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AD HOC TECHNICAL EXPERT GROUP ON RISK ASSESSMENT AND RISK MANAGEMENT UNDER THE CARTAGENA PROTOCOL ON BIOSAFETY
Third meeting
Mexico City, 30 May - 3 June 2011

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

INTRODUCTION

1. The third meeting of the Ad Hoc Technical Expert Group (AHTEG) on Risk Assessment and Risk Management under the Cartagena Protocol on Biosafety was held in Mexico City from 30 May to 3 June 2011.

2. The Group was established by the Conference of the Parties serving as the meeting of the Parties to the Cartagena Protocol on Biosafety in its decision BS-IV/11. The mandate of the Group was extended by the Parties to the Protocol in their subsequent decision BS-V/12.

3. In decision BS-V/12, the Group was mandated to work, primarily online and together with the Open-ended Online Forum, to: (i) revise and test the first version of the Guidance on the basis of the results of a scientific review process, the testing associated with capacity-building activities and any testing initiated by the AHTEG and organized by the Executive Secretary; and (ii) assess the overall applicability and utility of the Guidance to living modified organisms across different taxa and receiving environments, with the view to achieving the following expected outcomes:

(a) A revised version of the "Guidance on Risk Assessment of Living Modified Organisms";

(b) A mechanism, including criteria, for future updates of the lists of background materials;

(c) Further guidance on new specific topics of risk assessment, selected on the basis of the priorities and needs by the Parties and taking into account the topics identified in the previous intersessional period.

4. Eighteen participants from seventeen Parties (Austria, Belize, Brazil, China, Croatia, Cuba, Egypt, Germany, Japan, Malaysia, Mexico, Netherlands, Niger, Nigeria, Norway, Republic of Moldova and Slovenia), as well as six observers from two non-Parties (Canada and United States of America) and four organizations (Bayer CropScience, Federation of German Scientists, Monsanto Company, Public Research and Regulation Initiative) attended the meeting. AHTEG members from one Party (Nigeria), one non-Party (Australia) and two organizations (University of Canterbury, New Zealand, and Acción Ecológica, Ecuador) were unable to attend the meeting due to unforeseen circumstances. The list of participants is attached in annex IV to this report.

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ITEM 1. OPENING OF THE MEETING

5. The meeting was opened on Monday, 30 May 2010 at 9.30 a.m. by Mr. Helmut Gaugitsch (Austria), Chair of the AHTEG. The opening ceremony was also attended by Mr. Luis Alberto Lopez Carbajal, Director of the Mexican Ministry of Environment and Natural Resources (SEMARNAT) and Mr. Reynaldo Ariel Alvarez Morales, Executive Secretary of the Inter-Secretarial Commission on Biosafety of Genetically Modified Organisms (CIBIOGEM).

6. In his opening remarks, Mr. Gaugitsch welcomed the participants and thanked the Government of Mexico for its kind offer to host the meeting. He also noted the importance of the task ahead of the Group and invited the participants to provide their best technical input in achieving the expected outputs.

7. Mr. Charles Gbedemah of the Secretariat of the Convention on Biological Diversity welcomed the participants on behalf of the Executive Secretary and expressed the gratitude of the Secretariat to the Government of Mexico for hosting the meeting and to the European Union for its generous financial assistance in support of the meeting. He also complimented the members for the good work done to date and highlighted the scientific review of the "Guidance" as requested by the Parties. He noted that the results of the scientific review show that the Parties are very appreciative of the draft Guidance. He further urged the Group to continue its good work in the same fruitful and cooperative manner as exhibited in its earlier meetings.

Mr. Alvarez welcomed the members of the AHTEG to Mexico, on behalf of the Government of Mexico and the many governmental institutions to which the CIBIOGEM reported.[1] He also highlighted the importance of the task ahead of the AHTEG and the specific challenges of developing countries in balancing the precautionary approach as reaffirmed by the Cartagena Protocol with the potential offered by biotechnology.

ITEM 2. ORGANIZATIONAL MATTERS

2.1. Adoption of the agenda

8. The Group adopted the provisional agenda[2] without amendments.

2.2. Organization of work

9. The Chair noted that the meeting would focus on the three main topics highlighted in the expected outcomes as set out in the decision BS-V/12 as well as an action plan for the intersessional period for the Group. He then proposed that the Group work primarily in plenary and, if needed, in break-out groups.

10. The Chair reiterated the working guidelines as highlighted in the final report of the AHTEG to the Parties at their fifth meeting,[3] in which it was noted that the AHTEG work was a multi-stakeholder consultative process led by the Parties; in its deliberations, whenever a situation arises whereby a consensus could not be reached, a solution was to be found with the agreement by the Parties.

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[1] CIBIOGEM is composed of the Ministers of Agriculture, Livestock, Rural Development, Fisheries and Food; Environment and Natural Resources; Health, Education; Finance; Economics and the Director General of the National Council of Science and Technology.

[2] Contained in document UNEP/CBD/BS/AHTEG-RA&RM/3/1.

[3] See UNEP/CBD/BS/COP-MOP/5/12.

ITEM 3. SUBSTANTIVE ISSUES

3.1. Revision of the "Guidance on Risk Assessment of Living Modified Organisms"

11. Under this agenda item, the Chair recalled the terms of reference for the AHTEG as set out in decision BS-V/12.

12. The Chair noted that, as requested in the decision BS-IV/12 of the Parties, the Guidance was translated into all the six official United Nations languages and made available to the Parties, other Governments and relevant organizations for their scientific review between 4 February and 15 March 2011. He further explained that the scientific review was conducted by 18 Parties, two other Governments and 12 organizations, totaling 33 submissions. He also noted that the Parties were very positive in their evaluation of the Guidance.

13. The Chair also recalled that the Secretariat convened a round of online discussion groups under the Open-ended Online Forum, with participation of the AHTEG, from 28 March 2011 to 18 April 2011 on topics derived from the expected outcomes listed in paragraph 3 above. A total of 160 interventions were posted on the three topics under discussion. He noted that the comments provided a useful basis for the revision of the Guidance. He also thanked the AHTEG members who actively participated in the online discussion.

14. On the basis of the scientific review and the online discussions, the Chair described how he, in consultation with the Bureau and the Secretariat, had prepared a draft text, which had been sent to all AHTEG members on 20 May 2011, for the revision of the Guidance.

15. The Chair noted that in preparing the draft, he had attempted as much as possible to incorporate all comments. The draft, he further noted, involved some major reorganization and changes to the content but essentially ensuring that the original concepts were not lost. An attempt had also been made to improve the readability of the Guidance.

