself (see considerations regarding the likelihood and consequences of gene flow and introgression in steps 2 and 3).

Figure 6 – Gene flow to conventional crops and distant relatives through "genetic bridges"



Source: Heinemann (2007).

Toxicity to non-target organisms – The potential for an introduced gene product to be toxic to organisms in the environment is typically addressed by controlled exposure in the environment or by direct toxicity testing, or by a combination of the two. Non-target organisms may include, for instance, herbivores, natural enemies (e.g. parasitoids and predators), pollinators and pollen feeders, soil (micro-)organisms and weeds. The need and extent of toxicity tests will depend on characteristics of the LMO and the level of exposure of other organisms to the LMO.

If toxicity testing is needed, it typically follows a sequential series of tiered tests. Early tier studies involve highly controlled laboratory environments where representative or surrogate test species are exposed to high concentrations of the gene product being studied (i.e. worst case exposures) to determine if there are any toxic effects. If toxic effects are observed in early tier tests or if unacceptable uncertainty exists, e.g. regarding effects in multi-throphic interactions (see below), more realistic conditions representative of field-level exposures can be tested to determine the extent of the risk.

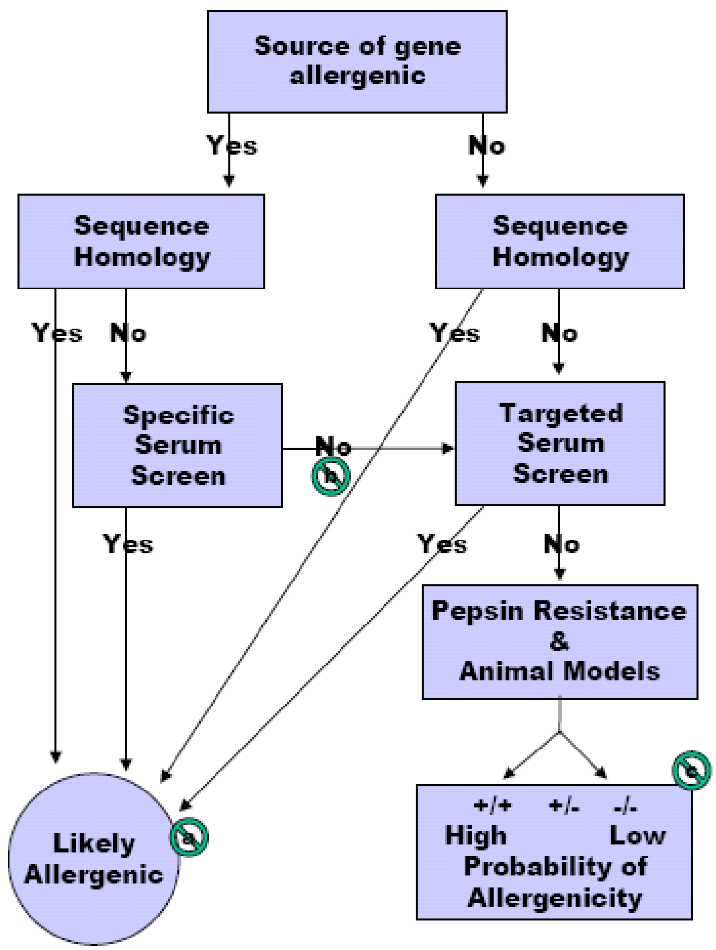
The gene products of the modified genetic elements in LMOs may be produced in very small quantities thus may be difficult to isolate in the amounts required for toxicity testing. If this is the case, and it is determined that toxicity tests are required, the risk assessor may consider results from tests using gene products obtained from alternate (surrogate) sources (e.g. bacterial expression systems or the organism from which the transgene was derived) provided that these gene products are chemically and functionally equivalent.

Allergenicity **–** Allergies are a type of adverse immunological response that affect individuals who are predisposed to certain types of substances (i.e. allergens). Allergens are often proteins or peptides.

In considering allergenicity caused by LMOs, it is important to take into account the exposure to proteins newly expressed by the LMO, including some variants of these proteins (e.g. structural variants of proteins having sometimes very few difference(s) in amino acids composition – or no difference in amino acids composition but carrying slightly different saccharide branches – that may display different allergenic properties through differences in spatial structure) that may be produced uniquely by the LMO. As a consequence, some allergenicity studies must be carried out with proteins isolated from the LMO itself, and not obtained from an alternate (surrogate) source such as a bacterial expression system.

It is also possible that allergens known to exist in the recipient or parental organism(s) are produced in higher amounts, for example by over-expression of the gene that encodes a protein that is known to be a common allergen.

Figure 7 – Assessment of the allergenic potential of foods derived from modern biotechnology



Source: FAO/WHO (2001).

***Multi-trophic interactions and indirect effects* –** "Multi-trophic interactions" involve more than two trophic levels in a food web. They are an important concept in ecology and occur when a change at one trophic level indirectly affects trophic levels which are more than one step away. Consideration of tri-trophic interactions and indirect effects may be relevant to biodiversity protection goals.

Example 21 – Multi-trophic interactions and indirect effects

An important feature of non-target effects is that they can involve knock-on food-web effects, such as effects on predators and parasitoids that are exposed to the transgenic product through their prey or hosts that feed on the GM crop (known as tritrophic exposure), or more complicated linkages. If the prey or host are unaffected by the transgenic product themselves, they may expose their predators or parasitoids over a prolonged period of crop growth, and they may also concentrate the transgenic protein in their bodies to levels higher than those found in the plant tissues.

