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AD HOC TECHNICAL EXPERT GROUP ON RISK ASSESSMENT AND RISK MANAGEMENT UNDER THE CARTAGENA PROTOCOL ON BIOSAFETY
Second meeting
Ljubljana, 20-23 April 2010

FINAL REPORT OF THE AD HOC TECHNICAL EXPERT GROUP ON RISK ASSESSMENT AND RISK MANAGEMENT UNDER THE CARTAGENA PROTOCOL ON BIOSAFETY

INTRODUCTION

1. At its fourth meeting, the Conference of the Parties serving as the meeting of the Parties to the Cartagena Protocol on Biosafety, in its decision BS-IV/11, established an open-ended online forum on specific aspects on risk assessment (referred to hereinafter as the "Open-ended Online Forum")[1] through the Biosafety Clearing-House (BCH) and an Ad Hoc Technical Expert Group (AHTEG) on Risk Assessment and Risk Management in accordance with the terms of reference annexed to that decision.

2. The Executive Secretary was requested to convene two meetings of the AHTEG prior to the fifth meeting of the Parties to the Protocol, to be held in Nagoya, Japan, from 11 to 15 October 2010. The Executive Secretary was also requested to convene ad hoc discussion groups of the Open-ended Online Forum and at least one real-time online conference per region prior to each of the meetings of the AHTEG.

3. To implement the various elements of the decision in a systematic manner, the Secretariat, with the approval of the COP-MOP Bureau, established a continuous process comprising: (i) an open-ended online forum; (ii) discussion groups on specific topics; (iii) two series of regional real-time online conferences (one prior to each AHTEG meeting); and (iv) two meetings of the AHTEG.

4. The first meeting of the AHTEG on Risk Assessment and Risk Management under the Cartagena Protocol on Biosafety was held in Montreal from 20 to 24 April 2009.

5. The main achievements during the first meeting of the AHTEG were:

(a) A draft of the roadmap, which formed the basis for further work during the inter-sessional period;

(b) Identification and prioritization of specific issues of risk assessment for the development of guidance documents;

(c) Establishment of four sub-working groups (SWGs) to focus on each of the specific issues identified (i.e. the roadmap, living modified mosquitoes, living modified crops with tolerance to abiotic stress and living modified organisms (LMOs) with stacked genes); and

[1] Available at http://bch.cbd.int/onlineconferences/forum_RA.shtml .

(d) Development of an action plan containing a summary of the terms and procedures for the development of guidance documents prior to the second meeting of the AHTEG.

6. The report of the first meeting of the AHTEG is available as document UNEP/CBD/BS/COP-MOP/5/INF/13.

7. A number of activities were carried out by the AHTEG between its two meetings. These include several rounds of online discussions, discussions under the Open-ended Online Forum, a face-to-face meeting of the SWG on the Roadmap and teleconferences of the AHTEG Bureau as listed in annex II hereto.

8. At its second meeting, the Group was tasked with the following under its terms of reference:

(a) Revise and finalize the "Roadmap" for the effective use of guidance documents on risk assessment;

(b) Make recommendations to the Secretariat on how to integrate the "Roadmap" and tools for retrieval of guidance materials available in the Biosafety Information Resources Centre of the BCH that are relevant at the different stages of risk assessment;

(c) Review the action plan established in the first meeting of the AHTEG;

(d) Consider possible modalities for cooperation in identifying LMOs or specific traits that may have adverse effects on the conservation and sustainable use of biological diversity, taking also into account risks to human health; and

(e) Prepare a report for consideration by the fifth meeting of the Parties.

9. The second meeting was attended by fourteen members from Parties (Austria, Brazil, China, Croatia, Egypt, Germany, Japan, Malaysia, Netherlands, Niger, Norway, Republic of Moldova and Slovenia), as well as two from non-Parties (Canada, United States of America) and four from organizations (Bayer CropScience, Federation of German Scientists, Monsanto Company and University of Canterbury). However, due to a volcanic eruption in Iceland immediately prior to the meeting, major European airports were closed for several days and some participants were not able to travel to Slovenia. At the request of some AHTEG members and in order to ensure full participation, given the circumstances, of members of the Group in its final deliberations, a system was set up to enable remote voice-participation of AHTEG members. This was established via “Skype”, an internet application. The system enabled the following to participate, to the extent possible, in the deliberations: one member from Parties (Mexico), one from non-Parties (Australia) and one from organizations (Public Research and Regulation Initiative). The complete list of AHTEG members is attached hereto as annex I.

ITEM 1. OPENING OF THE MEETING

10. The meeting was opened on Tuesday, 20 April 2010 at 9.15 a.m. by Mr. Helmut Gaugitsch, Chair of the AHTEG.

11. In his opening remarks, Mr. Gaugitsch welcomed the participants and thanked the Government of Slovenia for hosting the meeting. He also expressed his appreciation to the Group, particularly the Chairs of the four sub-working groups, for their dedication and commitment in the development of guidance on risk assessment. He also expressed his appreciation to the Group on progress that had been made since its first meeting,, through a combination of online and face-to-face discussions. He noted the tremendous work that was ahead but expressed his optimism that the work of the AHTEG could be completed successfully.

12. Mr. Zoran Kus, State Secretary, Ministry of the Environment and Spatial Planning of Slovenia welcomed the participants to Slovenia, noted the importance of risk assessment in the implementation of the Protocol by the Parties and wished the Group successful deliberations.

13. Mr. Charles Gbedemah on behalf of Mr. Ahmed Djoghlaf, Executive Secretary of the Convention on Biological Diversity, welcomed the AHTEG members and thanked the Government of Slovenia for

hosting the meeting and the Governments of the Netherlands and Norway for their continued financial support for biosafety in general, but in particular for the risk assessment process.

ITEM 2. ORGANIZATIONAL MATTERS

2.1. Adoption of the agenda

14. The Group adopted the provisional agenda circulated by the Secretariat (UNEP/CBD/BS/AHTEG-RA&RM/2/1) without amendment.

2.2. Organization of work

15. The Group agreed to proceed on the basis of organization of work contained in the annex III to the annotations to the provisional agenda prepared by the Secretariat in consultation with the AHTEG Chair (UNEP/CBD/BS/AHTEG-RA&RM/2/1/Add.1).

16. The Group further agreed to work in plenary and to break into smaller groups only if needed.

ITEM 3. SUBSTANTIVE ISSUES

17. The Group was invited to start its deliberations on the substantive issues on the basis of the background documents made available by the Secretariat for this meeting.[2/]

3.1. Development of guidance on specific aspects of risk assessment

(a) Finalization of the draft guidance documents

18. Under this agenda item, the Chairs of the sub-working groups provided an overview of the main issues that were discussed under the Open-ended Online Forum and within the sub-working groups and circulated the latest versions of the draft documents, which were produced on the basis of document UNEP/CBD/BS/AHTEG-RA&RM/2/4 following consultations during the preparatory meetings of the sub-working groups held in Ljubljana on 19 April 2010.

19. The Chair reiterated that the draft guidance documents produced by the sub-working groups were intended as guidelines and that there could be instances when different views were reflected in the draft documents since the AHTEG was a multi-stakeholder consultative process led by the Parties. He further explained that, in settling divergent views, an attempt was made to include all views by seeking the endorsement of Parties. Ultimately, when different views could not be reconciled, the inclusion of text in the final documents was by agreement by the Parties.

20. Recalling its terms of reference with regard to the development of guidance on specific aspects of risk assessment, and recognizing that the guidance drafts address the technical components of risk management in line with paragraph 8 (e) of Annex III to the Protocol, while leaving out the decision-making components of risk management, the Group agreed to remove "risk management" from the titles of all drafts while retaining the current text on the identification of risk management strategies.

21. In its deliberations on the final draft guidance documents, the Group considered the format in which to submit the draft guidance documents to the fifth meeting of the Parties, The Group agreed that the four draft documents be merged into a single document entitled "Guidance on Risk Assessment of Living Modified Organisms" and divided into two main sections entitled "Part I: Roadmap for Risk Assessment of Living Modified Organisms" and "Part II: Specific Types of Living Modified Organisms and Traits". This document is attached hereto as Annex III.

22. The Group further agreed that "Part II" should include the sub-sections containing the guidance developed on specific aspects of risk assessment (i.e. risk assessment of LM mosquitoes, LMOs with stacked genes and LM crops with tolerance to abiotic stress).

[2] Background documents are available at: http://www.cbd.int/doc/?meeting=BSRARM-02.

23. The Group also agreed that, pending future decisions by the COP-MOP, both parts of the document could be updated and additional guidance on specific types of LMOs or traits added to Part II of the document.

(b) Recommendations on a mechanism for integrating the AHTEG guidance documents and tools for retrieval of reference guidance materials in the Biosafety Clearing-House

24. Ms. Manoela Miranda of the Secretariat of the Convention on Biological Diversity made a brief presentation on how the guidance documents and the background materials linked to the guidance documents could be made publicly available through the Biosafety Clearing-House.

25. Under this agenda item, the Group considered the format in which these materials could be linked to the guidance documents and how they could be submitted, displayed and updated in the Biosafety Clearing-House.

26. The Group agreed that the list of background materials should be updated with the view to maintaining the lists in line with the available background materials and current new developments in the relevant subjects. Moreover, the Group agreed that additional background materials may be sent to the SWG chairs as soon as possible but no later than 15 June 2010 and after consultation with the whole AHTEG added to the existing list no later than the 31 August 2010.

3.2. Review of the AHTEG action plan

27. Under agenda item 3.2, the Group considered the action plan produced during its first meeting and assessed the accomplishment of the activities proposed therein as well as the terms and procedures for reviewing the modalities for the development of guidance documents between the two meetings of the Group. A list of the activities carried out by the AHTEG is attached hereto as Annex II.

28. The Group noted that not only have all the activities for the development of the guidance documents and first testing of the draft Roadmap been carried out as outlined in the action plan, but also that additional online discussions took place during the intersessional period.

29. The Group also noted that the drafting of the "Guidance on Risk Assessment of Living Modified Organisms" has benefited from multiple rounds of online discussions that alternated between the Open-ended Online Forum and the AHTEG sub-working groups providing the means for various rounds of feedback between a large group of experts in the relevant subjects. The challenges for interactivity and discussions in the online fora were noted.

30. In conclusion, the Group noted that the action plan developed during its first meeting had been successfully implemented.

3.3. Consideration of possible modalities for cooperation in identifying living modified organisms or specific traits that may have adverse effects on the conservation and sustainable use of biological diversity, taking also into account risks to human health

31. The Group discussed possible modalities for cooperation under this agenda item taking into consideration the recommendations made during the online discussions under the Open-ended Online Forum.