16. The Group agreed to conduct its work under agenda item 3.1 on the basis of the Chair's draft text.

17. The Group carried out its revision of the Guidance based on the Chair's draft text by going through two readings during the meeting. After the second round of comments and amendments, the Group agreed that the revised Guidance as of 3 June 2011 (contained in annex I below), would form the basis for further work through the Open-ended Online Forum during the intersessional period before the fourth meeting of the AHTEG.

18. The Chair explained that the flowchart would be revised to reflect the structural and language changes agreed upon by the Group during the meeting, and the revised flowchart would be included in the current revised version of the Guidance annexed hereto. Further discussions on the flowchart would be carried out online during the intersessional period.

19. Due to time constraints, the Group agreed that the discussions on the "Use of terms" section of the Guidance would be done online from 18 to 25 June 2011 as per action plan in annex III.

20. Further, no agreement could be reached on the contents of the section "Related issues". It was therefore agreed that this section, as was reflected at the second meeting of the AHTEG and welcomed by the Parties at their fourth meeting in Nagoya, is to be maintained in the current version of the Guidance and will be subjected to further discussion during the intersessional period.

21. The Group agreed that, when appropriate, the Guidance would be submitted to scientific editing for the attention of the sixth meeting of the Parties.

3.2. Possible mechanisms, including criteria, for future updates of the lists of background materials

22. Under agenda item 3.2, the Group was invited to consider criteria for the selection of relevant background documents to be linked to the Guidance and to propose a way forward for the revision of the current list of background materials based on the agreed criteria.

23. Following a general discussion on this topic, the Group agreed to explore a possible mechanism for the expected outcome with the following arrangement: (i) a mechanism during the period of the AHTEG, and (ii) recommendations to the Parties at their sixth meeting on a mechanism for future updates.

24. For the duration of the AHTEG mandate, and in a similar manner as was arranged during the previous AHTEG cycle, the Group agreed to maintain the responsibility of updating the list of background materials through the AHTEG Chair in consultation with the Bureau and Secretariat.

25. The Group also agreed that the Secretariat sends out a invitation to all Parties, non-Parties, relevant organizations and all users of the Biosafety Clearing-House, to submit background materials for the Guidance that may be taken into consideration by the AHTEG before the end of its mandate.

26. With reference to future updates of the background materials for the Guidance after the mandate of the AHTEG, the Group agreed on the following mechanism:

(a) The Secretariat will invite Parties, non-Parties, relevant organizations and all BCH users, on an annual basis, to update the list of proposed background materials of the Guidance.

(b) A regionally balanced group of experts (e.g. 10 experts, 2 experts per region), appointed periodically by the Parties (e.g. every 4 years) will have the responsibility of updating, rearranging or removing background materials linked to the Guidance.

(c) The group of experts will work online on the basis of proposed background materials submitted by any BCH user, specifically for this purpose, to the Biosafety Information Resource Centre of the BCH (BCH-BIRC).

(d) All documents added to the list of background materials by the group of experts will be re-validated by the same group of experts 5 years after their inclusion in the list. Documents not revalidated after five years will be initially labelled for one year as “possibly outdated” and later deleted from the list of background materials linked to the Guidance after an additional year. These documents will remain in the BIRC labelled as “previously linked to the Guidance on Risk Assessment of LMOs”.

3.3. New specific topics of risk assessment for the development of further guidance

27. Under agenda item 3.3, the Group was invited to consider the need for further guidance on new specific topics of risk assessment, selected on the basis of the priorities and needs by the Parties, taking into account the topics identified in the previous intersessional period.

28. Following some discussions, the Group agreed to develop guidance on the first two topics of the list resulting from the priority-setting exercise conducted in the Open-ended Online Forum, namely:

(a) Post-release monitoring and long-term effects of LMOs released into the environment; and

(b) Risk assessment of living modified trees.

29. The Group noted that, during its intersessional work, it will work closely with the Open-ended Online Forum in order to draw on the additional scientific expertise available in the Forum.

30. The Group also agreed on using a *modus operandi* similar to that applied in the development of guidance during the previous intersessional period including the establishment of sub-working groups. Members of the Group, depending on the topics of interest, split into two sub-working groups. Members of the Group who were not present at the meeting will be requested to select a sub-working group.

31. The two sub-working groups carried out initial discussions on the chosen two topics and developed an outline as basis for further discussion on the development of guidance.

32. Annex II below contains the composition of the the two sub-working groups and the outlines for development of the guidance.

3.4. Action plan for achieving the expected outcomes

33. Under agenda item 3.4, the Group was invited to develop an action plan for its work, primarily online and in close collaboration with the Open-ended Online Forum, in accordance with decision BS-V/12.

34. The action plan which contains a detailed summary of the activities to be followed prior to the fourth meeting of the Group is attached hereto as annex III.

ITEM 4. OTHER MATTERS

35. Mr. Charles Gbedemah, Head of the Biosafety Division of the Secretariat of the Convention on Biological Diversity, announced that the fourth meeting of the AHTEG is tentatively scheduled in May 2012, at a venue to be identified.

ITEM 5. ADOPTION OF THE REPORT

36. The present report was adopted as amended by the AHTEG on 3 June, 2011.

ITEM 6. CLOSURE OF THE MEETING

37. The meeting was closed at 7.20 p.m. on Friday, 3 June 2011.

Annex I

GUIDANCE ON RISK ASSESSMENT OF LIVING MODIFIED ORGANISMS

(Revised on 3 June 2011)

PREFACE

In accordance with the precautionary approach[1] the objective of the Protocol is "to contribute to ensuring an adequate level of protection in the field of the safe transfer, handling and use of living modified organisms resulting from modern biotechnology that may have adverse effects on the conservation and sustainable use of biological diversity, taking also into account risks to human health, specifically focusing on transboundary movements".[2] For this purpose, Parties shall ensure that ***risk assessments*** are carried out to assist in the process of making informed decisions regarding living modified organisms (LMOs).

According to Article 15 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.[3]

Annex III of the Protocol, under general principles, 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". "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".[4]

The general principles of annex III also state that "Lack of scientific knowledge or scientific consensus should not necessarily be interpreted as indicating a particular level of risk, an absence of risk, or an acceptable risk".[5]

This document was developed by the Open-ended Online Expert Forum and the Ad Hoc Technical Expert Group (AHTEG) on Risk Assessment and Risk Management in accordance with terms of reference set out by the Conference of the Parties serving as the meeting of the Parties to the Cartagena Protocol on Biosafety (COP-MOP) in its decisions BS-IV/11 and BS-V/12 in response to an identified need for

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[1] "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) at: (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.