Source: Underwood *et al*. (2013).

Observations and experimentation to identify such effects are challenging because of the complexity of ecological interactions, the difficulty of establishing causality between observed variation and treatment effects (e.g. the presence of the modified genetic element or its products), and natural variability in populations over time. Moreover, in a food chain (or food web), effects at the trophic levels may become observable only at a later stage.

***Resistance development* –** The extensive use of herbicides and insect resistant LM crops has the potential to result in the emergence of resistant weeds and insects. Similar breakdowns have routinely occurred with conventional crops and pesticides. Several weed species have developed resistance to specific herbicides which are extensively used in combination with herbicide-resistant LM crops. Insect-resistant Bt-crops similarly could lead to the emergence of Bt-resistant insects (FAO, 2004).

The extent of the adverse effect and possible consequences of the insurgence of resistant weeds and insects should be thoroughly considered in a risk assessment. Some regulatory frameworks require that risk management strategies are identified in order lower the risk of resistance development.

Elements of a case-by-case risk assessment of LMOs

The case-by-case approach in risk assessment is based on the premise that risks that may arise from the release of an LMO depend on three main elements: (i) the LMO itself; (ii) the likely potential receiving environment; and (iii) the intended use of the LMO in question. In order to identify and assess risks, each of these elements needs to be characterized in a concerted manner and as appropriate for the specific risk assessment. Moreover, it is important to note that while these three elements may be sufficient to establish the boundaries of a risk assessment, potential adverse effects may extend past these elements, for instance, beyond the likely potential receiving environment and the intended use(s) of the LMO.

The information required for each of these elements in a risk assessment may vary in nature and level of detail from case to case. The following sections provide examples of information that may be relevant for the characterization of each element above. These sections include several of the "points to consider" as indicated in paragraph 9 of Annex III of the Protocol.

A large portion of the information listed here is usually included in the LMO request triggering the risk assessment. The risk assessors can determine whether or not the information provided is sufficient and adequate for conducting a scientifically sound risk assessment. If needed, they can obtain additional information by, for instance, carrying out their own investigation or requesting it from the applicant.

Example 22 – The case-by-case approach

"A risk assessment performed for a particular LMO intended to be introduced to one environment may not be sufficient when assessing the possible adverse effects that may arise if that LMO is to be released under different environmental conditions, or into different receiving environments. A risk assessment performed for a particular use of a particular LMO may not be sufficient when assessing the possible adverse effects that may arise if that LMO is to be used in different ways. Because of this, it is important for each case to be addressed separately, taking into account specific information on the LMO concerned, its intended use, and its potential receiving environment."

Source: IUCN (2003).

Living modified organism

Characterization of the recipient organism

In order to identify whether or not the LMO possesses characteristics that may cause potential adverse effects (see above), it is first necessary to have information about the non-modified recipient organism (or parental organisms).

For many LMOs, the biology of the recipient organism will strongly influence the potential interactions of the LMO in the receiving environment. Information on the recipient organism is therefore essential as it will help the risk assessor identify the exposure, its scenarios and, ultimately, if any risk is posed by an LMO.

The information that is needed for the characterization of the recipient organism will vary depending on each case. For example, the nature and detail of information about the recipient organism that is required may differ between small-scale releases for experimental purposes and large-scale commercial releases. It normally includes the biological and reproductive characteristics of the recipient organism that can be important for determining the potential exposure of other organisms, such as predators, prey, competitors or pathogens, to the LMO in question in the likely potential receiving environment.

For many species of LMOs, information on the recipient organism can be found in biology documents, such as those published by the Organization for Economic Co-operation and Development (OECD)[27] and the Canadian Food Inspection Agency (CFIA).[28]

The LMO will, in most cases, share most of its genetic characteristics with its actual recipient organism (i.e. the one used in the modification) rather than with other genotypes of the same species. Thus, it is also important to consider, whenever possible, comparative data from the actual non-modified recipient organism (see the section on "The choice of comparators").

Information about recipient organism to be considered may include:

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27 See http://bch.cbd.int/database/record-v4.shtml?documentid=48496.
28 See http://www.inspection.gc.ca/english/plaveg/bio/dir/biodoce.shtml.

Taxonomic status – This information is useful for identifying the recipient organism and ensuring that information provided and cited during the assessment pertains to the organism for which the assessment is being carried out. Typically, the taxonomic status includes the scientific name (i.e. genus and species, for example, *Zea mays*) and information about the taxonomic family (e.g. Poaceae). This may also include other information used to further classify (e.g. sub-species, variety, strain) or differentiate the recipient or parental organism(s) (e.g. ploidy level or chromosome number).

Common name – The familiar or colloquial names for the recipient organism that may be commonly used in the country of introduction and in international trade may be useful for finding information relevant to the biology of the organism. Caution is recommended when using information about recipient organism when only common names (versus the scientific name) are used because the same common name can be applied to more than one species.

Biological characteristics – Information on the biological characteristics of the recipient organism, such as the production of endogenous toxins and allergens, its reproductive biology, dispersal of seeds and vegetative propagules, and growth habits, are also important points for consideration.

Origin – The origin of the recipient organism refers to its place of collection and may be important because populations within a species (e.g., variety, strain, isoline, etc.) may have significantly different characteristics. For domesticated species, this may be supplemented with a pedigree map where available.