32. Possible modalities noted included, for instance, information exchange via the Biosafety Clearing-House, workshops, an ad hoc technical expert group, as well as cooperation in the testing of LMOs.

33. A number of members of the Group agreed that a step-wise process should be established for identifying LMOs or specific traits that may have adverse effects on the conservation and sustainable use of biological diversity taking also into account risks to human health. This process may be initiated by a phase for gathering information then followed by a second phase for the analysis of the information.

34. The Secretariat highlighted that a very small number of decisions on the "non-approval" or "approval of with conditions" of LMO applications is available in the BCH and that, even in cases where these decisions have a risk assessment summary attached, it is difficult to identify the reason for the conditions or rejections.

35. In this context, a number of participants noted the importance of understanding why this type of information is not available in the Biosafety Clearing-House and raised questions as to whether this information does not exist or was not submitted to the Biosafety Clearing-House.

36. It was also noted that the lack of information in the Biosafety Clearing-House may arise from the fact that applications may be withdrawn before national authorities reach a formal decision on them and that this information is not usually published in the Biosafety Clearing-House.

37. Some participants further noted that a lack of post-release environmental monitoring data may hamper the identification of adverse effects.

38. Some participants, recalling the submissions made by non-Parties and organizations on the identification of LMOs or specific traits that may have adverse effects on the conservation and sustainable use of biological diversity, taking also into account risks to human health issue,[3] were of the opinion that since risk assessments under the Protocol should be carried out on a case-by-case basis, the general question asked by the Conference of the Parties serving as the meeting of the Parties to the Protocol should be subdivided into further questions and the task should be redesigned into different components on the basis of the submissions above.

3.4. Recommendations of the AHTEG to the Conference of the Parties serving as the meeting of the Parties to the Protocol at its fifth meeting

39. The Group discussed the need for the further development of guidance on additional topics of risk assessment, particularly on those specific issues of risk assessment that were identified and prioritized during the Open-ended Online Forum and first meeting of the AHTEG.

40. On the basis of the discussions under the agenda items above, the Group has prepared a set of recommendations to the Parties at their fifth meeting. These recommendations are attached hereto as annex IV.

ITEM 4. OTHER MATTERS

41. AHTEG members from Parties, non-Parties and organizations expressed their appreciation particularly to the Chair of the AHTEG, Dr. Helmut Gaugitsch, for the able and efficient manner in which he handled the proceedings of the Group to a successful completion. The members also expressed their appreciation to the Secretariat for their efficient and hard work. The Chair also expressed his appreciation to all members and the Government of Slovenia for their hospitality while Mr. Charles Gbedemah on behalf of the Secretariat also thanked the Government of the Netherlands for its support to the biosafety programme in general and the risk assessment process in particular.

ITEM 5. ADOPTION OF THE FINAL REPORT OF THE AHTEG

42. The present final report was adopted by the Group on 23 April 2010.

ITEM 6. CLOSURE OF THE MEETING

43. The meeting was closed at 8:30 p.m. on Friday, 23 April 2010.

[3] UNEP/CBD/BS/AHTEG-RA&RM/2/2.

Annex I

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Annex II

ACTIVITIES CARRIED OUT BY THE AD HOC TECHNICAL EXPERT GROUP ON RISK ASSESSMENT AND RISK MANAGEMENT

Activity	Date / Location
First Meeting of the Ad Hoc Technical Expert Group (AHTEG) on Risk Assessment and Risk Management (report available at http://www.cbd.int/doc/meetings/bs/bsrarm-01/official/bsrarm-01-03-en.doc)	20 – 24 April 2009, Montreal, Canada
Meeting of the AHTEG Bureau	24 April 2009, Montreal, Canada
Online discussions within the AHTEG Sub-working Groups for further drafting of the guidance documents (transcripts available at http://bch.cbd.int/onlineconferences/ahteg_ra.shtml)	May – June 2009
Teleconference of the AHTEG Bureau	24 July 2009
Online discussions within the AHTEG Sub-working Groups for further drafting of the guidance documents and testing of the Roadmap (transcripts available at http://bch.cbd.int/onlineconferences/ahteg_ra.shtml)	August – October 2009
Progress reports on the work of the AHTEG Sub-working Groups	October 2009
Meetings of the AHTEG Sub-working Group on the Roadmap and AHTEG Bureau	12 – 14 October 2009, The Hague, Netherlands
Online discussions within the AHTEG Sub-working Groups for further drafting of the guidance documents and testing of the Roadmap (transcripts available at http://bch.cbd.int/onlineconferences/ahteg_ra.shtml)	November 2009
Online discussions within the AHTEG Sub-working Groups for further drafting of the guidance documents (transcripts available at http://bch.cbd.int/onlineconferences/ahteg_ra.shtml)	January 2010
Online discussions of the AHTEG for final drafting of the guidance documents in preparation for the second AHTEG meeting (transcripts available at http://bch.cbd.int/onlineconferences/ahteg_ra.shtml)	March 2010
Teleconference of the AHTEG Bureau	7 April 2010
Preparatory meetings of the AHTEG Sub-working Groups	19 April 2010, Ljubljana, Slovenia
Second Meeting of the Ad Hoc Technical Expert Group (this report)	20-23 April 2010, Ljubljana, Slovenia

Annex III

GUIDANCE ON RISK ASSESSMENT OF LIVING MODIFIED ORGANISMS

This document was developed by the Ad Hoc Technical Expert Group (AHTEG) on Risk Assessment and Risk Management under the Cartagena Protocol on Biosafety.[1/]

This is intended to be a **"**living document**"** that will be improved with time as new experience becomes available and new developments in the field of applications of living modified organisms (LMOs) occur, as and when mandated by the Parties to the Cartagena Protocol on Biosafety.

PART I:

ROADMAP FOR RISK ASSESSMENT OF LIVING MODIFIED ORGANISMS

This "Roadmap" provides an overview of the process of environmental risk assessment for a living modified organism (LMO) in accordance with Annex III [2/] to the Cartagena Protocol on Biosafety (hereinafter "the Protocol") and all other articles related to risk assessment. This Roadmap was developed in response to decision BS-IV/11 [3/] of the Conference of the Parties serving as the meeting of the Parties to the Protocol (COP-MOP). Annex III is the basis of the Roadmap. Accordingly, this Roadmap is a guidance document and does not replace Annex III. The overall aim of the Roadmap is facilitating and enhancing the effective use of Annex III by elaborating the technical and scientific process of how to apply the steps and points to consider in the process of risk assessment.

The purpose of this Roadmap is to provide further guidance on using Annex III with additional background material and links to useful references relevant to risk assessment. The Roadmap may be useful as a reference for risk assessors when conducting or reviewing risk assessments and in capacity building activities.

The Roadmap applies to all types of LMOs [4/] and their intended uses within the scope and objective of the Protocol, and in accordance with Annex III. However, it has been developed based largely on living modified crop plants because of the extensive experience to date with environmental risk assessments for these organisms. It is intended to be a "living document" that will be modified and improved on over time as and when mandated by COP-MOP, and in the light of new experience, information and developments in the field of applications of LMOs, e.g. when other types of LMOs have been evaluated more extensively in environmental risk assessments.

1/ The AHTEG on Risk Assessment and Risk Management was established by the Conference of the Parties serving as the meeting of the Parties to the Cartagena Protocol on Biosafety (COP-MOP) in its decision BS-IV/11. The terms of reference for the AHTEG as set out by the Parties may be found in the annex to decision BS-IV/11 (http://bch.cbd.int/protocol/decisions/decision.shtml?decisionID=11690).

2/ http://www.cbd.int/biosafety/articles.shtml?a=cpb-43 .

3/ http://www.cbd.int/biosafety/cop-mop/results/?id=11690 .

4/ Including products thereof, as described in paragraph 5 of Annex III to the Protocol.

INTRODUCTION

General introduction

Background

In accordance with the precautionary approach [5/] 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 LMOs 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, specifically focusing on transboundary movements".[6/]

For this purpose, Parties shall ensure that risk assessments are carried out when making informed decisions regarding LMOs.

An LMO and its use may have several effects, which may be intended or unintended, taking into account that some unintended effects may be predictable. The objective of risk assessment is to *identify* and *evaluate* the potential adverse effects of LMOs on the conservation and sustainable use of biological diversity in the likely potential receiving environment, taking also into account risks to human health.[7/] The risk assessment is performed on a case-by-case basis. What is considered an adverse effect depends on protection goals and assessment end-points taken into consideration when scoping the risk assessment. The choice of protection goals by the Party could be informed by Articles 7(a), 7(b) and 8(g) and Annex 1 of the Convention on Biological Diversity.

According to the general principles of Annex III of the Protocol, risk assessments shall be based, at a minimum, on information provided in accordance with Article 8 and other available scientific evidence in order to identify and evaluate the possible adverse effects of LMOs on the conservation and sustainable use of biological diversity, taking also into account risks to human health.[8/]

Annex III states that 'risk assessment should be carried out in a scientifically sound and transparent manner, and can take into account expert advice of, and guidelines developed by, relevant international organizations. 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.' 'Risk assessment should be carried out on a case-by-case basis. The required information may vary in nature and level of detail from case to case, depending on the LMO concerned, its intended use and the likely potential receiving environment.'[9/]

The risk assessment process

Risk assessment is a structured process. Paragraph 8 of Annex III provides a description of the key steps of the risk assessment process to identify and evaluate the potential adverse effects and manage risks. Paragraph 9 describes, depending on the case, points to consider in this process. The steps describe an integrated process whereby the results of one step may be relevant to other steps. Also, risk assessment may need to be conducted in an iterative manner, where certain steps may be repeated or re-examined to increase or re-evaluate the confidence in the conclusions of the risk assessment. When new information arises that could change its conclusions, the risk assessment may need to be re-examined accordingly. Similarly, the issues mentioned in the 'overarching issues' section below can be taken into consideration

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5/ "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" (Principle 15 of the Rio Declaration on Environment and Development, (http://www.unep.org/Documents.Multilingual/Default.asp?DocumentID=78&ArticleID=1163), and in line with Articles 10.6 and 11.8 of the Protocol.

6/ http://www.cbd.int/biosafety/articles.shtml?a=cpb-01 .

7/ Annex III, 1.

8/ Article 15, paragraph 1.

9/ Annex III, paragraphs 3, 4 and 6.

again at the end of the risk assessment process to determine whether the objectives and criteria that were set out at the beginning of the risk assessment have been met.