[2] http://bch.cbd.int/protocol/text/article.shtml?a=cpb-01.

[3] Article 15, paragraph 1.

[4] Annex III, paragraphs 3 and 6.

[5] Annex III, paragraphs 4.

further guidance on risk assessment of LMOs.[6] It is intended to be a "living document" that will be modified and improved as and when mandated by the Parties to the Cartagena Protocol on Biosafety.

This Guidance consists of two parts. In part I, the Roadmap for Risk Assessment of LMOs is presented. In part II, specific guidance is provided on the risk assessment of specific types of LMOs and traits. The topics contained in Part II were identified and prioritized by the Open-ended Online Expert Forum and the AHTEG in accordance with the terms of reference in decisions BS-IV/11 and BS-V/12, and taking into account the need of Parties for additional guidance.

PART I:

ROADMAP FOR RISK ASSESSMENT OF LIVING MODIFIED ORGANISMS

BACKGROUND

This "Roadmap" provides guidance on environmental risk assessment for living modified organisms (LMOs)[7] consistent with Annex III[8] to the Cartagena Protocol on Biosafety (hereinafter "the Protocol") and all other articles related to risk assessment. Accordingly, this Roadmap does not replace, but complements Annex III. The Roadmap is meant to facilitate and enhance the effective use of Annex III by elaborating the steps and points to consider in environmental risk assessment.

The purpose of this Roadmap is to provide additional guidance on using Annex III and to point to background materials 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.

This Roadmap provides a set of information that is broadly relevant in the risk assessment of LMOs belonging to different taxa and their intended uses within the scope and objective of the Protocol in accordance with Annex III. However, it has been developed based largely on living modified (LM) crop plants because of the experience to date with environmental risk assessments has been mainly gained from these organisms.[9]

The Roadmap applies to all types of environmental releases of LMOs, including those of limited duration and scale as well as large scale releases, taking into account that the amount and type of information available and needed to support risk assessments of the different types of intentional release into the environment may vary from case to case.

INTRODUCTION

Risk assessment of LMOs is a structured process conducted in a scientifically sound manner and on a *case-by-case* basis to identify and evaluate the potential adverse effects of LMOs,[10] and their *likelihood* and *consequences* as well as a recommendation as to whether or not the risks are acceptable or manageable. This Roadmap reflects a process comprised of "Overarching Issues in the Risk Assessment Process", "Planning Phase of the Risk Assessment"; and "Conducting the Risk Assessment" as a basis for decision-making.

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[6] The Open-ended Online Expert Forum and the AHTEG on Risk Assessment and Risk Management were established by the COP-MOP in decision BS-IV/11. These groups were extended by the COP-MOP in decision BS-V/12. The terms of reference for these groups may be found in the annexes to decisions BS-IV/11 and BS-V/12 (http://bch.cbd.int/protocol/decisions/decision.shtml?decisionID=11690, http://bch.cbd.int/protocol/decisions/decision.shtml?decisionID=12325).

[7] Including products thereof, as described in paragraph 5 of Annex III to the Protocol.

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

[9] Decisions on LMOs may be found, *inter alia*, in the BCH (http://bch.cbd.int) and links to national and intergovernmental websites relevant for this purpose.

[10] Annex III, paragraph 1.

The novel combination of genetic material in an LMO may lead to environmental effects which may vary depending on the LMO itself, the environment exposed to the LMO and how the LMO is used. The effects may be intended or *unintended*, beneficial or adverse. These considerations may be similar as those for the introduction of any other organism into the environment.

What is considered an adverse effect as well as an "acceptable risk" depends on *protection goals* and *assessment endpoints*. The choice of protection goals by the Party could be informed by Annex 1 of the Convention. In addition to the environmental considerations that are the subject of this guidance, protection goals and assessment endpoints may also be based on societal and economic considerations (see Related Issues section).

Paragraph 8 of Annex III describes the key steps of the risk assessment process to identify and evaluate the potential adverse effects and to identify strategies to manage risks. The steps of risk assessment under the Protocol are similar to those used in other risk assessment frameworks. Although the terminology varies among the various approaches to risk assessment, in general terms, they comprise actions for "hazard identification", "hazard characterization", "exposure assessment", and "risk characterization".

Paragraph 9 of Annex III describes, depending on the case, points to consider in the process for LMO risk assessment.

In drawing from Annex III, the Roadmap includes five steps that 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 (see Flowchart). When new information arises or a change in circumstances has occurred that could change its conclusions, the risk assessment may need to be re-examined accordingly. Similarly, the issues mentioned in the 'Setting the context and scope' section below can be taken into consideration 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.

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: 'Related Issues'.

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

›› See references relevant to "Introduction":
http://bch.cbd.int/onlineconferences/roadmapref_ahteg_ra.shtml#introduction

OVERARCHING ISSUES IN THE RISK ASSESSMENT PROCESS

Overarching issues can be considered to ensure the quality and relevance of the information used as well as the outcome of the risk assessment. For example:

- Criteria for assessing the relevancy of the data in the context of a risk assessment – e.g. data may be considered relevant if they are linked to protections goals or assessment endpoints, contribute to the identification and evaluation of the potential adverse effects of the LMO, or can affect the outcome of the risk assessment.

- Criteria for the inclusion of scientific information.

    - Data of acceptable scientific quality should be used in the risk assessment. 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, data from relevant peer reviewed scientific literature as well as data and experience from previous risk assessments, regarded as of acceptable scientific quality, in particular for the same or

similar LMOs.[11] Sound statistical tests should be used, where appropriate, in the risk assessment and be fully described in the risk assessment report. Also, it is important to have expertise in multiple fields even when this leads to diverging or contradictory views;

- Data of acceptable scientific quality requires the reporting of data and methods used to provide this data in sufficient detail and transparency to allow independent verification and reproduction. This would include ensuring the accessibility of data by the risk assessors (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 confidentiality of information;

- Useful information can also be gained from international standards and guidelines and, in the case of LM crop plants, also from the knowledge and experience of farmers, growers, scientists, regulatory officials, and indigenous and local communities.

- Availability of experts who have the relevant technical background to conduct risk assessments.