Centres of origin and centres of genetic diversity – Knowledge of the centre(s) of origin and genetic diversity can provide information on the presence of sexually compatible species and the likelihood of ecological interactions in the receiving environment. In the absence of more specific information, the centre of origin can also offer insight into the biology of the species (e.g. habitats to which the species is adapted).

Habitat where the recipient or parental organism(s) may persist or proliferate – Information about the ecosystems and habitats (e.g. temperature, humidity, altitude, etc) where the recipient organism is known to be native and where it may have been introduced and is now established provides useful baseline information. This allows the risk assessors to understand the range of habitats in which the species exists, the range of behaviours exhibited in those habitats, and how characteristics of the species determine the range of habitats where it can persist or proliferate. This information can be very valuable in determining the likely potential receiving environment and, consequently, the level of exposure to the LMO. Likewise, the ecological characteristics of the recipient organism will help determine which organisms in the likely potential receiving environment are likely to come into contact, either directly or indirectly, with the LMO and will help determine the exposure pathways. For more details on the type of information that may be useful, see the section “Likely potential receiving environment” below.

The history of use can be very valuable as well. If an organism persists in heavily managed environments (e.g. agriculture, sylviculture or recreationally managed land) then this will provide information about the conditions necessary for its survival. It may also provide direct indications of how the LMO will behave in other managed environments.

<u>Description of the genetic modification</u>

Information on the genetic material that was introduced or modified, as well as the method used for the genetic transformation is useful in identifying novel properties of the LMO such as, what new gene products are expressed and which of the endogenous genes of the recipient or parental organism(s) may be affected by the genetic modification.

Typically the description of the genetic modification includes information on (i) the "donor organism(s)" or the source of the inserted genetic element(s); (ii) characteristics of each modified genetic element, including their intended and known biological function(s); (iii) the vector used, if applicable; and (iv) the transformation method. Below is a brief explanation on each of these points:

Donor organism(s) – The relevant information on the donor organism(s) includes its taxonomic status, common name, origin and relevant biological characteristics.

Modified genetic elements **–** The relevant information on the modified genetic elements encompasses the name, sequence, function and other characteristics of all the nucleic acid sequences that were inserted, deleted or modified in the LMO. These include not only the target gene(s) but also, for example, all marker genes, regulatory sequences, and any non-coding DNA. If available, a history of use may be important with regards to potential toxicity or allergenicity of the gene products derived from the donor organism. If the genetic elements originate from a donor organism that is known to be a pest or pathogen it is also relevant to know if and how these elements contribute to the pest or pathogenic characteristics.

Vector – In molecular biology, a vector is a nucleic acid molecule used as a vehicle to transfer foreign genetic material into a cell. If a vector, for example a plasmid, was used for the transformation, relevant information includes its identity, source or origin, and its host range.

Transformation method – Specifying the method that was used in the transformation (e.g. *Agrobacterium* mediated, particle gun, etc.) is also relevant when describing the genetic modification. Depending on the transformation method, parts of the vector(s) may also be incorporated into the genome of the newly developed LMO.

Characteristics of the modification **–** This refers to information about whether or not the inserted or modified genetic elements are present and functioning as expected in the LMO. Normally this involves confirmation that the DNA insert or modified genetic element is stable in the genome of the LMO. Information such as the insertion site in the genome of the recipient or parental organism(s), cellular location of the insert (e.g. chromosomal, extrachromosomal, or chloroplast DNA), its mode of inheritance and copy number may also be relevant.

Identification of the LMO

With regard to the identification of the LMO, the following are important points to consider:

Unique identifiers – A Unique identifier is a code provided by the LMO developer to a transformation event[29] derived from recombinant DNA techniques to enable its unequivocal identification. Each unique identifier is made up of a sequence of 9 alphanumeric digits, for example MON-89788-1, assigned according to the OECD guidance document (OECD, 2006).

Detection and identification methods **–** The availability of methods for detection and identification of the LMO may be considered as well as their specificity, sensitivity and reliability. This information may be relevant not only for assessing risks but also when considering possible monitoring and risk management strategies (see step 5 below). Some regulatory frameworks require a description of such methods as a condition for regulatory approval in order to ensure the tools to assist with monitoring and risk management are available.

29 An LMO with a specific modification that is the result of the use of modern biotechnology according to Article 3 (i) (a) of the Protocol.

The Biosafety Clearing-House of the Cartagena Protocol maintains an LMO registry[30] containing, amongst other things, information on unique identifiers, molecular characteristics and available detection methods for the LMOs addressed in countries' decisions.

Example 23 – CFIA Detection and identification method criteria

According to the Canadian Food Inspection Agency, acceptable methods for detection and identification of LMOs must address the following:

Test Type - Methods must be suitable and may be protein, RNA or DNA based. Phenotypic based methods will not generally be considered suitable.

Limit of detection - Methods must meet the following sensitivity and accuracy requirement:

- For those methods that are grain based, the method must be able to detect 0.2% modified grain (2 grains in 1000) with a 95% confidence interval.
- For those methods that are not grain based (e.g. single ingredient feed) the method must be able to detect 0.2% modified material in a sample with a 95% confidence interval.

Procedural clarity -The method must be complete and laid out in a step wise fashion that may be easily followed by a person unfamiliar with the method. Detailed descriptions of sample size, replicates, extraction procedure, expected results (figures/sequences), interpretation and acceptance criteria must be included.

Cross reactivity - The method must be shown to be specific to the PNT of interest. Any potential for cross reactivity must be clearly stated. Cross reactivity data must be provided demonstrating that the method does not cross-react with other commercially available PNTs of the same species with similar traits/modifications that are currently available in the Canadian marketplace.