Risk assessment is done in a comparative manner, meaning that risks associated with living modified organisms should be considered in the context of the risks posed by the non-modified recipient organism in the likely potential receiving environment.[10/] Additionally, experience with the same, or, as appropriate, similar, genotypic or phenotypic characteristics may be taken into consideration along with the non-modified recipient organism in the risk assessment of an LMO. For instance, the comparison with the (near-)isogenic or closely related non-modified recipient is used in Step 1 of the risk assessment (see below) where the novel genotypic or phenotypic characteristics associated with the LMO are identified. But when the potential consequences of adverse effects are evaluated, broader experience, such as mentioned in Step 3 (a), may be taken into account, when establishing a baseline. Results from experimental field trials or other environmental information and experience with the same LMO may be taken into account as information elements in a new risk assessment for that LMO. In all cases where information, including baseline data, is derived from other sources, it is important to establish the validity and relevance of the information for the risk assessment. For instance, it should be taken into account that the behavior of a transgene,[11/] as that of any other gene, may vary because it depends on the genetic and physiological background of the recipient as well as on the ecological characteristics of the environment that the LMO is introduced into.

The concluding recommendations derived from the risk assessment in Step 5 are required to be taken into account in the decision-making process on an LMO. In the decision-making process, other Articles of the Protocol or other relevant issues may also be taken into account and are addressed in the last paragraph of this Roadmap: 'Issues related to decision-making'.

A flowchart illustrating the risk assessment process according to this Roadmap is annexed hereto.

(*See references relevant to "General Introduction"*).

Overarching issues in the risk assessment process

There are some overarching issues to consider in the design/planning phase of the risk assessment process to ensure the quality and relevance of the information used. These entail, among others:

- Setting criteria for relevancy in the context of a risk assessment – e.g. data may be considered relevant if they can affect the outcome of the risk assessment.
- Establishment of scientifically robust criteria for the inclusion of scientific information.
    - Data should be of an acceptable scientific quality. Data quality should be consistent with the accepted practices of scientific evidence-gathering and reporting and may include independent review of the methods and designs of studies. Data may be derived from a variety of sources, e.g. new experimental data as well as data from relevant peer reviewed scientific literature.
    - Sound science is based on transparency, verifiability, and reproducibility (e.g. reporting of methods and data in sufficient detail, so that the resulting data and information could be confirmed independently), and on the accessibility of data (e.g. the availability of relevant, required data or information or, if requested and as appropriate, of sample material), taking into account the provisions of Article 21 of the Protocol on the

10/ Annex III, paragraph 5.

11/ For the purpose of this document, a transgene is 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.

confidentiality of information. The provisions of sound science serve to ensure and verify that the risk assessment is carried out in a scientifically sound and transparent manner.

- Identification and consideration of uncertainty.

  According to the Protocol, "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".[12/]

  Uncertainty is inherent in the concept of risk. To date, "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".[13/] [14/]

  It should be kept in mind that uncertainty cannot always be reduced by providing additional information. For example, new uncertainties may arise as a result of the provision of additional information.

  Considerations of uncertainty strengthen the confidence and scientific soundness of a risk assessment. In communicating the results of a risk assessment, it is important to consider and analyze in a systematic way the various forms of uncertainty that can arise at each step and in combination at Step 4 of the Roadmap. An analysis of uncertainty includes considerations of its source and nature.

  The *source(s)* of uncertainty may stem from the data/information itself and/or the choice of study design including the methods used, and the analysis of the information.

  The *nature* of uncertainty may be described for each identified source of uncertainty arising from: (i) imperfect knowledge or lack of available information, which may be reduced with more research/information, and (ii) inherent variability.

(*See references relevant to "Identification and consideration of uncertainty"*).

Context and scoping of the risk assessment

In setting the context and scope for a risk assessment, a number of aspects should be taken into consideration, as appropriate, that are specific to the Party involved and to the specific case of risk assessment. These aspects include:

- (i) Existing policies and strategies based on, for instance, regulations and the international obligations of the Party involved; (ii) Guidelines or regulatory frameworks that the Party has adopted; and (iii) Protection goals, assessment end-points, risk thresholds and management strategies. Setting the context and scope for a risk assessment that are consistent with these policies, strategies and protection goals may involve a process that includes risk assessors, decision-makers and various stakeholders prior to conducting the actual risk assessment;

12/ Annex III, paragraph 8(f).

13/ An Explanatory Guide to the Cartagena Protocol on Biosafety, paragraph 57 (http://data.iucn.org/dbtw-wpd/edocs/EPLP-046.pdf).

14/ Article 10, paragraph 6 of the Protocol: Lack of scientific certainty due to insufficient relevant scientific information and knowledge regarding the extent of the potential adverse effects of a living modified organism on the conservation and sustainable use of biological diversity in the Party of import, taking also into account risks to human health, shall not prevent that Party from taking a decision, as appropriate, with regard to the import of that living modified organism intended for direct use as food or feed, or for processing, in order to avoid or minimize such potential adverse effects.

- (i) Framing the risk assessment process; (ii) Taking into account the expected (potential) conditions of handling and use of the LMO; (iii) Taking into account customary practices and habits that could affect the protection goals or end-points; identification of relevant questions to be asked for that purpose;
- Identification of methodological and analytical requirements, including any reviewing mechanisms, that is required to achieve the objective of the risk assessment as laid down, for instance, in guidelines published or adopted by the Party that is responsible for conducting the risk assessment (i.e. typically the Party of import according to the Protocol);
- The nature and level of detail of the information required may depend on the intended use of the LMO and the likely potential receiving environment. For small scale field releases, especially at early experimental stages, less information may be available compared to the information available for large scale environmental release, and for commercial scale planting;
- Experience and history of use of the non-modified recipient, taking into account its ecological function;[15/] and
- Establishing criteria for describing the level of the (potential) environmental adverse effects of LMOs, as well as criteria for the terms that are used to describe the levels of likelihood (Step 2), the magnitude of consequences (Step 3) and risks (Step 4) and the manageability of risks (Step 5; see risk assessment steps below).

(*See references relevant to "Context and scoping of the risk assessment"*).

THE RISK ASSESSMENT

To fulfill its objective under Annex III, as well as other relevant Articles of the Protocol, risk assessment is performed in five steps, as appropriate. These five steps are indicated in Paragraph 8 (a)-(e) of Annex III and also detailed below. Their titles have been taken directly from the paragraphs 8 (a)-(e) of Annex III.

For each step a rationale and points to consider are provided. Some points to consider are taken from paragraph 9 of Annex III, whereas others have been added based on generally accepted methodology of LMO risk assessment and risk management. The relevance of each point to consider will depend on the case being analyzed.

(*See references relevant to "Risk Assessment in general"*).

Step 1: "An identification of any novel genotypic and phenotypic characteristics associated with the living modified organism that may have adverse effects on biological diversity in the likely potential receiving environment, taking also into account risks to human health." [16/]

Rationale:

The purpose of this step is to identify biological changes resulting from the genetic modification(s), including any deletions, compared to the non-modified organism, and identify what, if any, changes could cause adverse effects on the conservation and sustainable use of biological diversity, taking also into account risks to human health. This step is similar to the 'hazard identification step' in other risk

15/ The term 'ecological function' (or: 'ecological services)' provided by an organism refers to the role of the organism in ecological processes. Which ecological functions or services are taken into account here will be dependent on the protection goals set for the risk assessment. For example, organisms may be part of the decomposer network playing an important role in nutrient cycling in soils or be important as a pollen source for pollinators and pollen feeders.

16/ The bold printed headings of each step are direct quotes from Annex III of the Protocol.

assessment guidance. The comparison of the LMO is performed with the non-modified recipient, or a (near-)isogenic line or, as appropriate, with a non-modified organism of the same species, taking into consideration the new trait(s) of the LMO.

In this step, scientifically plausible scenarios are identified in which novel characteristics of the LMO could give rise to adverse effects in an interaction with the likely potential receiving environment. The novel characteristics of the LMO to be considered can be genotypic or phenotypic, biological. They may be intended or unintended, predicted or unpredicted. The points to consider below provide information elements on which hazard identification can be built.

The type and level of detail of the information required in this step may vary from case to case depending on the nature of the modification of the LMO and on the scale of the intended use of the LMO. For small scale field releases, especially at early experimental stages, less information may be available and some of the resulting uncertainty may typically be addressed by risk management measures (see Step 5).

Points to consider regarding the characterization of the LMO:

(a) Relevant characteristics of the non-modified recipient (e.g. (i) its biological characteristics, in particular those that, if changed, or interacting with the new gene products or traits of the LMO, could cause changes in the behavior of the non-modified recipient in the environment in a way that may cause adverse effects; (ii) its taxonomic relationships, (iii) its origin, centers of origin and centers of genetic diversity); (iv) ecological function, and (v) as a component of biological diversity that is important for the conservation and sustainable use of the biological diversity in the context of Article 7(a) and Annex I of the Convention;

(b) Relevant characteristics of the genes and of other functional sequences, such as promoters, that have been inserted into the LMO (e.g. functions of the gene and its gene product in the donor organism with particular attention to characteristics that could cause adverse effects in the recipient);

(c) Molecular characteristics of the LMO related to the modification (e.g. (a) characteristics of the insert(s) which may include (i) gene products (intended and unintended), (ii) levels of expression, (iii) functions, (iv) insertion site in the genome of the recipient and any effects of insertion, (v) stability or integrity within the genome of the recipient; (b) (i) the transformation method, (ii) the characteristics of the vector if and, as far as it is present in the LMO, including its identity, source or origin and host range) with particular attention paid to any characteristics that are related to potential adverse effects. The availability and relevance of this information may vary according to the type of application. Characteristics related to adverse effects may also result from changed expression levels of endogenous genes due to effects of a transgene or from combinatorial effects;[17/]

(d) Consideration of genotypic (see point to consider (c) above) and phenotypic, biological changes in the LMO, either intended or unintended, in comparison with the non-modified recipient, considering those changes that could cause adverse effects. These may include changes at the transcriptional and translational level and may be due to the insert itself or to genomic changes due to the transformation or recombination processes.

Point to consider regarding the receiving environment:

(e) Characteristics of the likely potential receiving environment, in particular its attributes that are relevant to potential interactions of the LMO that could lead to adverse effects (see also

17/ For the purpose of this document, the term ‘combinatorial effects’ refers to effects that may arise from the interactions between two (or more) genes. The effects may occur at the level of gene expression, or through interactions between RNA, or among gene products. The effects may be qualitative or quantitative; quantitative effects are often referred to as resulting in antagonistic, additive or synergistic effects.

paragraph (g) below),[18/] taking into account the characteristics that are components of biological diversity;

(f) The intended scale and duration of the environmental release.