- 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 or monitoring the living modified organism in the receiving environment".[12] The issue of uncertainty is dealt with – sometimes differently – in each international instrument incorporating precautionary measures.[13, 14]

Uncertainty is an inherent and integral element of scientific analysis and risk assessment. As such, the various forms of uncertainty should be considered and described in steps 1 to 4 of the risk assessment. In addition, when communicating the results of a risk assessment, it is important to describe, quantitatively or qualitatively, what impact uncertainty may have on the conclusions and recommendations of the risk assessment.

Considerations of uncertainty strengthen the scientific validity of a risk assessment. An analysis of uncertainty includes considerations of its source and nature and focuses on uncertainties that can have a significant impact on the conclusions of the risk assessment.

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

For each identified source of uncertainty, the *nature* of the uncertainty may be described as arising from: (i) lack of information, (ii) incomplete knowledge, and (iii) inherent variability, for example, due to heterogeneity in the population being studied.

Because in some cases more information will not necessarily contribute to a better understanding of the potential adverse effects, risk assessors should look to ensure that any further information requested will contribute to better evaluations of the risk(s). It should be taken into account that, while uncertainties originating from lack of information may be reduced by further research, uncertainties arising from incomplete knowledge or from inherent variability may be irreducible

[11] Risk assessments can be found, *inter alia*, in the BCH (http://bch.cbd.int) and ICGEB (http://rasm.icgeb.org).

[12] Annex III, paragraph 8 (f).

[13] *An Explanatory Guide to the Cartagena Protocol on Biosafety*, paragraphs 52-66 (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 the living modified organism in question (…), in order to avoid or minimize such potential adverse effects."

by additional measurements or studies. In such cases, instead of reducing uncertainty, the provision of additional information may actually give rise to new uncertainties.

In cases where the nature of the uncertainty implies that it cannot be addressed through the provision of more data during the risk assessment, it may need to be dealt with by monitoring or possibly *risk management* (see step 5).

›› See references relevant to "Identification and consideration of uncertainty":
http://bch.cbd.int/onlineconferences/roadmapref_ahteg_ra.shtml#uncertainty

PLANNING PHASE OF THE RISK ASSESSMENT

Setting the context and scope

A risk assessment carried out on a case-by-case basis starts by setting its context and scope in a way that is consistent with the country's protection goals, assessment endpoints, *risk thresholds* and *management strategies* and policies.

Setting the context and scope for a risk assessment in line with the country's policies and regulations may involve an information and consultation process of risk assessors, decision-makers and various stakeholders prior to conducting the actual risk assessment to identify which protection goals, assessment endpoints and risk thresholds may be relevant. It may also involve framing the risk assessment process and identifying questions to be asked that are relevant to the case being considered. The risk assessor should be informed of national criteria for acceptability of the risks at the outset of the process.

A number of aspects may be taken into consideration, as appropriate, that are specific to the Party involved and to the specific case of risk assessment. These aspects include:

- Existing environmental and health policies and strategies based on, for instance:
  - (i) Regulations and the international obligations of the Party involved;
  - (ii) Guidelines or regulatory frameworks that the Party has adopted; and
  - (iii) Protection goals, assessment endpoints, risk thresholds and management strategies as laid down, for instance, in the relevant legislation of the Party;
- Intended handling and use of the LMO taking into account use habits, patterns and specific practices;
- The nature and level of detail of the information that is required, which may, amongst other things, depend on the biology/ecology of the recipient organism, the intended use of the LMO and its likely *potential receiving environment*, and the scale and duration of the environmental *exposure*, e.g. whether it is for import only, field testing or for commercial use. For small scale releases, especially at early experimental stages, the nature and detail of the information that is required or available may differ as compared to the information for large scale or commercial environmental release;
- 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);
- Experience and history of use of the non-modified recipient organism, taking into account its *ecological function*; and
- Criteria for describing the level of the potential adverse effects of LMOs, as well as criteria for the terms that are used to describe the likelihood (step 2), the magnitude of consequences (step

3) and risks (step 4) and the acceptability or manageability of risks (step 5; see risk assessment steps below).

Some risk assessment approaches combine the process of setting the context and scope of the risk assessment with the identification of potential adverse effects associated with the modifications of the LMO into a single step called "Problem formulation" (see step 1).

›› See references relevant to "Setting the context and scope":
http://bch.cbd.int/onlineconferences/roadmapref_ahteg_ra.shtml#context

The choice of comparators

Risks associated with LMOs should be considered in the context of the risks posed by the non-modified recipients or parental organisms in the likely potential receiving environment.[15] The comparative approach aims at identifying changes between the LMO and its comparator that may lead to adverse effects. The choice of comparator can have large effects on the relevance, interpretation and conclusions drawn from the risk assessment process. The comparator that will be used as a basis for the comparison enables the generation of information that is consistent and relevant for the risk assessment.

Some risk assessment frameworks use a single genotype, the (near-)isogenic non-modified organism, as the primary choice of comparator.[16] In these frameworks, the comparators that are going to provide the basis for comparison are grown or live at the same time and location as the LMO under consideration.

In risk assessments where the (near-)isogenic non-modified recipient organism is used as the comparator, additional comparators may prove useful depending on the biology of the organism and types of modified traits under assessment. In practice, the (near-)isogenic non-modified organism is used in step 1 and throughout the risk assessment. When the likelihood and potential consequences of adverse effects are evaluated, broader knowledge and experience with additional comparators may also be taken into consideration, as appropriate, along with the non-modified recipient organism. Results from experimental field trials or other environmental information and experience with the same or similar LMOs may also be taken into account.

In certain cases, the (near-)isogenic non-modified comparator may not be sufficient to establish a good basis for a comparative risk assessment, such as for the risk assessment of LM plants tolerant to abiotic stress, stacked LMOs and certain LM mosquitoes (please refer to Part II of this Guidance).

In other risk assessment frameworks, the choice of an appropriate comparator depends on the specific case, the step in the risk assessment and on the questions that are being asked. In such cases, the choice of appropriate comparators will be based on the biology of the organism and types of modified traits under assessment, or on the ability to provide key information regarding the identification of harm.

CONDUCTING THE RISK ASSESSMENT

To fulfill its objective under Annex III, as well as other relevant Articles of the Protocol, risk assessment as described in Annex III is conducted in steps in an integrated process and iterative manner, as appropriate. These steps are indicated in Paragraph 8 (a)-(e) of Annex III and also described below in further detail.

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 assessed.

[15] Annex III, paragraph 5.