Reference material - The company must provide appropriate reference materials to the CFIA upon request. Appropriate reference material will be determined by the CFIA based on the method provided.

Contact information - The company must provide contact information for a technical support person.

Source: CFIA (website).

Likely potential receiving environment(s)

The Protocol calls for the characterisation of the "likely potential receiving environment" of an LMO. According to UNEP (1995), the "potential receiving environment" is the range of environments (ecosystem or habitat, including other organisms) which are likely to come in contact with a released organism due to the conditions of the release or the specific ecological behaviour of the organism. In other words, the likely potential receiving environment of an LMO encompasses both the environments where the LMO will be intentionally introduced as well as other environments which are likely to be exposed to the LMO.

30 http://bch.cbd.int/database/organisms/.

As such, during a risk assessment, in addition to the area where the LMO will be intentionally introduced, the relevant characteristics of the likely potential receiving environment of an LMO should also be thoroughly examined with particular attention given to areas where exposure levels to the LMO will be the highest.

The characterization of the likely potential receiving environment takes into account its ecological characteristics, including physical location/geography, climate, its biological entities and their interactions. The characterization of the likely potential receiving environment will help in selecting appropriate assessment endpoints for the risk assessment (see Module 2) and will also affect the assessment of the potential interactions of the LMO with other organisms.

To determine the likely potential receiving environment, risk assessors may consider potential pathways for dispersal of the LMO as well as the habitats where the recipient/parent organism(s) may persist or proliferate.

An analysis of possible dispersal routes and mechanisms is important when establishing the likely potential receiving environments. Different dispersal mechanisms may exist and could be inherent either to the LMO (e.g. altered seed characteristics), its intended use (e.g. shipment practices) or the receiving environment (e.g. proximity to a river). A scientifically sound risk assessment takes into consideration all possible dispersal mechanisms, keeping in mind the biology of the LMO and non-modified recipient or parental organism(s), in a concerted manner for each case.

Information about the likely potential receiving environment can include considerations on both large scale (e.g. climate) and small scale characteristics (e.g. microclimate) depending on the complexity of the environment. The type of information on the likely potential receiving environment and the level of detail depend on the nature of the LMO and its intended use, in accordance with the case-by-case principle.

It may not be possible or practical to consider every possible interaction between the LMO and the receiving environment. Such challenges and limitations should be acknowledged during the risk assessment process.

Below are descriptions of some physical and biological characteristics of the likely potential receiving environment(s) that can be considered in the risk assessment of LMOs. This is an indicative list thus the information required to satisfy the needs of the assessment will vary depending on the nature of the LMO and its intended use.

The physical or "abiotic" characteristics of the likely potential receiving environment may have a great impact on the ability of an LMO to survive and persist.

Geography and climate – Geography encompasses characteristics such as latitude, which will influence day-length, and altitude. Climate encompasses temperature, precipitation, humidity, wind and other meteorological measures over long periods of time. For the purposes of environmental risk assessment, geography and climate are among the most important factors impacting the ability of an LMO to survive and persist. For LM plants, temperature and precipitation are likely to be key determinants. Seasonality (variations in climate on an annual cycle) can also be an important consideration in the potential survival and persistence of an LMO.

Soil – The type and quality of soil can greatly influence the ability of an LM plant to survive or persist without land management. The type and quality of a soil are heavily influenced by the organisms living in its proximity, but abiotic factors such as climate, geography and topography will also all play a role in determining its characteristics (e.g. mineral content, moisture level, texture etc.).

Management status – The management status of an environment is a measure of how much human intervention takes place in order to maintain a particular condition. A separate but related concept is "disturbance" which can be considered the amount of human activity that affects the environment but without the intention of maintaining a particular condition. Management and disturbance may greatly influence the ability of an LMO to survive and persist in the environment. Likely potential receiving environments can range from highly managed to unmanaged and from highly disturbed to undisturbed.

The biological characteristics of the likely potential receiving environment consist of all the living organisms present in the environment, its biological communities and the interactions among them.

Both managed and unmanaged environments contain complex biological characteristics that pose challenges for environmental risk assessments.

As with any other organism, an LMO released into the environment is expected to have many interactions with other organisms. For the purposes of environmental risk assessment, it is critical to develop verifiable risk scenarios and identify the appropriate species that may be impacted by the presence of the LMO in the environment. For example, gene flow and possibly introgression may occur when sexually compatible species are present in the likely potential receiving environment. The selection of suitable representative species in the likely potential receiving environment is also informative (see section on "Selecting relevant assessment endpoints or representative species").

Intended use

The characteristics of the intended use of an LMO and management practices associated with it, such as tilling and the use of pesticides, can provide valuable information and context for the risk assessment process. Understanding the intended use also helps a risk assessor to perform an exposure assessment starting with the environment where the LMO will be deliberately introduced followed by considering whether or not the LMO is likely to disseminate or persist outside of this environment.

To illustrate how the intended use can affect the likelihood of a risk posed by an LMO, a hypothetical case of an LM tree being used for wood production could be considered, in which the first flowering would occur after 15 years of planting, but logging would take place after only 10 years. As such, the intended use would result in the LM tree being logged before its first flowering. Consequently, in this hypothetical case, the intended use would influence the likelihood of potential outcrossing[31] of this LM tree.

Information regarding the intended use of the LMO may also take into account any new or changed use in comparison to the recipient or parental organism(s), for example, in cases where the recipient or parental organism(s) is a crop for human consumption but the intended use of the LMO is the production of a compound for pharmaceutical or industrial use.