Points to consider regarding the potential adverse effects resulting from the interaction between the LMO and the receiving environment:

(g) Characteristics of the LMO in relation to the receiving environment (e.g. information on phenotypic traits that are relevant for its survival in, or its potential adverse effects on the likely receiving environment – see also paragraph (e) above);

(h) Considerations for unmanaged and managed ecosystems (such as agricultural, forest and aquaculture systems) that are relevant for the likely potential receiving environment. These include the potential for dispersal of the LMO through, for instance, seed dispersal or outcrossing within or between species, or through transfer into habitats where the LMO may persist or proliferate;

(i) Potential consequences of outcrossing and flow of transgenes from an LMO to other sexually compatible species, which could lead to introgression of the transgene(s) into the population of sexually compatible species;

(j) Effects on non-target organisms;

(k) Cumulative effects;[19/]

(l) Effects of the incidental exposure of humans to (parts of) the LMO (e.g. exposure to pollen), and the toxic or allergenic effects that may ensue;

(m) Potential adverse effects as a consequence of horizontal gene transfer (HGT) of transgenic sequences from the LMO to any other organism in the likely receiving environment. With regard to HGT to micro-organisms (including viruses), particular attention may be given to cases where the LMO is also a micro-organism; and

(n) A consideration of uncertainty arising in step 1 that may significantly impact the identification of hazards in this step (see "Identification and consideration of uncertainty" under Context and scoping of the risk assessment above).

(*See references relevant to "Step 1"*).

Step 2: "An evaluation of the likelihood of adverse effects being realized, taking into account the level and kind of exposure of the likely potential receiving environment to the living modified organism."

Rationale:

18/ Examples of relevant attributes of the receiving environment include, among others: (i) ecosystem type (e.g., agroecosystem, horticultural or forest ecosystems, soil or aquatic ecosystems, urban or rural environments); (ii) extension of dimension (small, medium, large or mixed scale); (iii) previous use/history (intensive or extensive use for agronomic purposes, natural ecosystem, or no prior managed use in the ecosystem); (iv) the geographical zone(s) in which the release is intended, including climatic and geographic conditions and the properties of soil, water and/or sediment; (v) specific characteristics of the prevailing faunal, floral and microbial communities including information on sexually compatible wild or cultivated species; and (vi) biodiversity status, including the status as centre of origin and diversity of the recipient organism and the occurrence of rare, endangered, protected species and/or species of cultural value.

19/ For the purpose of this document, the term 'cumulative effects' refers to effects that occur due to the presence of multiple LMOs in the receiving environment.

The potential adverse effects identified in Step 1 may result in risks, but this depends on the likelihood and the consequence of the effects. In order to determine and characterize the overall risk (in Step 4), the likelihood of each adverse effect being realized has to be assessed and evaluated beforehand.

One aspect to be considered is whether the receiving environment will be exposed to the LMO in such a way that the identified adverse effects may actually occur, e.g. taking into consideration the intended use of the LMO, and the expression level, dose and environmental fate of transgene products as well as plausible pathways leading to adverse effects.

Other aspects to be considered here are (i) the potential of the LMO (or its derivatives resulting from outcrossing) to spread and establish beyond the receiving environment (in particular into protected areas), and whether that could result in adverse effects; and (ii) the possibility of occurrence of adverse (e.g. toxic) effects on organisms (or on organisms other than the 'target organism' for some types of LMOs).

The levels of likelihood may be expressed, for example, by the terms 'highly likely', 'likely', 'unlikely', 'highly unlikely'. Parties may consider describing these terms and their uses in risk assessment guidelines published and/or adopted by them.

Points to consider:

(a) Information relating to the type and intended use of the LMO, including the scale and duration of the release, bearing in mind, as appropriate, user habits, patterns and agronomic practices;

(b) The relevant characteristics of the likely potential receiving environment that may experience or may be a factor in the occurrence of the potential adverse effects (see also Step 1 (e), (f) and (g)), taking into account the variability of the environmental conditions and any long-term adverse effects. Levels of expression in the LMO and persistence and accumulation in the environment (e.g. in the food chain) of substances with potentially adverse effects newly produced by the LMO, such as insecticidal proteins, toxins and allergens;

(c) Available information on the location of the release and the receiving environment (such as geographic and biogeographic information, including, as appropriate, coordinates, information on the sexually compatible species and whether they are co-localized with the LMO and whether flowering occurs at the same time, or in general, interbreeding can occur);

(d) For the case of outcrossing and outbreeding from an LMO to sexually compatible species, the considerations would include: (i) the biology of the sexually compatible species, (ii) the potential environment where the sexually compatible species may be located, (iii) the chance of introgression of the transgene into the sexually compatible species;

(e) Expected exposure to the environment where the LMO is released and means by which incidental exposure could occur at that location or elsewhere (e.g. gene flow or incidental exposure due to losses during transport and handling);

(f) A consideration of uncertainty arising in Step 2 (see "Identification and consideration of uncertainty" under Context and scoping of the risk assessment above).

(*See references relevant to "Step 2"*).

Step 3: "An evaluation of the consequences should these adverse effects be realized."

Rationale:

This step describes an evaluation of the magnitude of the consequences in the likely potential receiving environment, taking into account, among others, results of tests done under different conditions such as laboratory experiments or experimental field releases. The evaluation is comparative and should be considered in the context of the adverse effects caused by the non-modified recipient or, if more appropriate, by a near-isogenic or other non-modified organism of the same species. The evaluation may also be considered in the context of the adverse effects that occur in the environment and which are

associated with existing practices such as various agronomic practices, for example, for pest or weed management if such information is available and relevant. The evaluation of the consequence of adverse effects may be expressed as, for instance, 'major', 'intermediate', 'minor' or 'marginal'. Parties may consider describing these terms and their uses in risk assessment guidelines published and/or adopted by them.

Points to consider:

(a) Relevant experience with the consequences of existing practices with the non-modified recipient or, if more appropriate, with a non-modified organism of the same species in the likely potential receiving environment, may be useful in order to establish baselines to evaluate, for example, the consequences of (i) agricultural practices, such as the level of inter- and intra-species gene flow, dissemination of the recipient, abundance of volunteer plants in crop rotation; occurrence of pests and/or beneficial organisms such as pollinators and pest predators; or (ii) pest management, including effects on non-target organisms in pesticide applications while following accepted agronomic practices;

(b) Adverse effects which may be direct and indirect, immediate and delayed. Some of these adverse effects may result from combinatorial and cumulative effects;

(c) Results from laboratory experiments examining, *inter alia*, dose-response relationships (e.g., EC 50s, LD 50s) and from field trials evaluating, for instance, potential invasiveness;

(d) For the case of outcrossing to sexually compatible species, the possible adverse effects that may occur, after introgression, due to the expression of the transgenes in the sexually compatible species; and

(e) A consideration of uncertainty arising in step 3 that may significantly impact the evaluation of consequences should the adverse effects be realized (see "Identification and consideration of uncertainty" under Context and scoping of the risk assessment above).

(*See references relevant to "Step 3"*).

Step 4: "An estimation of the overall risk posed by the living modified organism based on the evaluation of the likelihood and consequences of the identified adverse effects being realized."

Rationale:

The purpose of this step is to determine and characterize the level of the overall risk based on the identified individual risks posed by the LMO on the conservation and sustainable use of biological diversity, taking also into account human health. The individual risks are determined on the basis of an analysis of the potential adverse effects identified in Step 1, their likelihood (Step 2) and consequences (Step 3), and also taking into consideration any relevant uncertainty that emerged in the preceding steps.

It should then be determined whether the assessed risks meet the criteria set out in the protection goals, assessment endpoints and thresholds, as established in relevant legislation of the Party or in its practice. 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 LMO in the receiving environment (see also Step 5). Description of the risk characterization may be expressed as, for instance, 'high', 'medium', 'low', 'negligible' or 'indeterminate due to uncertainty or lack of knowledge'. Parties may consider describing these terms and their uses in risk assessment guidelines published and/or adopted by them.

To date, there is no universally accepted method to estimate the overall risk but rather a number of methods are available for this purpose. The outcome of this step may be, for example, a description explaining how the estimation of the overall risk was performed.

Points to consider:

(a) The identified potential adverse effects (Step 1);

(b) The assessments of likelihood (Step 2);

(c) The evaluation of the consequences (Step 3);

(d) Any interaction between the identified individual risks;

(e) Any cumulative effect due to the presence of multiple LMOs in the receiving environment; and

(f) A consideration of uncertainty arising in this and the previous steps (see "Identification and consideration of uncertainty" under Context and scoping of the risk assessment above).

(*See references relevant to "Step 4"*).

Step 5: "A recommendation as to whether or not the risks are acceptable or manageable, including, where necessary, identification of strategies to manage these risks"

Rationale:

In this way, Step 5 provides an interface between the process of risk assessment and the process of determining whether risk management measures are necessary and, if so, which measures could be implemented to manage the risks associated with the LMO.

The evaluation of the overall risk on the basis of the identified individual risks conducted in the previous step may lead to the conclusion that the identified risks are not acceptable in relation to the established protection goals, assessement end-points and risk thresholds, also when taking into account risks posed by the non-modified recipient and its use. Then the question arises whether risk management options can be identified that have the potential to remove the identified risks or reduce their magnitude. In the process of the formulation of risk management options, the effect of the proposed options on the identified risks should be explained. The appropriate steps of the risk assessment should then be reiterated by taking into account the implementation of the risk management options to estimate the new levels of likelihood, consequence and risk and to assess if the risk management measures are appropriate and sufficient.

The issues mentioned in the 'overarching issues' section can be taken into consideration again at the end of the risk assessment process to evaluate whether the objectives and criteria that were set out at the beginning of the risk assessment have been met.

The recommendation of acceptability of risk(s) should acknowledge the previously identified uncertainties. Some uncertainties may be reduced by monitoring (e.g. checking the validity of assumptions about the ecological effects of the LMO), requests for more information, or implementing the appropriate risk management options.

The recommendation(s) as to whether or not the risks are acceptable or manageable and recommendations for risk management options are submitted for consideration in the decision-making process.

Points to consider related to the acceptability of risks:

(a) The criteria for the establishment of acceptable/unacceptable levels of risk, including those set out in national legislation or guidelines, as well as the protection goals of the Party, as identified when setting the context and scope for a risk assessment;

(b) In establishing a baseline for the comparison of the LMO, any relevant experience with the use of the non-modified recipient, and practices associated with its use in the potential receiving environment; and

(c) The feasibility of the adoption of risk management or monitoring strategies.