[16] EFSA (2011) Guidance on selection of comparators for the risk assessment of genetically modified plants and derived food and feed. Available at http://www.efsa.europa.eu/en/efsajournal/doc/2149.pdf.

›› See references relevant to "Conducting the Risk Assessment":
http://bch.cbd.int/onlineconferences/roadmapref_ahteg_ra.shtml#riskassessment

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." [17]

Rationale:

The purpose of this step is to identify potential adverse effects that may result from changes due to the genetic modification(s), including any deletions, compared to the non-modified recipient organism, and identify what, if any, of those changes could cause adverse effects on the conservation and sustainable use of biological diversity, taking also into account risks to human health.

The question that is asked in this step is what adverse effect could occur, why and how. The step is similar to the 'hazard identification step' in other risk assessment guidance, such as risk assessment of chemicals. In some other risk assessment approaches, this step is performed together with the context and scoping phase in the so-called "Problem formulation" step, which is not limited to the identification of hazards, but also takes into account making operational the protection goals and the identification of appropriate assessment endpoints.

In performing this step of the risk assessment, the difference in the concepts of "*risk*" and "*hazard*" has to be taken into account (see Use of Terms).

In this step, scientifically plausible scenarios and risk hypotheses are identified in which novel characteristics of the LMO could give rise to adverse effects in an interaction with the likely potential receiving environment. In this regard, it may be important to define a causal link or pathway between a characteristic of the LMO and a possible adverse effect,[18] otherwise the risk assessment may generate information that will not contribute to reaching a recommendation that will be useful for the decision-making process. It should be taken into account that adverse effects may be direct or indirect, immediate or delayed.

The comparison of the LMO carried out in step 1 is performed with the non-modified recipient or parental organisms in the likely potential receiving environment, taking into consideration the new trait(s) of the LMO (see 'The choice of comparators' in the chapter on 'Planning Phase').

The novel characteristics of the LMO to be considered can be described in *genotypic* or *phenotypic* terms. These include any changes in the LMO, ranging from the nucleic acid, to gene expression level to morphological changes. The novel characteristics of the LMO that may cause adverse effects may be intended or unintended, predicted or unpredicted, taking into account that an adverse effect may also be caused by, for example, changes in the expression levels of endogenous genes as a result of the genetic modification or by *combinatorial effects* of two or more genes, gene products or physiological pathways. The points to consider below provide information elements on which hazard identification can be built.

The nature 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, on its intended use, and on the scale and duration of the environmental release. For example, the information needed to conduct the risk assessment for an LMO to be intentionally released into the environment will likely differ from the information needed for an LMO to be imported for direct use as food, feed or for processing. Alternatively, different information may be available in the case of releases whose objective is to generate information for further risk assessments, such as small-scale trials, especially at early experimental stages. Likewise, in cases where the exposure of the environments to the LMO is limited, such as for some early-

[17] The bold printed headings of each step are direct quotes from Annex III of the Protocol.

[18] See also article 2, paragraph 2(b) of the Nagoya-Kuala Lumpur Supplementary Protocol on Liability and Redress (http://bch.cbd.int/protocol/NKL_text.shtml).

stage experimental releases, less information may be available or needed in performing this step of the risk assessment. The resulting uncertainty in such cases may 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 organism, such as:

(i) its biological characteristics, in particular those that, if changed or interacting with the new *gene products* or traits of the LMO, could lead to changes 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) whether it is a component of biological diversity that is important for the conservation and sustainable use of biological diversity in the context of Article 7(a) and Annex I of the Convention;

(b) Characteristics related to the transformation method, including the characteristics of the *vector* such as its identity, source or origin and host range and information on whether the transformation method results in the presence of (parts of) the vector in the LMO, including any marker genes;

(c) 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);

(d) Molecular characteristics of the LMO related to the modification, such as characteristics of the modified genetic elements; insertion site(s) and copy number of the inserts; stability, integrity and genomic organization in the recipient organism; levels of gene expression and intended and *unintended gene products*;

(e) Genotypic (see point to consider (d) above) and phenotypic 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 due to the insert itself or to genomic changes that have occurred due to transformation or recombination.

Point to consider regarding the receiving environment:

(f) The intended scale and duration of the environmental release taking into account user habits, patterns and practices;

(g) 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 paragraph (i) below),[19] taking into account the characteristics that are components of biological diversity particularly in centers of origin and genetic diversity;

[19] 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.

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

(h) Protection goals or assessment endpoints (see Planning phase, Setting the context and scope);

(i) 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 (g) above);

(j) Considerations for *unmanaged* and *managed ecosystems* concerning the use of an LMO and that are relevant for the likely potential receiving environment. These include the potential effects resulting from the use of an LMO including, for instance, changes in farm management practices, dispersal of the LMO through ways such as seed dispersal or *outcrossing* within or between species, or through transfer into habitats where the LMO may persist or proliferate, as well as effects on species distribution, food webs and changes in bio-geochemical characteristics;

(k) Potential for outcrossing and transfer of *transgenes*, via *vertical gene transfer*, from an LMO to other sexually compatible species that could lead to *introgression* of the transgene(s) into the population of sexually compatible species, and whether these would lead to adverse effects;

(l) Potential adverse effects on target and non-target organisms;

(m) Potential adverse 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; and

(n) Whether *horizontal gene transfer* of transgenic sequences from the LMO to other organisms in the likely receiving environment could occur and whether this would result in potential adverse effects. With regard to horizontal gene transfer to micro-organisms (including viruses), particular attention may be given to cases where the LMO is also a micro-organism;

(o) *Cumulative effects* with any other LMO present in the environment; and

(p) A consideration of uncertainty arising in step 1 (see "Identification and consideration of uncertainty" under the "Overarching Issues in the risk assessment process").

›› See references relevant to "Step 1":
http://bch.cbd.int/onlineconferences/roadmapref_ahteg_ra.shtml#step1

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:

In order to determine and characterize the overall risk of an LMO in Step 4, the likelihood that each of the adverse effects identified in Step 1 will potentially occur has to be assessed and evaluated.

One aspect to be considered is whether the receiving environment will be exposed to an LMO for which adverse effects have been identified 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 of a hazard leading to adverse effects. In determining the route of exposure to the LMO being assessed or its products, if possible, the causality between the LMO and the potential adverse effect should be established. This can be done by building conceptual models describing relationships between the LMO, and pathways of exposure and potential effects in the environment. For example, concerning an LMO producing a potentially toxic gene product, oral, respiratory or dermal exposure could be relevant.