The scale and type of the introduction into the environment, for example, field trials versus commercial releases, and whether or not any risk management strategy is being proposed, may also be relevant when

31 "Outcrossing" refers to the transmission of genetic elements from one group of individuals (e.g., population, crop variety) to another. In plants, outcrossing most commonly results from cross-pollination.

considering the intended use. Many regulatory frameworks, for instance, require that submissions for field trials be accompanied by information on risk management strategies to reduce exposure to the LMO.

Considerations on the intended use may also take into account national and regional experiences with similar organisms, their management and exposure to the environment.

Step 2: Evaluation of the likelihood

This step entails an evaluation of the likelihood, i.e. probability, of the adverse effect occurring, taking into account the level and kind of exposure of the likely potential receiving environment to the LMO.

After the potential adverse effects of the LMO have been identified, the risk assessment proceeds to a formal analysis of the likelihood and consequence of these effects with respect to the identified assessment endpoints.

Although the steps of evaluating likelihood and consequences are dealt with separately in Annex III of the Protocol, some risk assessment approaches consider these steps simultaneously or in reverse order.

The likelihood of an adverse effect is dependent upon the probability of one or a series of circumstances actually occurring.

It is difficult to describe in detail an evaluation of likelihood or consequence without using an example because the evaluation is dependent on the nature of the LMO, the receiving environment and, if appropriate, on the risk scenario used. The following are two examples:

- In a case where outcrossing of the transgene with a non-modified organism is determined to be possible (i.e. the two species are sexually compatible), the risk assessment may consider both the likelihood of the outcrossing and, if relevant, the likelihood of the LMO progeny to persist or proliferate. Considerations on the latter may be based, for example, on assessing whether or not the transgene would affect the fitness level of the progeny (i.e. the capability of individuals to compete and reproduce in a given environment). If the transgene induces a positive fitness effect, the likelihood that the population resulting from the outcrossing would increase is high. On the other hand, transgenes that have a negative fitness effect would result in a low likelihood that the resulting population would increase. Transgenes that have a neutral impact on fitness may persist in populations at low levels depending on the rate of outcrossing or introgression as well as the overall population dynamics of the species.
- In a case where the risk scenario involves the potential toxicity of an LM plant (or a substance produced by an LM plant) to a herbivorous insect: the analysis of likelihood may consider the probability that the insect will be present, that the insect will feed on the LMO and that the insect will ingest a sufficient quantity of the LMO to suffer an adverse effect. Likelihood may consider probabilities on an individual level (e.g. what are the chances an individual insect may consume the LM plant) or on a population level (e.g. what percentage of the population of insects will come into contact with the LMO) or both.

Example 24 – Likelihood of introgression

"To evaluate a possible ecological effect of an inserted gene being introgressed into a natural population it is important to estimate the probability of introgression. Such a probability estimate can be obtained from measurements of hybridisation rates, assumed selective advantage of inserted gene, and fitness measurements of parent plants, hybrid plants, and plants from the first and second back-cross generations.

If hybrids are formed and it is likely that these hybrids are able to survive the consequences should be discussed."

Source: Ministry of Environment and Energy Denmark (1999).

Step 3: Evaluation of the consequences

The consequence of an adverse effect is the outcome, extent and severity of an adverse effect associated with exposure to an LMO, its handling and use, or its products (in the context of Annex III paragraph 5). Should adverse effects occur, they may be severe, minimal, or anywhere in between. The evaluation of the consequences may consider the effects on individuals (e.g. mortality, reduced or enhanced fitness, etc.) or on populations (e.g. increase or decrease in number, change in demographics, etc.) depending on the adverse effect under evaluation.

The risk assessment should consider the consequences of each adverse effect based on a concerted analysis of what is known about the LMO, the likely potential receiving environment and the assessment endpoints, as well as the likelihood assessment.

Example 25 – Consequences of effects to non-target organisms

When the inserted trait cause the plant to produce potentially toxic compounds, or if flower characteristics are changed, i.e. colour, flowering period, pollen production etc. then effects on pollinators has to be measured. A test of effects on honeybees (*Apis melliferae*) is obligatory because of the importance of honeybees as pollinators of both wild and crop species and because standardised test protocols testing for effects of conventional pesticides exists for this pollinator. These tests include exposure through nectar and pollen.

Source: Ministry of Environment and Energy Denmark (1999).

Also using an example where gene flow and introgression could lead to a potential adverse effect, what impact the presence of a transgene will have on biodiversity will depend on its effect on individual fitness as well as on the importance of that species relative to the protection goals. For instance, if a sexually compatible species, present in the receiving environment, is directly relevant to a biodiversity protection goal (e.g. it is a protected species) then the impact on biodiversity can be assessed by looking directly at the impact of the transgene on the population. If the sexually compatible species is not directly related to a biodiversity management goal, then the impact of the expression of the transgene will be dependent on indirect interactions. Indirect effects may be challenging to assess (see step 1), and are dependent on the ecological importance of the species.

Step 4: Estimation of the overall risk

This step consists of the integration of the likelihood and consequence of each of the individual risks identified through the preceding steps and takes into account any relevant uncertainty that emerged thus far during the process. In some risk assessment approaches, this step is referred to as “risk characterization”.