Points to consider related to the risk management strategies:

(d) Existing management practices, if applicable, that are in use for the non-modified recipient organism or for other organisms that require comparable risk management and that might be appropriate for the LMO being assessed, e.g. isolation distances to reduce outcrossing potential of the LMO, modifications in herbicide or pesticide management, crop rotation, soil tillage, etc.;

(e) Methods to detect and identify the LMO and their specificity, sensitivity and reliability in the context of environmental monitoring (e.g. monitoring for short- and long-term, immediate and delayed effects; specific monitoring on the basis of scientific hypotheses and supposed cause/effect relationship as well as general monitoring) including plans for appropriate contingency measures to be applied in case the results from monitoring call for them;

(f) Management options in the context of the intended use (e.g. mitigating the effect of an LMO producing insecticidal proteins by the use of refuge areas to minimize the development of resistance against these proteins).

(*See references relevant to "Step 5"*).

RELATED ISSUES

Some members of the AHTEG considered some issues to be related to risk assessment and decision-making process but outside the scope of this Roadmap. These issues were, *inter alia*:

- Risk Management (Article 16);
- Capacity-building (Article 22);
- Public Awareness and Participation (Article 23);
- Socio-economic Considerations (Article 26);
- Liability and Redress (Article 27);
- Co-existence;
- Ethical issues.

Annex

FLOWCHART FOR RISK ASSESSMENT

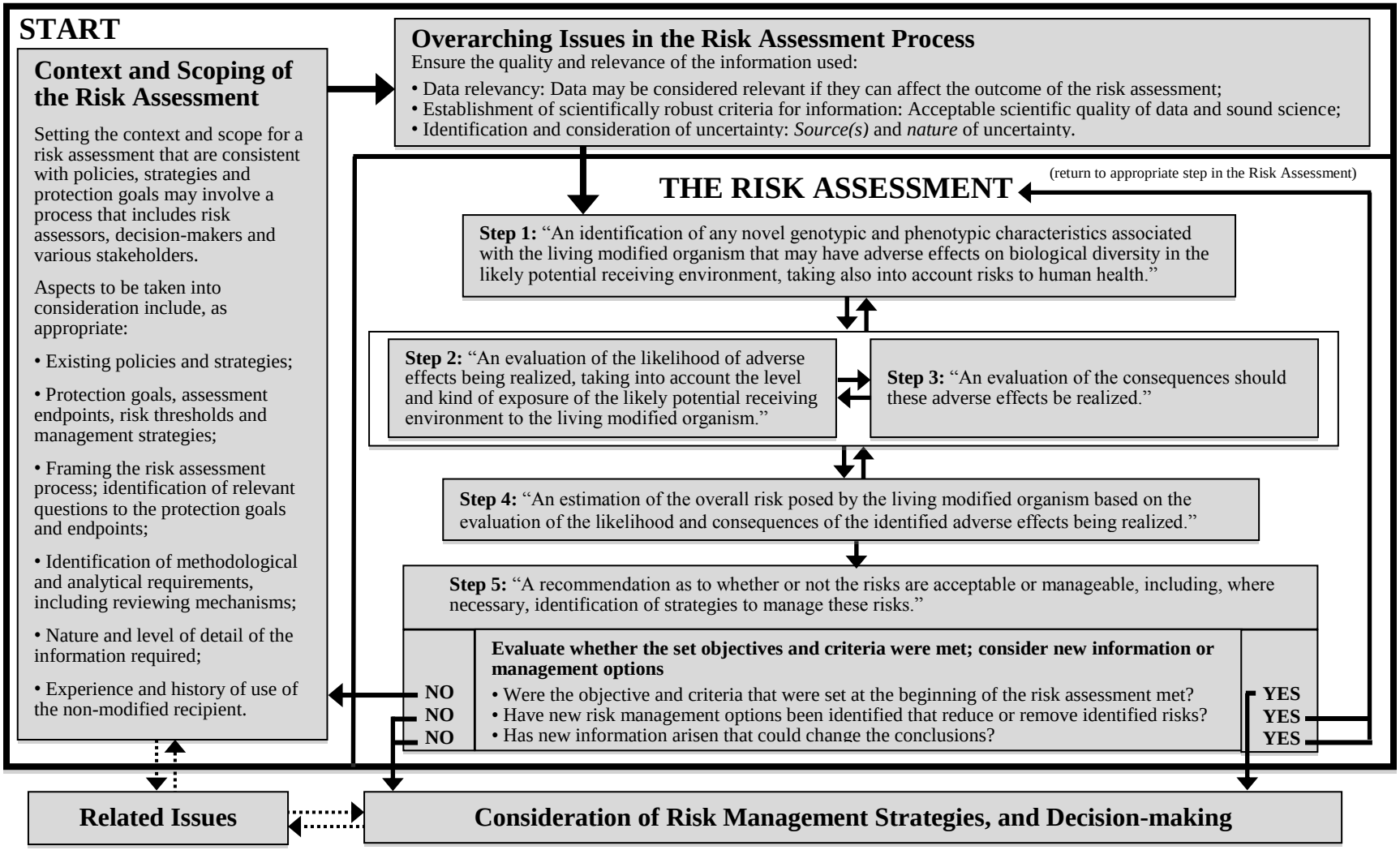

Figure 1. The Roadmap for Risk Assessment. The flowchart represents the steps to *identify* and *evaluate* the potential adverse effects of LMOs on the conservation and sustainable use of biological diversity in the likely potential receiving environment, taking also into account risks to human health. The box around steps 2 and 3 shows that these steps may sometimes be considered simultaneously or in reverse order.

PART II:

SPECIFIC TYPES OF LMOs AND TRAITS

A. RISK ASSESSMENT OF LIVING MODIFIED ORGANISMS WITH STACKED GENES OR TRAITS

INTRODUCTION

Worldwide, a growing number of LMOs with stacked transgenic traits, particularly LM crops, are being developed for commercial uses. As a result, the number of stacked genes in a single LMO and the number of LMOs with two or more transgenic traits is growing.

Stacked transgenic traits can be produced through different approaches. In addition to the cross-hybridising of two LMOs, multiple trait characters can be achieved by transformation with a multigene cassette, retransformation of an LMO or simultaneous transformation with different transgene cassettes (i.e., cotransformation).

This guidance document focuses on stacked transgenic traits that have been produced through cross-breeding of two or more LMOs.

LMOs with multiple transgenic traits resulting from re-transformation, co-transformation or transformation with a multigene cassette should be assessed according to the Roadmap.

This guidance document complements the Roadmap for Risk Assessment developed by the AHTEG on Risk Assessment and Risk Management, and focuses on issues that are of particular relevance to the risk assessment of LMOs with stacked events generated through cross breeding of single or multiple event LMO.

This is intended to be a "living document" that will be shaped and improved with time as new information and/or experience becomes available and new developments in the field of applications of LMOs occur, as and when mandated by the Parties to the Protocol.

OBJECTIVE

The objective of this document is to give additional guidance on the risk assessment (RA) of LMOs with stacked events generated through conventional crossing of single or multiple event LMOs. Accordingly, it is meant to complement the Roadmap for Risk Assessment[1/] and address special aspects of LMOs with stacked transgenes/traits resulting from the conventional crossing. For the time being it will be restricted to plant LMOs.[2/]

USE OF TERMS

Transformation event (TraEv)

1/ In accordance with a mandate from the Parties to the Cartagena Protocol on Biosafety (the Protocol), the AHTEG has developed 'a "roadmap", such as a flowchart, on the necessary steps to conduct a risk assessment in accordance with Annex III to the Protocol and, for each of these steps,' has provided 'examples of relevant guidance documents'. The Roadmap is presented, together with the present document, to the Parties of the Protocol on the occasion of the fifth meeeting of the Conference of the Parties serving as the meeting of the Parties.

2/ It is also restricted to those LMO generated through the methods of Modern Biotechnology as defined in Art. 3 (i)(a) of the Protocol. LMOs derived from fusion of cells are not covered in this document.

For the purpose of this document, a transformation event (TraEv) is an LM plant which results from the use of modern biotechnology applying *in vitro* nucleic acid techniques[3/] that may involve, but is not limited to, single or multiple gene transformation cassettes. In either case, the result will be one transformation event.

Stacked event (StaEv)

For the purpose of this document, a stacked event (StaEv) is an LM plant generated through conventional cross breeding of two or more single parental transformation events (TraEvs) or two already stacked events. Accordingly the transgene[4/] cassettes may be physically unlinked (i.e. located separately in the genome) and may segregate independently.

Unintentional stacked event

Unintentional stacked events are the result of outcrossing of stacked events into other LMOs or compatible relatives in the receiving environment. Depending on the segregation pattern of the stacked genes this may result in new and/or different combinations of TraEvs.

SCOPE

This guidance document focuses on stacked events (StaEv) resulting from conventional crossings between two or more single transformation events (TraEv) as parental lines so that the resulting LMO contains two or more transgenic traits. It is understood that the individual TraEvs making up the StaEv have been assessed previously in accordance with Annex III of the Cartagena Protocol on Biosafety and as described in the Roadmap.

ISSUES TO BE CONSIDERED IN THE RISK ASSESSMENT

Assessment of sequence characteristics at the insertion sites and genotypic stability *(see Step 1, Point to consider (c) of the Roadmap for Risk Assessment)*

Rationale:

Although recombination, mutation and rearrangements are not limited to LMOs, the combination of transgenic traits via cross breeding may further change the molecular characteristics of the inserted genes/gene fragments at the insertion site and/or influence the regulation of the expression of the transgenes. In addition, changes to the molecular characteristics may influence the ability to detect the LMO, which may be needed in the context of risk management measures (see Step 5 of the Roadmap. The reappraisal of the molecular sequence at the insertion sites, and the intactness of the transgenes may be confirmative to the molecular characteristics of the parental LMOs, but may also be a basis for assessing any intended or unintended possibly adverse effects on the conservation and sustainable use of biological diversity in the likely potential receiving environment and of potential adverse effects on human health. The extent of the reexamination may vary case by case and take into account the results of the parental LMO risk assessment.

3/ See Article 3 (i)(a) of the Protocol.

4/ For the purpose of this document, a transgene is a nucleic acid sequence that results from the application of modern biotechnology as described in Article 3(i)(a) of the Protocol.

Assessment of potential interactions between combined events and the resulting phenotypic effects *(see Step 1, Point to consider (d) of the Roadmap for Risk Assessment)*

Rationale:

The combination of two or more TraEvs resulting in a StaEv may influence the expression level of each of the transgenes and there may be interaction between the genes and the expressed products of the different transgenes. In addition, the stacked transgenes may alter the expression of endogenous genes.

Therefore, in addition to information about the characteristics of the parental single-TraEv LMOs, specific information on potential for interactions between the altered or inserted genes, stacked proteins or modified traits and endogenous genes and their products in the StaEv LMO should be considered and assessed. For example, it should be assessed whether the different transgenes affect the same biochemical pathways or physiological processes, or are expected to or may have any combinatorial effects that may result in potential for new or increased adverse effects relative to the parent LMOs.