Models, including conceptual ones, tested through experimental studies complemented by expert input, may be used for an assessment of the potential level and kind of exposure, combined with the use of statistical tools relevant for each case.

Examples of issues to be considered in this step include (i) the potential of the LMO (or its derivatives resulting from outcrossing) to spread and establish in and beyond the receiving environment (in particular into protected areas and centers of origin and genetic diversity), 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 (e.g. those producing insecticidal proteins).

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 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 practices. For example, in the case of field trials, the level of exposure in the receiving environment may be low due to the scale of the release, its temporary nature and the implementation of management measures;

(b) The relevant characteristics of the likely potential receiving environment that may be a factor in the occurrence of the potential adverse effects (see also step 1 (f), (g) and (i)), taking into account the variability of the environmental conditions and long-term adverse effects related to the exposure to the LMO.

(c) 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. In the case of field trials, the level of persistence and accumulation in the receiving environment may be low due to the scale of the release, its temporary nature and the implementation of management measures;

(d) Information on the location of the release and the receiving environment (such as geographic and biogeographic information, including, as appropriate, coordinates);

(e) Factors that may affect spread of the LMO, such as its reproductive ability (e.g. time to seeding, number of seed and vegetative propagules, dormancy, pollen viability), its spread by natural means (e.g. birds, wild animals, wind, water, etc);

(f) Factors that affect presence or persistence of the LMO that may lead to its establishment in the environment, such as, in the case of LM plants, lifespan, seed dormancy, ability of LM seedlings to establish amongst existing vegetation and whether they reach reproductive stage, or the ability to propagate vegetatively;

(g) When assessing the likelihood of outcrossing and *outbreeding* from the LMO to sexually compatible species, the following issues are relevant:

(i) the biology of the sexually compatible species;

(ii) the potential environment where the sexually compatible species may be located;

(iii) Introgression of the transgene into the sexually compatible species;

(iv) Persistence of the transgene in the ecosystem;

(h) Expected kind and level of exposure of the environment where the LMO is released and means by which incidental exposure could occur at that location or elsewhere (e.g. through *gene flow* or incidental exposure due to losses during transport and handling, and intentional or unintentional spread by people, such as deliberate spread, accidental spread by machinery and mixed produce); and

(i) A consideration of uncertainty arising in step 2 (see "Identification and consideration of uncertainty" under the "Overarching issues in the risk assessment process").

›› See references relevant to "Step 2":

http://bch.cbd.int/onlineconferences/roadmapref_ahteg_ra.shtml#step2

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 of the possible adverse effects, based on the risk scenarios established in step 1, paying special attention to protected areas and centres of origin and centres of genetic diversity, and taking into account protection goals and endpoints of the country where the risk assessment is being carried out. The use of well-formulated risk hypothesis (step 1) may be helpful in assessing the consequences of potential adverse effects.

In this step, results of tests done under different conditions, such as laboratory experiments or experimental releases, may be considered. The scale of the intended use (e.g. small or commercial) should be taken into account. The evaluation can be comparative and considered in the context of the adverse effects caused by the (near-)isogenic non-modified recipient organism, other non-modified organisms of the same species or other comparators (see Planning Phase of the Risk Assessment). 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 or the introduced management system related to the LMO (such as various agronomic practices, for example, for pest or weed management) if such information is available and relevant.

It is important to also assess in this step whether the consequence of an adverse effect is of short or long term, direct or indirect, or either reversible or irreversible.

The evaluation of the consequence of adverse effects may be expressed qualitatively or quantitatively. For instance, terms such as 'major', 'intermediate', 'minor' or 'marginal' may be used. Parties may consider describing these terms and their uses in risk assessment guidelines published or adopted by them.

Points to consider:

(a) Relevant knowledge and experience with the non-modified recipient or parental organisms in the likely potential receiving environment. This may include the effects of:

(i) agricultural practices on the level of inter- and intra-species gene flow, dissemination of the recipient, abundance of volunteer plants in crop rotation, change in abundance of pests, beneficial and other organisms such as pollinators and pest predators;

(ii) pest management affecting non-target organisms through pesticide applications or other management approaches while following accepted agronomic practices;

(iii) the behaviour of relevant wild-type populations of unmodified animal or insect species, including interactions between predators and prey, disease transmission and interaction with humans or animal species;

(b) Consequences resulting from combinatorial and cumulative effects in the likely potential receiving environment;[20]

(c) Results from laboratory experiments examining, *inter alia*, dose-response relationships (e.g., *EC50*, *LD50*), sub-chronic effects and immunogenic effects as information elements in the context of determining effects on non-target organisms, 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

[20] See "Use of terms" section.

(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 "Overarching issues in the risk assessment process" above).

›› See references relevant to "Step 3":
http://bch.cbd.int/onlineconferences/roadmapref_ahteg_ra.shtml#step3

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 individual risks that were identified on the basis of scientifically plausible scenarios and risk hypotheses and an analysis of the potential adverse effects 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.

To date, there is no universally accepted method to estimate the overall risk but rather a number of methods are available for this purpose. For example, the characterization of the overall risk often derives a best estimate of risk from multiple lines of evidence. These lines of evidence may be quantitatively weighted and combined. Risk matrixes are often used for this purpose.

A description of the risk characterization may be expressed qualitatively or quantitatively. Terms such as 'high', 'medium', 'low', 'negligible' or 'indeterminate' (e.g. due to uncertainty or lack of knowledge) have been used to characterize the overall risk of an LMO. Parties could consider describing these terms and their uses in risk assessment guidelines published or adopted by them.

The outcome of this step may include 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) Risk management options, if identified in step 5;

(e) Any interaction, such as addition or synergism, between the identified individual risks;

(f) Broader landscape considerations, including cumulative effects due to the presence of various LMOs in the receiving environment; and

(g) A consideration of uncertainty arising in this and the previous steps (see "Identification and consideration of uncertainty" under "Overarching issues in the risk assessment process" above).

›› See references relevant to "Step 4":
http://bch.cbd.int/onlineconferences/roadmapref_ahteg_ra.shtml#step4

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 step 5, risk assessors prepare a report summarizing the risk assessment process and the identified risks, and provide recommendation(s) as to whether or not the risks are acceptable or manageable and, if needed, recommendation(s) for risk management options that could be implemented to manage the risks

associated with the LMO. This recommendation could include a comparison with other existing agricultural practices as well as user habits, patterns and practices.