To date, there is no universally accepted method to estimate the overall risk but a variety of guidance materials are available that address this topic (see for instance, documents under “Scientific and technical issues / risk assessment” in the Biosafety Information Resource Centre, BIRC).[32]

In rare instances, the risk characterization results in a quantitative value (e.g. 6% of a population will be exposed to a stressor, and of that percentage half will experience mortality). More frequently, the risk characterization for an LMO will be qualitative. In such cases, description of the risk characterization may be expressed as, for instance, ‘high’, ‘medium’, ‘low’, ‘negligible’ or ‘indeterminate due to uncertainty or lack of knowledge’.

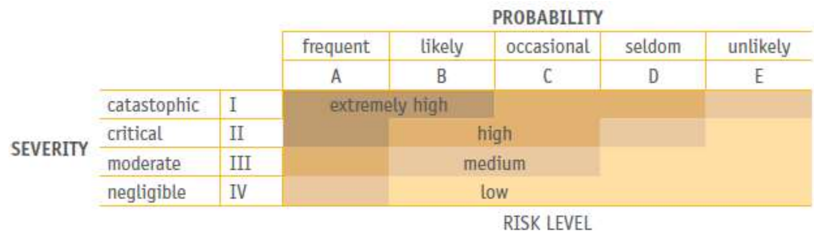
The outcome of this step is the assessment of the overall risk of the LMO. Once this is achieved, it is helpful to determine, as an internal quality control, whether the risk assessment has met the criteria established at the beginning of the process taking into account also those criteria established in the relevant policies in practice with regard to the protection goals, assessment endpoints and risk thresholds (i.e. the level of tolerance to a certain risk or the level of change in a particular variable beyond which a risk is considered unacceptable).

Figure 8 – Estimation of overall risk

Source: ERMA NZ (1998)

32 http://bch.cbd.int/database/resources.

Figure 9 –Classification of risk



Source: FAO (2011b).

Step 5: Acceptability of risk and identification of risk management and monitoring strategies

Annex III of the Protocol states that the risk assessment methodology may entail “a recommendation as to whether or not the risks are acceptable or manageable, including, where necessary, identification of strategies to manage these risks” and “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”.[33]

For the “acceptability” of risks, please refer to the section “Recommendations as to whether or not the risks are acceptable or manageable” below.

Risk management

Risk management strategies refer to measures to ensure that risks identified in the risk assessment are reduced or controlled which may be implemented after the LMO is introduced into the environment (or placed in the market, if applicable). Risk management strategies can be useful to increase confidence when dealing with uncertainty or, in the case where risks have been identified, to reduce the likelihood or impact of the potential adverse effect.

Example 26 – Application of management strategies for risks from the deliberate release or marketing of LMO(s)

“The risk assessment may identify risks that require management and how best to manage them, and a risk management strategy should be defined.”

Source: The European Parliament and the Council of the European Union (2001).

Risk management strategies may aim to reduce the likelihood or consequences of potential adverse effects and are referred to as “*preventive measures*” and “*mitigation measures*”, respectively. Some approaches to risk assessment may also include the identification of measures to control an adverse effect should it occur.

33 Paragraphs 8(e) and (f) of Annex III.

For LMOs, common risk management strategies have typically been designed to reduce the likelihood of exposure, but depending on the specific case, management options might include a variety of measures that are directly or indirectly related to the LMO. Some examples of risk management strategies for LMOs include: minimum distances from sexually compatible species if there is evidence that gene flow could cause adverse effects, destruction of seeds remaining in the field or of volunteers after harvest, restrictions from introduction into specified receiving environments, etc.

Certain risk assessment steps, particularly the evaluation of likelihood and consequences may need to be re-evaluated to take into account each of the identified risk management strategies since these may affect the estimation of the overall risks.

Monitoring

A risk assessor may identify the need for a strategy to monitor the receiving environment for adverse effects that may arise after the introduction of the LMO and include it as part of the recommendations for the Competent National Authority(ies). This may happen, for instance, when the level of uncertainty could affect the overall conclusions of the risk assessment. Moreover, some biosafety frameworks may have a policy to request a plan for monitoring as part of the risk assessment of all or particular types of LMOs.

Monitoring after the release of the LMO aims at detecting changes (e.g. in the receiving environment(s) or in the LMO) that could lead to adverse effects.

Example 27 – Post-market monitoring

"Post-market monitoring may be an appropriate risk management measure in specific circumstances. Following the safety assessment, the need and utility for post-market monitoring should be considered, on a case-by-case basis, during risk assessment and its practicability should be considered during risk management."

Source: Health Canada (2006).

Monitoring strategies may be designed on the basis of the protection goals identified by national legislation and regulation, if available, and parameters that are relevant to the indication of any increasing risk to the assessment endpoints in a "top-down" approach, or on the basis of specific risks in a "bottom-up" approach.

The strategies may include "general surveillance" that can make use of existing, broader monitoring programs that may identify unexpected effects of the LMOs or traits, such as long-term effects; or be "case-specific" where potential adverse effects identified during the risk assessment are investigated. Monitoring for the development of resistance in insect pests following introduction of pesticide producing LM crops would be an example of a "case-specific" scenario. Monitoring for the abundance of beneficial insect species in an environment would be an example of "general surveillance".

Example 28 – Case-specific monitoring and general surveillance of LM plants

"The environmental monitoring of the GM plant will have two focuses: (1) the possible effects of the GM plant, identified in the formal risk assessment procedure, and (2) to identify the occurrence of adverse unanticipated effects of the GM plant or its use which were not anticipated in the environmental risk assessment. […] Appropriate case-specific monitoring measures should be developed on a case-by-case approach depending upon the outcomes of the risk assessment. Possible risks identified in the environmental risk assessment should be studied in hypothesis-driven experiments and tests.