Assessment of combinatorial and cumulative effects of stacked event LMOs on the conservation and sustainable use of biological diversity in the likely potential receiving environment, taking also into account potential adverse effects to human health *(see Step 1, Point to consider (c), Step 2, Point to consider (c) and Step 3, Point to consider (b) of the Roadmap for Risk Assessment)*

Rationale:

Assessment of combinatorial and cumulative effects[5/] is based on the environmental risk assessment data for the StaEv LMO in comparison to the closely related non-modified recipient species and the parent LMOs in the likely receiving environment, taking into consideration the results of the genotypic and phenotypic assessments outlined above.

If potential new or increased adverse effects on the conservation and sustainable use of biological diversity or on human health are identified in relation to the StaEv through the above analysis of possible interactions, additional supporting data on StaEv may be required, such as:

(i) Phenotypic characteristics, including the levels of expression of any introduced gene products or modified traits, compared to the parent LMOs and to relevant non-modified recipient organisms (plants);

(ii) Compositional analysis (e.g. levels of expression in the LMO and persistence and accumulation in the environment, such as in the food chain) of substances with potentially harmful effects newly produced by the StaEv, (e.g. insecticidal proteins, allergens, anti-nutritional factors, etc.) in amounts that differ from those produced by the parental LMOs or non-modified recipient organisms;

(iii) Additional information depending on the nature of the combined traits. For example, further toxicological analysis of the StaEv may be required to address any combinatorial effects arising from the stacking of two or more insecticidal traits that result in a broadened target range or increased toxicity.

Also, indirect effects due to changed agricultural management procedures, combined with the use of the transgenic stacked event LMO, should be taken into consideration.

Intentional and unintentional StaEvs may have altered environmental impacts as a result of cumulative and combinatorial effects of the stacked traits prevalent in different LMOs of the same species in the receiving environment. Unintentional StaEvs may arise from outcrossing with other LMOs of the same species or cross compatible relatives (see "Use of Terms"). If a number of different StaEvs are cultivated in the same environment a number of varying unintentional StaEvs may occur. Changed impacts on non-

5/ See definition of combinatorial and cumulative effects in the Roadmap (footnotes x and y, respectively).

target organisms or a change in the range of non-target organisms in the likely receiving environment should be taken into account.

Development of specific methods for distinguishing the combined transgenes in a stacked event from the parental LMOs *(see Step 5, Point to consider (d) of the Roadmap for Risk Assessment)*

Rationale:

Some of the risk management strategies for StaEvs may involve methods for the detection and identification of these LMOs in the context of environmental monitoring. Currently, many detection methods for LMOs rely on DNA-based techniques, such as polymerase chain reaction (PCR) or protein based ELISA tests targeted to single transformation events. The methods used to detect the transgene in the parental lines may not be sensitive or specific enough to differentiate between single parental transformation events and the same event being part of a stacked event. A special problem may arise particularly in the cases where the StaEv contains multiple transgenes with similar DNA sequences. Therefore, the detection of each and all individual transgenes in a StaEv may become a challenge and need special consideration.

BIBLIOGRAPHIC REFERENCES

See references relevant to the "*Guidance Document on Risk Assessment of LMOs with Stacked Genes or Traits*".

B. RISK ASSESSMENT OF LIVING MODIFIED CROPS WITH TOLERANCE TO ABIOTIC STRESS

INTRODUCTION

The aim of this document is to provide further guidance for the risk assessment of living modified (LM) crops with improved tolerance to abiotic stress.

This guidance document should be considered in the context of the Cartagena Protocol on Biosafety. The elements of Articles 15 Annex III of the Protocol also apply to LM crops with tolerance to abiotic stress. Accordingly, the methodology and points to consider[28/] contained in Annex III are also applicable to this type of LMO.

The potential environmental adverse effects of an LM crop with abiotic stress tolerance depends on (i) the receiving environment; (ii) the modified crop, (iii) phenotypic changes resulting from the genotypic changes made to the plant and (iv) its intended use. A risk assessment would be performed on a case-by-case basis in accordance with Annex III of the Protocol.

This guidance document complements the Roadmap for Risk Assessment developed by the AHTEG on Risk Assessment and Risk Management, and focuses on issues that are of particular relevance to the risk assessment of LM crops tolerant to abiotic stress.

USE OF TERMS

Abiotic stresses are environmental conditions caused by non-living factors that are detrimental or suboptimal to the growth, development and/or reproduction of a living organism. Types of abiotic stresses include, for example, drought, salinity, cold, heat, soil pollution and air pollution (e.g., nitrous oxides, ozone).

RISK ASSESSMENT

While the same general principles used in the risk assessments of other types of LMOs also apply to LM crops with increased tolerance to abiotic stress, there are a number of specific issues that may be of particular importance when assessing the risks of LM crops tolerant to abiotic stresses.

Questions that may be relevant to the risk assessment of LM crops with tolerance to abiotic stress in connection with the intended use and receiving environment include:

- Would the tolerance trait have the potential to increase the invasiveness, persistence or weediness of the LM crop that causes adverse effects to other organisms?
- Would a LM plant expressing tolerance to a particular abiotic stress have other advantages in the targeted receiving environment that cause adverse effects?
- Would any LMO arising from outcrossing with the abiotic stress tolerant LM crop, have the potential to colonize an ecosystem beyond the targeted receiving environment?
- Would the abiotic stress tolerance trait, for example, via pleitropic effects, have the potential to affect, *inter alia*, pest and disease resistance mechanisms of the LM crop?

Some of the potential adverse effects to be evaluated in the risk assessment, from the introduction of crops tolerant to abiotic stress into the environment include, for example: a) increased selective advantage(s) other than the intended tolerance trait; b) increased persistence in agricultural areas and increased invasiveness in

28/ Paragraphs 8 and 9 of Annex III, respectively.

natural habitats; c) adverse effects on organisms exposed to the crop; and d) consequences of potential gene flow to wild or conventional relatives. While these adverse effects may exist regardless of whether the tolerant crop is a product of modern biotechnology or conventional breeding, some specific issues may be more relevant in the case of abiotic stress tolerant LM crops.

Characterization of the LM crop with tolerance to abiotic stress in comparison with its non-modified crop *(see Step 1 of the Roadmap for Risk Assessment)*

Rationale:

The first step in the risk assessment process involves the characterization of genotypic or phenotypic, biological, intended and unintended changes associated with the abiotic stress tolerant LM crop that may have adverse effects on biodiversity in the likely receiving environment, taking into account risks to human health. This step is the 'hazard identification step' in other risk assessment guidance.

The identification of genotypic and phenotypic changes in the abiotic stress tolerant LM crop, either intended or unintended, is typically done in comparison with the non-modified recipient organism (see Step 1 of the Roadmap). The non-modified comparator provides the baseline information for comparison of trials when it is grown at the same time and location as the LM crop. Comparisons with the observed range of changes in the non-modified crop in different environments, also provides baseline information.

Challenges with respect to experimental design: Abiotic stress crops may present unique challenges in experimental design for risk assessment. In some cases, for instance, an approach uses different reference plant lines, which typically include a range of genotypes representative of the natural variation in the crop species. In such conditions, choosing appropriate comparators could be a challenge and there are several proposals on whether and how the comparative approach can be used to characterize LM crops tolerant to abiotic stress in these likely receiving environments. Another important consideration is whether the experimental design properly controlled for the effect of the abiotic stress trait. In the extreme case, when the non-modified crop has never been grown in the range of conditions of the receiving environment because the abiotic stress conditions prevent or severely affect the growth of the non-modified crop, a comparative approach between the LM crop and the non-modified crop will need to be adjusted.

The use of non-isogenic reference lines can make it more difficult to identify statistically meaningful differences. In some situations when a comparator may not be available to carry out a meaningful comparison, a characterization of the abiotic stress tolerant LM crop as a novel genotype in the receiving environment may be conducted. In the future, information available from "omics" technologies, for example, "transcriptomics" and "metabolomics", if available, may help to detect phenotypes (e.g., the production of a novel allergen or anti-nutrient) that cannot be detected using a comparison between field grown plants at a suboptimal condition.

Points to consider:

(a) Characteristics of the LM crop under the abiotic stress and non-stress conditions and under different stresses, if applicable;

(b) Likelihood of gene flow to wild or domestic relatives; and

(c) Whether one or more suitable comparators are available and the possibility of their use in the appropriate experimental design.

Unintended characteristics *(see Step 1 of the Roadmap for Risk Assessment)*

Rationale:

Both intended and unintended changes to the LM crop which are directly or indirectly associated with the abiotic stress tolerance that may have adverse effects should be identified. These include changes to the biology of the crop plant (e.g. if the genes alter multiple characteristics of the plant) or to its distribution range in relation to the potential receiving environment (e.g. if the plant can grow where it has not grown before), that may cause adverse effects.

The abiotic stress tolerant LM crop may have unintended characteristics such as tolerances to other types of biotic and abiotic stresses, which could lead to a selective advantage of these crop plants under conditions other than that related to the modified trait. For instance, crops modified to become tolerant to drought or salinity may be able to compete better than their counterparts at lower and higher growing temperatures.

It is also possible the LM crops with enhanced tolerance to an abiotic stress could have changes in seed dormancy, viability, and/or germination rates under other types of stresses. Particularly if genes involved in abiotic stress are also involved in crucial steps in physiology, modifications involving these genes may, therefore, have pleiotropic effects. Such LM crops may also transfer genes for stress tolerance at higher frequencies than observed in non-modified crops.

A potential mechanism for interactions between abiotic and biotic stresses may exist in plants. For example, drought or salinity-tolerant LM crops may acquire a changed tolerance to biotic stresses, which could result in changed interactions with their predators, parasitoids and pathogens, and, therefore, have both direct and indirect effects on organisms that interact with them.

Points to consider:

(a) Any intended or unintended change that may lead to selective advantage or disadvantage acquired by the LM crop under other abiotic or biotic stress conditions that could cause adverse effects;

(b) Any change in the resistance to biotic stresses and how these could affect the population of organisms interacting with the LM crop; and

(c) A change in the substances (e.g., toxin, allergen, or nutrient profile) of the LM crop that could cause adverse effects.

Increased persistency in agricultural areas and invasiveness of natural habitats *(see Steps 1, 3 and 5 of the Roadmap for Risk Assessment)*

Rationale:

Climate change, water depletion or elevated salt content are examples of factors that limit the growth, productivity, spread or persistence of a crop. Expression of the genes for abiotic stress tolerance could result in increased persistence of the modified crop in agricultural areas. Expression of these genes may also alter the capacity of LM crops to spread to and establish in climatic and geographic zones beyond those initially considered as the likely or potential receiving environments.