This step is an interface between the process of risk assessment and the process of decision-making. It requires that the risk assessor provides a recommendation as to whether or not the risks are acceptable or manageable. Whether or not to approve the LMO is up to the decision maker to decide.

The "acceptability" of risks is typically decided at a political level and may vary from country to country. On the basis of the criteria for the acceptability of risk that were identified in the planning phase of the risk assessment, a recommendation to the decision makers as to whether the overall risk posed by the LMO is acceptable or not is made in relation to established protection goals, assessment endpoints and risk thresholds, also taking into account risks posed by the non-modified recipient organism and its use.

In evaluating the acceptability of the overall risk of the LMO, a question arises as to whether risk management options can be identified that could reduce the identified risks and uncertainties. If such measures are identified, the preceding steps of the risk assessment may need to be revisited in order to evaluate how the application of the proposed risk management measures would change the outcome of the steps.

The recommendation on the acceptability of risk(s) should take into account risks associated with other existing user habits, patterns and practices and also acknowledge the identified uncertainties. For assessments associated with uncertainties, it is imperative that the difficulties encountered during the risk assessment be made transparent to the decision makers. In such cases, it may also be useful to provide an analysis of alternative management options to assist the decision makers.

Some uncertainties may be dealt with by monitoring (e.g. checking the validity of assumptions about the effects of the LMO on components of the ecosystem and environment), requests for more information, or implementing the appropriate risk management options.

Monitoring can be applied as a tool to detect unexpected and long-term adverse effects. Monitoring can also be a means to reduce uncertainty, address assumptions made during the risk assessment and to validate its conclusions on a wider (e.g. commercial) level of application and to establish a causal link or pathway between LMOs and adverse effects. Monitoring may also be used as an instrument providing for effective risk management, including the detection of adverse effects before the consequences are realized.

The issues mentioned in the 'Setting the context and scope' section may 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(s) are submitted, typically in the form of a risk assessment report, for consideration in the decision-making process.

*Points to consider related to the acceptability of risks**:***

(a) Established criteria and thresholds for the 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) Any relevant experience with the use of the non-modified recipient organism(s) used to establish *baselines* for the risk assessment, and practices associated with its use in the likely potential receiving environment;

(c) Ability to identify, evaluate and contain adverse effects as well as to take appropriate response measures;

(d) Sources and nature of the overall uncertainty identified throughout the steps of the risk assessment.

Points to consider related to the risk management strategies:

(e) 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.;

(f) 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;

(g) Management options in the context of the intended use (e.g. isolation distances to prevent outcrossing, and the use of refuge areas to minimize the development of resistance to insecticidal proteins); and

(h) The feasibility of the implementation of the proposed risk management or monitoring strategies and methods for measuring their efficacy and effectiveness.

›› See references relevant to "Step 5":
http://bch.cbd.int/onlineconferences/roadmapref_ahteg_ra.shtml#step5

RELATED ISSUES

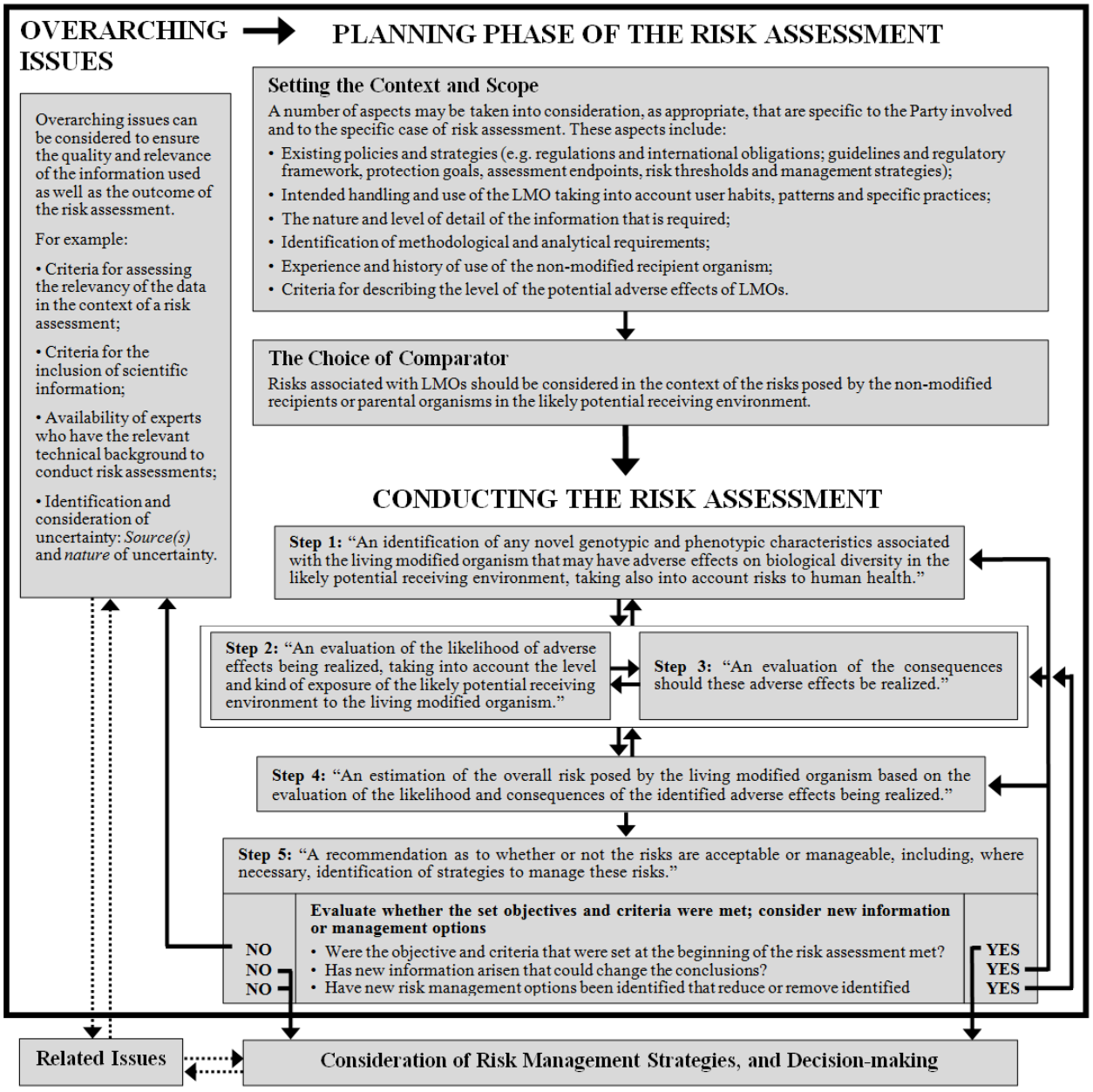
Some members of the AHTEG considered some issues to be related to the risk assessment and decision-making process but outside the scope of this Roadmap. These issues were, *inter alia*:

- 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.