The objective of general surveillance is to identify the occurrence of unanticipated adverse effects of GM plants or their use on human health or the environment that were not anticipated in the environmental risk assessment. Since no specific risk is identified, no hypothesis of risk can be tested, so it is difficult to propose specific methods to carry out general surveillance."

Source: EFSA (2006).

Where it is appropriate, other potential adverse effects such as delayed, cumulative, combinatorial [34] or indirect effects resulting from the LMO, the trait or the inserted or modified genes may be considered in the post-release monitoring strategies.

The level of specificity of the monitoring strategies may vary depending on the LMO(s), the intended use(s) and/or the likely potential receiving environment(s). Therefore, it is essential that a detailed methodology for each identified strategy also be identified. The methodology may include, for example, the frequency, locations and methods of sampling, as well as methods of analysis (e.g. laboratory testing).

Preparing a risk assessment report and recommendation

The outcomes of a risk assessment are often presented in the form of a written report prepared by the risk assessor(s). The report is primarily intended to assist the decision makers in making informed decisions regarding the safe use of an LMO.

Presenting the results of a risk assessment could be categorized as a form of risk communication. As in any form of communication, risk assessors should be mindful of the intended recipients, which in addition to decision makers may also include regulators, risk managers, other risk assessors and the general public amongst others.

34 "Cumulative effects" are effects due to the presence of multiple LMOs or their products in the receiving environment. "Combinatorial affects" are effects that arise from the interactions between two (or more) genes in one organism, including epistatic interactions.

Example 29 – Risk communication

Risk communication is the interactive exchange of information and opinions among assessors, risk managers, consumers, industry, the academic community and other interested parties throughout the risk analysis process. The information exchange concerns risk related factors and risk perceptions, including the explanation of risk assessment findings and the basis of risk management decisions. It is vitally important that risk communication with the public comes from credible and trusted sources.

Source: FAO (2001).

It is important that the report is presented in a well-structured form, which not only facilitates the deliberations of decision makers, but also allows for an easier exchange of information and experience. The context and scope of the risk assessment should be clearly explained as other institutions (e.g. in the same or in different countries) may have an interest in understanding how the risk of a particular LMO was assessed.

With regard to the sharing of information, a Party to the Protocol is required to submit to the Biosafety-Clearing House (BCH) all "summaries of its risk assessments or environmental reviews of living modified organisms generated by its regulatory process, and carried out in accordance with Article 15, including, where appropriate, relevant information regarding 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" (Article 20). This will include all risk assessments generated to support decisions regarding LMOs for intentional introduction into the environment (Articles 8, 10 and 13) or for direct use as food or feed, or for processing (Article 11) whether they are triggered by a transboundary movement or by an internal request.

The required contents and format of a risk assessment report are generally defined by the Competent National Authority(ies) that have the responsibility to make decisions on the LMO(s) in the context of the national biosafety framework.

A risk assessment report typically comprises of an analytic synthesis of all the relevant steps and results of the risk assessment process, including an overview of the context and scope of the risk assessment, methodology used and a detailed summary of the results of the overall risk estimation, including the identification of individual risks, as well as the likelihood and consequences of the potential adverse effects.

The report may also contain an evaluation of the availability and quality of the scientific and technical information that was deemed necessary to perform the assessment and characterize the risks, and whether or not there were gaps in the information.

An analysis of all identifiable uncertainties and how they may impact the overall conclusions of the assessment is also a critical element of the report. This includes uncertainties identified at each step of the risk assessment process as well as those remaining at the end of the risk assessment.

Finally, the risk assessment report often contains a set of recommendations regarding the acceptability and manageability of the risks posed by the LMO and the identification of appropriate risk management and monitoring strategies.

The information above can be organized under five broad topics depending on the requirements of the National Authority that is responsible for the risk assessment:

(a) Background, context and scope of the risk assessment;
(b) Characterization and estimation of risks;
(c) Description of risk management and monitoring strategies identified during the risk assessment;
(d) Consideration of remaining uncertainty; and
(e) Recommendations as to whether or not the risks are acceptable or manageable.

An overview of the information which may be included under each of these topics may be found in the following sections.

Background, context and scope of the risk assessment

This part of the report focuses on describing the issues that were considered while setting the context and scope of the risk assessment. Basically, this section of the report sets the scene for the reader to follow a clear progression through the subsequent sections of the report.

A risk assessment report usually specifies the mandate that was given to the risk assessor(s) and includes a description of the procedure that was followed in conducting the risk assessment, an indication of which institution has carried out the risk assessment, and which, if any, other institutions were consulted or were part of the process. Any other information that helps in understanding the context in which the risk assessment was carried out is also typically included in this part of the report.

Previous approvals or prohibitions of the same LMO, if any, including the regulatory status of the LMO in the country of export or import as well as in any other country may also be included in this section, if appropriate.

The report describes how the requirements of the national regulatory framework were taken into account including which protection goals were identified as relevant in the context of the risk assessment and how assessment endpoints were selected.

In summary, the following information may be included in this section of the report:

(a) Contact details of the LMO developer;
(b) Type of approval sought (e.g. introduction into the environment);
(c) Contact details of the institution responsible for the risk assessment;
(d) Relevant regulation;
(e) Relevant protection goals and assessment endpoints;
(f) Previous approvals or prohibitions of the same LMO;
(g) Overview of the terms of reference for the risk assessment; and
(h) Consulted experts or panel of experts, if applicable, and how the involved experts were chosen and how possible conflict of interests were identified and was managed.