The gene(s) inserted for tolerance to, for instance, drought and salinity might also affect molecular response mechanisms to other forms of abiotic stress, such as cold temperatures. For example, when the genetic modification affects genes that also regulate key processes in seeds, such as abscisic acid (ABA) metabolism, physiological characteristics such as dormancy and accumulation of storage lipids may also be changed. In such cases, the seeds of a tolerant crop, modified for drought or salinity tolerance, may acquire in addition tolerance to cold resulting in an increased winter survivability of the seeds. Therefore, an abiotic stress-tolerant crop may acquire the potential to persist better than its conventional counterpart under different abiotic stress conditions.

Points to consider:

(a) Consequences of the increased potential for persistency of the modified crop in agricultural habitats and consequences of increased potential for invasiveness in natural habitats;

(b) Need for control measures if the abiotic stress-tolerant crop shows a higher potential for persistency in agricultural or natural habitats, that could cause adverse effects;

(c) Characteristics that are generally associated with weediness such as prolonged seed dormancy, long persistence of seeds in the soil, germination under a broad range of environmental conditions, rapid vegetative growth, short lifecycle, very high seed output, high seed dispersal and long-distance seed dispersal; and

(d) Effects of climate change on agriculture and biodiversity and how this could change the habitat range of the LM crop in comparison to the non modified crop.

(e) If the LM crop expressing tolerance, would have a change in its agriculture practices.

BIBLIOGRAPHIC REFERENCES

See references relevant to the "Guidance Document on Risk Assessment of LM Crops with Tolerance to Abiotic Stress".

C. RISK ASSESSMENT OF LIVING MODIFIED MOSQUITOES

INTRODUCTION

Living Modified (LM) mosquitoes are being developed through modern biotechnology to reduce transmission of vector borne human pathogens, particularly those that cause malaria, dengue and chikungunya. Control, including eradication of such diseases, is a recognized public health goal. Some of the strategies being developed are to control mosquito vectors by suppressing their population or reducing their competence. These strategies can be subcategorized according to the technology involved and the method used. Some are intended to develop LM mosquitoes that are genetically modified to be sterile or self-limiting (i.e., unable to pass the modified trait on indefinitely through subsequent generations). Modern biotechnology techniques for developing sterile LM mosquitoes are different from those based on the use of irradiation to induce male sterility.

Other modern biotechnology strategies are also being used for developing LM mosquito populations that are self-sustaining or self-propagating (i.e., heritable modifications intended to spread through the target population). The strategy used is an important factor to be considered in the risk assessment and risk management process since there might be different points to be considered, depending on the specific strategy used.

The biology and ecology of mosquitoes on the one hand, and their impact on public health as vectors of human and animal diseases on the other hand, pose new considerations and challenges during the risk assessment process, which have mainly dealt with LM crop plants thus far.

This guidance document provides information for the risk assessment of environmental releases of LM mosquitoes and aims at helping to conduct risk assessments for environmental releases of LM mosquitoes. Although the focus of this guidance is on LM mosquitoes, in principle, it may also be useful for the risk assessment of similar non-LM mosquito strategies.

The main emphasis of this guidance document is the assessment of potential risks to biodiversity. Nevertheless, the potential adverse effects to human health arising from environmental releases of LM mosquitoes should also be considered.

This guidance document complements the Roadmap for Risk Assessment developed by the AHTEG on Risk Assessment and Risk Management and focuses on specific issues that may need special consideration on the risk assessment for environmental releases of LM mosquitoes.

OBJECTIVE

The objective of this document is to give additional guidance on the risk assessment (RA) of LM mosquitoes in accordance with Annex III to the Cartagena Protocol on Biosafety.[29/] Accordingly, it aims at complementing the Roadmap for Risk Assessment on specific issues that may need special consideration for the environmental release of LM mosquitoes.

29/ The Parties to the Cartagena Protocol on Biosafety have mandated the AHTEG to ‘develop a “roadmap”, such as a flowchart, on the necessary steps to conduct a risk assessment in accordance with Annex III to the Protocol and, for each of these steps, provide examples of relevant guidance documents’. The Roadmap is meant to provide reasoned guidance on how, in practice, to apply the necessary steps for environmental risk assessment as set out in Annex III of the Protocol. The Roadmap also demonstrates how these steps are interlinked.

SCOPE

This document focuses on the specifics aspects of risk assessment of LM mosquitoes developed to be used in the control of human and zoonotic diseases such as malaria, dengue, chikungunya, yellow fever and West Nile.

ISSUES TO BE CONSIDERED IN THE RISK ASSESSMENT

(See Step 1 of the Roadmap for Risk Assessment of LMOs)

Specific and comprehensive considerations should be undertaken with respect to the potential adverse effects of a particular LM mosquito, taking into account the species of the mosquito, the LM trait, the intended receiving environment, and the objective and scale of the intended release. These considerations should focus on, for instance: (a) description of the genetic modification; (b) the kinds of possible adverse effects for which there are scientifically plausible scenarios; (c) the species and ecological processes that could be affected by the introduction of the LM mosquitoes; (d) the protection goals of the country where the LM mosquitoes will be introduced; and (e) a conceptual link between the identified protection goals and the introduction of the LM mosquito into the environment.

The biology and, to some extent, the ecology of the mosquito species that transmit malaria and dengue are well known in many regions of the world. However, in certain regions and in the environment where the LM mosquito is likely be released, more information may be needed depending on the nature and scale of the LM strategy to be deployed. In many of these environments few studies have been conducted to examine gene flow among vectors, their mating behaviour, the interactions between vectors sharing one habitat, how pathogens respond to the introduction of new vectors, etc. Such information may be needed to establish a baseline in order to successfully assess the risks of LM mosquitoes. Additionally, methods for the identification of specific ecological or environmental hazards are also needed.

Effects on biological diversity (species, habitats, ecosystems, and ecosystem services)

(*See Step 2 of the Roadmap for Risk Assessment of LMOs*)

Rationale:

The release of LM mosquitoes may have a negative impact on the target vector and pathogen[30/] and other species, such as:

New or more vigorous pests, especially those that have adverse effects on human health: (i) the released LM mosquitoes may not function as expected, for example gene silencing or production failures could result in the release of non-sterile or competent mosquitoes and thus increase the vector population or disease transmission; (ii) the released LM mosquitoes could transmit another disease more efficiently than indigenous non-LM mosquitoes, such diseases might include yellow fever, chikungunya, etc.; (iii) suppression of the target mosquito might result in the population of another vector species to increase and result in higher levels of the target disease or the development of a new disease in humans and/or animals. These other vector species may include other mosquito vectors of other diseases; (iv) the released LM mosquitoes might become pests; (v) the released LM mosquitoes might cause other pests to become more serious, including agricultural pests and other pests that affect human activities.

Harm to or loss of other species: The released LM mosquitoes might cause other species (for instance fish that rely seasonally on mosquitoes for food) to become less abundant. These include species of ecological, economic, cultural and/or social importance such as wild food, endangered, keystone, iconic and other

30/ For the purpose of this guidance, the term ‘target vector’ refers to the mosquito that transmits the disease and ‘target pathogen’ is the disease causing agent transmitted by the target mosquito.

relevant wildlife species. Ecological effects might result from competitive release if the target mosquito population is reduced or from trophic consequences of species that rely on mosquitoes for food at specific times of the year. Effects may also occur if (i) the target mosquitoes transmit a disease to animal species, (ii) the released LM mosquitoes transmit a disease to animal species more efficiently, (iii) another vector of an animal disease was released from control when the target mosquito population was reduced, or (iv) the population of a target pathogen is reduced or lost and this may affect other organisms that interact with it.

Although mosquitoes, like other insects, typically have strong reproductive isolating mechanisms that will not allow interspecific gene flow, if sterile interspecific mating between released LM mosquitoes and other mosquito species should occur, it could disrupt the population dynamics of these other species, leading to harm or loss of valued ecological species. Moreover, cessation of transmission of pathogens to other animals (e.g., West Nile virus to birds, Rift Valley fever virus to African mammals) might alter the population dynamics of those species, favouring increases in their numbers.

Disruption of ecological communities and ecosystem processes: The ecological communities in the ephemeral, small aquatic habitats occupied by the non-LM mosquitoes are unlikely to be disrupted beyond the possibilities already addressed above under "harm to or loss of other species." However, if the released LM mosquitoes were to inhabit natural habitats (e.g. tree-holes), disruption of the associated community is a possibility. The released LM mosquitoes might degrade some valued ecosystem process. This might include processes such as pollination or support of normal ecosystem functioning. These processes are often referred to as "ecosystem services". However, the valued ecosystem processes may also be culturally or socially specific. Under some circumstances, mosquito species are significant pollinators. In those cases, mosquito control of any kind might reduce the rate of pollination of some plant species or cause a shift to different kinds of pollinators. Habitats in which mosquitoes are the dominant insect fauna (e.g., high Arctic tundra, tree holes) would be changed if mosquitoes were eliminated; however, the common target vector species are usually associated with human activity and therefore not as closely tied to ecosystem services.

Points to consider:

(a) Impacts on the target mosquitoes and pathogens resulting from the use of the strategy under consideration;

(b) Whether the LM mosquitoes have the potential of causing adverse effects on other species which will result in the other species becoming agricultural, aquacultural, public health or environmental pests, or nuisance or health hazards;

(c) Whether the target mosquito species is native or invasive to a given area;

(d) The habitat range of the target mosquito species and whether the habitat range is likely to be affected by climate change;

(e) Any other species (e.g. animal hosts, larval pathogens or predators of mosquitoes) in addition to the pathogen, that typically interact with the LM mosquito in the likely receiving environment;

(f) Whether the release of LM mosquitoes is likely to affect other mosquito species that are pollinators or otherwise known to be beneficial to ecosystem processes;

(g) Whether the LM mosquitoes are likely to have an adverse effect on other interacting organisms, e.g. predators of mosquitoes;

(h) Whether species replacement by other disease vector species may occur, and if so, whether it can result in an increased incidence of the target disease or new diseases in humans or animals.

Gene Flow

(*See Steps 2 and 3 of the Roadmap for Risk Assessment of LMOs*)

Rationale:

With regard to the biosafety of LM mosquitoes, gene flow refers to the transfer of transgenes[31] or genetic elements from the LM mosquitoes to non-LM mosquitoes. It can occur via cross-fertilisation or other movement of the transgenes or genetic elements. Various factors may influence gene flow and any associated adverse effects, such as, the strategy, the transgenes, the gene drive system [32] and the stability of the trait(s) carried by the mosquito over generations, as well as the receiving environment, etc.