In some cases, the bulk of information presented in this section of the report may be extracted from the request triggering the risk assessment, the national regulatory framework, including environmental and biosafety policies or guidelines, and national biosafety-related databases.

Characterization and estimation of risks

This section of the report focuses on the outcomes of the risk assessment steps in accordance with the steps in Annex III of the Protocol and as described above.

Depending on the specific mandate and scope of the risk assessment, the following information may be included in this section of the report:

(a) Description of the LMO (e.g. recipient or parental organism(s), transformation method, inserted or modified sequences, novel traits, purpose of the genetic modification), its intended use and the likely potential receiving environment(s), including considerations on how the baselines were established and appropriate comparator(s) chosen;
(b) Considerations of the availability and quality of information used during the risk assessment;
(c) Methodology used in the risk assessment, explaining, if necessary, the use of terms;
(d) Description of the potential adverse effects and risk scenarios arising from the novel characteristics of the LMO;
(e) Analyses of the likelihood and consequences of each identified potential adverse effect; and
(f) Estimation of the overall risk posed by the LMO.

The information relevant to each of the items above may vary in nature and level of detail on case-by-case basis, depending on the LMO concerned, its intended use and the likely potential receiving environment.

While information related to the description of the LMO and its intended use may be obtained in part from the LMO application, the bulk of information to be presented in this section of the report is obtained through the risk assessment process for the specific case at hand.

Description of risk management and monitoring strategies

If risk management and monitoring strategies were identified during the risk assessment process (see step 5), the risk assessment report should contain a section detailing any strategies to minimize the risks identified.

The risk assessment report may include, for instance:

(a) How each identified strategy is expected to contribute to minimizing the likelihood or consequence of potential adverse effects (e.g. by reducing the exposure to the LMO or the consequences of the potential harm);
(b) Details of the methodology for each identified risk management or monitoring strategy including, for instance, the frequency, locations and methods of sampling, as well as methods of analysis, including laboratory testing when appropriate;
(c) Any uncertainty regarding the effectiveness of any such management or monitoring strategy;
(d) An indication as to whether and how different management strategies can be combined to further minimize uncertainty or identified risks; and
(e) Considerations on unintentional introduction into the environment and emergency measures as appropriate (see Article 17).

Consideration of remaining uncertainty

As seen in the section on “Overarching issues”, uncertainty is an inherent component of any risk assessment, and should be considered in a systematic manner at each step of the risk assessment process. Nevertheless, at the end of the risk assessment, uncertainties may still remain with regard to one or more specific steps in the process or about the likelihood or consequences of the potential adverse effects.

Annex III of the Protocol addresses this matter by requiring that “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”.[35]

Considerations of remaining uncertainties should be included in the risk assessment report. These considerations may include:

(a) Identification of major information gaps and, where appropriate, indication of whether gathering additional data (either before the release or after it by monitoring) would significantly increase the overall confidence in the results of the risk assessment;
(b) An analysis of uncertainty, including its types (e.g. gaps in the available information, limitations of the assessment methodology);
(c) Discussion on the level of scientific support to issues where there is uncertainty, including an analysis of different scientific views;
(d) Discussion of any assumption used in assessing the risks, including its strengths and weaknesses;
(e) Discussion of the potential for uncertainties to impact on the overall conclusions of the risk assessment; and
(f) Identification of any threats of serious or irreversible damage to the environment (basis for the adoption of the precautionary approach).

Example 30 – Uncertainty and an approach based on the precautionary principle

“The implementation of an approach based on the precautionary principle should start with a scientific evaluation, as complete as possible, and where possible, identifying at each stage the degree of scientific uncertainty. Decision-makers need to be aware of the degree of uncertainty attached to the results of the evaluation of the available scientific information. Judging what is an "acceptable" level of risk for society is an eminently *political* responsibility. […] Where possible, a report should be made which indicates the assessment of the existing knowledge and the available information, providing the views of the scientists on the reliability of the assessment as well as on the remaining uncertainties. If necessary, it should also contain the identification of topics for further scientific research.”

Source: Commission for the European Communities (2000).

Recommendations as to whether or not the risks are acceptable or manageable

Recommendations are one of the most important sections of a risk assessment report as they take into account the outcomes of the risk assessment to provide direct science-based advice to the intended

35 Paragraph 8(f) of Annex III.

recipients of the report. A recommendation as to whether or not the risks are acceptable or manageable should be kept within the scope of the risk assessment and based on its findings.

It is important to note that risk assessor(s) are requested to recommend whether the risks are “acceptable” or not. However, the definition of "acceptability" may not be part of a risk assessment but could be pre-established, for example, in thresholds included in government policies or in the mandate given to the risk assessor. Likewise, the final decision on whether to approve (with or without conditions) or prohibit the specific use of the LMO is taken during the decision-making process, which may take into account, depending of the national regulatory framework and among other things, government policies, public opinion, anticipated benefits, costs of the risk management measures and socio-economic considerations.

In addition to the issues mentioned above, the recommendations section of the report may also include any relevant information to be considered by the decision makers prior to making a decision. Some issues that may be relevant include:

(a) A recommendation as to whether or not one or more risk management or monitoring strategies should be implemented and, if so, the specific conditions for each such strategy;
(b) Considerations of remaining uncertainties; and
(c) A recommendation as to if and when the risk assessment should be re-visited.

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