Gene flow through cross-fertilisation: Some LM mosquitoes are being developed to spread the introduced trait rapidly through the target mosquito population. For instance, when introduced into *Anopheles gambiae*, the trait may be expected to spread throughout the *A. gambiae* species complex. Other LM mosquito technologies are designed to be self-limiting and, in such cases, spread of the transgenes or genetic elements in the target mosquito population is not intended or expected. For the self-limiting technologies, the potential for an unexpected spread of the introduced trait should be considered by focusing on the assumption that any management strategy to limit the spread could fail. Gene flow between different species should be considered for all of the LM mosquito technologies in spite of the fact that mosquitoes, like other insects, typically have strong reproductive isolating mechanisms that will not allow interspecific gene flow. Identifying the key reproductive isolating mechanisms and possible conditions that could lead to the breakdown of such mechanisms is of particular importance in the risk assessment of LM mosquitoes with this trait. In addition, the fitness conferred by the introduced trait and the population size and frequency of the introduction of the LM mosquito into the environment will also determine the likelihood and rate of spread of the transgenes or genetic elements.

Horizontal gene flow: For the purpose of this document, "horizontal gene flow", is the movement of genetic information from one organism to another through means other than sexual transmission. Gene drive systems for moving genes into wild populations may be the initial focus of the risk assessment. The risk of horizontal gene flow in LM mosquitoes that do not contain a gene drive system is likely to be smaller but should nevertheless be assessed on a case-by-case basis.

Persistence of the transgene in the environment. Some of the transgenes in LM mosquitoes are designed not to persist whereas others are expected to spread rapidly and/or persist through wild populations. In cases where the LM mosquitoes have been found through the risk assessment process to have the potential to cause adverse effects to the biological diversity, taking also into account human health, methods to reduce the persistence of the transgene in the environment needs to be considered

Points to consider:

(a) Whether LM mosquitoes have the potential to transfer the modified traits to wild mosquito populations (when it is not an intended strategy) and/or to non-related organisms, and if so, the occurrence of any potential undesirable consequences;

(b) Whether the LM mosquitoes have the potential to induce undesirable characteristics, functions, or behaviour within the target mosquito species, other wild related species or non-related organisms;

(c) Any undesirable consequence should the transgene persist in the environment.

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[31] For the purpose of this document, a transgene is 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.

[32] Gene drive systems are methods of effectively introducing the desired gene into a mosquito population (Selfish DNA versus Vector-Borne Disease, Environmental Health Perspectives (2008) 116 - http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2235231/pdf/ehp0116-a00066.pdf).

Evolutionary responses (especially in target mosquito vectors or pathogens of humans and animals)

(*See Step 1 of the Roadmap for Risk Assessment of LMOs*)

Rationale:

Any strong ecological effect also exerts an evolutionary selection pressure on the human and animal pathogens and the mosquito vectors. The main evolutionary effects are those that could result in a breakdown in the effectiveness of the technology and the resumption of previous disease levels. Some LM mosquito strategies aim at modifying the mosquito vector's ability to transmit diseases through changes in its physiological mechanisms. An evolutionary effect resulting in the development of resistance to physiological mechanisms in the targeted pathogen might occur when modifying mosquito vector competence. This might harm the effectiveness of the strategy used and result in a population of pathogens that may be transmitted more easily by all types of vectors.

Other evolutionary effects could be hypothesized, including effects resulting from climate change, but they would first require the occurrence of some adverse effect on a species, community or ecosystem effect. Therefore, consideration of secondary evolutionary effects can be postponed until such effects are identified and found to be significant.

Points to consider:

(a) Whether the target mosquito vector has the potential to evolve and avoid population suppression, regain vector competence or acquire new or enhanced competence to another disease agent, and if so, the occurrence of any possible undesirable consequences;

(b) Whether the trait has the potential to evolve and thus lose its effectiveness, or the pathogen to evolve and overcome the limitation posed by the genetic modification, and if so, the occurrence of any possible undesirable consequences.

RISK MANAGEMENT STRATEGIES

(*See Step 5 of the Roadmap for Risk Assessment of LMOs*)

Risk assessors may want to consider risk management strategies such as the quality control of the released LM mosquitoes and monitoring them and the environment for potential unintended adverse effects. There should also be strategies in place for halting the release and application of mitigation methods if an unanticipated effect occurs. Careful implementation of the technology including the availability of mitigations measures (such as an alternative set of control measures should a problem occur) and the integration of other population control methods should be considered. In some circumstances methods to reduce the persistence of the transgene in the environment or to mitigate adverse effects resulting from the expression of the transgene might be needed. Monitoring during and after the environmental release of the LM mosquitoes so as to address prompt detection of unexpected adverse effects may also be considered.

Points to consider:

(a) Availability of monitoring methods to:

(i) Measure the efficacy and effectiveness of LM mosquito technology;

(ii) Assess the potential evolutionary breakdown of the LM mosquito technology (monitoring for transgene stability and proper function over time);

(iii) Determine the level to which the identified adverse effects may be realized, including detection of unexpected and undesirable spread of the transgenic trait (monitor for undesirable functions or behaviours within target species and other wild related species).

(b) Availability of mechanisms to recall the LM mosquitoes and transgenes in case they spread unexpectedly (e.g. mass release of wild-type mosquitoes above a certain threshold, alternative control methods including genetic control);

(c) Availability of methods for managing the dispersal of the LM mosquitoes and ensuring that they do not establish themselves beyond the intended receiving environment (eg. vegetation-free zones, traps, high threshold gene drive systems);

(d) Availability of methods to manage potential development of resistance, e.g. in the target vector or pathogen.

OTHER ISSUES

There are other factors that may be taken into consideration in the decision for environmental releases of LM mosquitoes which are not covered by Annex III of the Protocol. They encompass, *inter alia*, social, economic, cultural and health issues associated with the application and acceptance of the technology.

BIBLIOGRAPHIC REFERENCES

See references relevant to the "*Guidance Document on Risk Assessment of LM Mosquitoes*".

Annex IV

RECOMMENDATIONS TO THE CONFERENCE OF THE PARTIES SERVING AS THE MEETING OF THE PARTIES TO THE CARTAGENA PROTOCOL ON BIOSAFETY AT THE OCCASION OF ITS FIFTH MEETING IN NAGOYA, JAPAN FROM 11 TO 15 OCTOBER 2010

The Ad Hoc Technical Expert Group (AHTEG) on Risk Assessment and Risk Management took note of the deliberations under the Open-ended Online Expert Forum on Risk Assessment and Risk Management in particular about the need for further guidance on specific aspects of risk assessment and considered the existing guidance materials on risk assessment of living modified organisms.

The AHTEG recognized the importance of involving experts in the various scientific and technical fields relevant to risk assessment in any future activity taking into account the limited financial and human resources.

The following recommendations were made by the AHTEG:

(a) The document "Guidance on Risk Assessment of Living Modified Organisms" should be published and distributed, including an online version under the Biosafety Clearing-House (BCH), in all UN languages;

(b) The "Guidance on Risk Assessment of Living Modified Organisms" should be further tested for example during regional workshops including cooperation with existing initiatives for capacity building and training, as appropriate;

(c) The "Guidance on Risk Assessment of Living Modified Organisms" should be revisited within two years and the need for an update of the list of background materials should be assessed within a year;

(d) Further development of guidance on risk assessment of living modified organisms should be considered. The topics identified and prioritized during the first meeting of the AHTEG as well as those mentioned at the second meeting could be the starting point for the further development of guidance on risk assessment (see list annexed hereto as Annex V);

(e) A process should be established for the incorporation of background materials, available in the Biosafety Information Resources Centre of the Biosafety Clearing-House, that are relevant in the different sections of the "Guidance on Risk Assessment of Living Modified Organisms". In order to assist this process, the Secretariat should be requested to revise the common format for submission of records to the Biosafety Information Resources Centre (BIRC) of the BCH with the view to identifying and including a mechanism to link BIRC records on risk assessment to specific sections of the guidance document;

(f) Recognizing that the exchange of information is a central element for identifying living modified organisms or specific traits that have been assessed as having the potential to cause adverse effects on the conservation and sustainable use of biological diversity taking also into account risks to human health, a process should be established by:

(i) Urging Parties and inviting non-Parties to submit relevant information to the BCH on experiences in conducting risk assessment with regard to this topic;

(ii) Requesting the Secretariat to undertake a regular analysis of the information contained in the BCH within the context of this process and reporting to the COP-MOP for that purpose;

(iii) Organizing workshops where the information submitted would be analyzed through a guided-process;

(g) The goals of the above recommendations (a) to (f) could be achieved by a combination of an extended Open-ended Online Expert Forum on Risk Assessment and Risk Management and an AHTEG

on Risk Assessment and Risk Management, as well as a combination of online conferences, *ad hoc* discussion groups and face-to-face meetings with a view to:

(i) Developing additional guidance documents on the basis of the "Guidance on Risk Assessment of Living Modified Organisms" on specific types of living modified organisms and traits;

(ii) Reviewing the text of the "Guidance on Risk Assessment of Living Modified Organisms" and updating the lists of background materials;

(iii) Incorporating background materials, available in the Biosafety Information Resources Centre of the Biosafety Clearing-House, that are relevant to the different sections of the "Guidance on Risk Assessment of Living Modified Organisms";

(iv) Analyzing the results of the workshops on living modified organisms or specific traits that have been assessed as having the potential to cause adverse effects.

(h) Human and financial resource implications should be considered for the process set up to achieve the above goals.

Annex V

TOPICS FOR THE DEVELOPMENT OF GUIDANCE MATERIALS ON RISK ASSESSMENT

Further topics indentified in the first meeting of the AHTEG as priorities for the development of guidance: 33/

- Post-release monitoring and long-term effects of LMOs released into the environment;
- Risk assessment and risk management in specific receiving environments;
- Risk assessment of living modified microorganisms and viruses;
- Risk assessment of living modified pharmaplants;
- Risk assessment of living modified crops;
- Risk assessment of living modified trees;
- Risk assessment of living modified fish;
- Risk assessment living modified organisms for production of pharmaceutical and industrial products;
- "Co-existence" between LMOs and non-LMOs in the context of small scale farming;
- Risk assessment of living modified plants for biofuels;
- Risk assessment of living modified organisms produced through synthetic biology.

Further topics identified in the second meeting of the AHTEG as possible priorities for the development of guidance:

- Uncertainty analysis;
- Establishment of criteria for transparency and reproducibility of information;
- Interface between risk assessment and risk management;
- Environmental risk assessment and monitoring taking into account human health;
- Unintentional transboundary movements;
- Risk assessment and management of LMOs intended for introduction into unmanaged environments.

33/ Annex II of the report of the first meeting of the Ad Hoc Technical Expert Group on Risk Assessment and Risk Management (UNEP/CBD/BS/AHTEG-RA&RM/1/3).