559 *Annex*

560 **FLOWCHART FOR THE RISK ASSESSMENT PROCESS**

561



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564 **Figure 1. The Roadmap for Risk Assessment.** The flowchart represents the risk assessment process,
565 which includes overarching issues, a planning phase of the risk assessment and conducting the risk
566 assessment, to *identify* and *evaluate* the potential adverse effects of LMOs on the conservation and
567 sustainable use of biological diversity in the likely potential receiving environment, taking also into
568 account risks to human health. Risk assessments may need to be conducted in an iterative manner, where
569 certain steps may be repeated or re-examined as shown by the solid arrows. The box around steps 2 and 3
570 shows that these steps may sometimes be considered simultaneously or in reverse order. Dotted arrows
571 indicate the flow to and from issues outside the risk assessment process.

572

PART II

SPECIFIC TYPES OF LMOs AND TRAITS

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

INTRODUCTION

Worldwide, a growing number of LMOs with stacked transgenic traits, particularly LM plants, 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 LMOs can be produced through different approaches. In addition to the cross-breeding of two LMOs, multiple traits can be achieved by transformation with a multi-gene *transformation cassette*, retransformation of an LMO or simultaneous transformation with different transgene cassettes (i.e., co-transformation).

OBJECTIVE AND SCOPE

This guidance complements the Roadmap for Risk Assessment of LMOs giving emphasis to issues that are of particular relevance to the risk assessment of LM plants with stacked traits generated through cross breeding. As such, risk assessments of this type of LM plants also follow the general principles outlined in the Roadmap, but take into account the specific issues outlined in this section of the present document.

For the purpose of this document, a stacked event is an LMO generated through *conventional* cross-breeding involving two or more LMOs that are either single *transformation events* or already stacked events. Accordingly, the cassettes containing the transgenes and other genetic elements that were inserted in the original transformation events may be physically unlinked (i.e. located separately in the genome) and can segregate independently.

It is understood that the individual transformation events making up the stacked event have been assessed previously in accordance with Annex III of the Cartagena Protocol on Biosafety and as described in the Roadmap.

LM plants with multiple transgenic traits or genes resulting from re-transformation, co-transformation or transformation with a multi-gene transformation cassette are outside the scope of this section and should be assessed according to the Roadmap.

Likewise, the scope of this section is restricted to those LM plants generated through the methods of modern biotechnology as defined in Art. 3(i)(a) of the Protocol. LM plants derived from fusion of cells are not covered in this guidance.

This guidance also includes some considerations on unintentional stacked events as the result of natural crossings of stacked events and other LMOs or compatible relatives in the receiving environment.

PLANNING PHASE OF THE RISK ASSESSMENT

The choice of comparators *(see "Planning Phase of the Risk Assessment", "The choice of comparators" in the Roadmap)*

Rationale:

As for any other type of LMO, the risk assessment of a stacked LM plant can be done in a comparative manner. In the case of stacked LM plants, in addition to using non-modified recipient organisms as seen under "The choice of comparators" section of the Roadmap, the LMOs that were involved in the cross-breeding process leading to the stacked LM plant under consideration may also be used as comparators, as appropriate and according to national regulations.

In cases of parental LMOs that have highly heterozygous genomes or significantly differ from each other, the resulting stacked LMOs will display high variability and a vast range of phenotypes. This variability should be taken into account during the establishment of a baseline for a comparative risk assessment.

(Near-)isogenic lines to be used as comparators may be lacking which may present challenges to the interpretation of data when establishing the baseline for the risk assessment of a stacked LM plant. Therefore, in risk assessment frameworks that rely on the (near-)isogenic non-modified recipient organism as the primary comparator, it may be useful to use the closest available non-modified genotype as comparator.

Moreover, stacked LM plants produced may be the result of multiple rounds of cross-breeding among many different genotypes and possibly involve several stacked events. In such cases, choosing the appropriate comparators among the single transformation LMOs and the intermediate stacked events that gave rise to the stacked LM plant under assessment may not be a straight forward action and the choice of comparator should be justified.

Points to consider:

(a) Level of heterozygosity between the non-modified recipient organisms used to produce the parental LMOs;

(b) Phenotypic variability between non-modified hybrids produced through crosses between the non-modified recipient organisms;

(c) Number of crossings and the use of intermediate stacked LMOs as additional comparators.

CONDUCTING THE RISK ASSESSMENT

Sequence characteristics at the insertion sites, genotypic stability and genomic organization *(see "Step 1", "Point to consider (d)" in the Roadmap)*

Rationale:

Plant breeding results in changes (mutations/recombinations) within a plant's genome and this may also occur at the insertion site(s) in the LM plant. During cross-breeding, changes may occur to the molecular characteristics of the inserted genes/genetic elements at the insertion site(s) as a result of recombination, mutation and rearrangements.

As with single event LMOs, molecular characterization of the stacked LM plant may be carried out in accordance with step 1 of the Roadmap, point to consider (d). If differences in relation to the parental LMOs are found, intended and unintended possible adverse effects need to be assessed. The extent to which a molecular characterization of the stacked LMO is needed may vary case by case and should take into account the results of the risk assessment of the parental LMOs.

In addition, changes to the molecular characteristics of the transgenes and other genetic elements may influence the ability to detect the LMO, which may be needed in the context of risk management measures (see below as well as Step 5 of the Roadmap).

Transgenes with similar genetic sequences may undergo recombination, since homologous recombination acts on genomic regions that have identical or highly similar sequence. Complex inserts with multiple repeats may be less stable and could be more likely to undergo rearrangements during cross-breeding. In many cases, such changes may result in the loss of the intended phenotype.

Points to consider:

(a) Availability, specificity and sensitivity of methods to carry out a molecular characterization of the stacked LM plant;

(b) Consequences for reliability of detection methods;

(c) Phenotypic changes that may suggest changes to any of the transgenes and genetic elements present in the stacked LM plant (e.g. loss of a trait present in the parental LMOs);

(d) Whether an identified change in the sequence of the transgenes and/or genetic elements could lead to an adverse effect.

Potential interactions between combined genes and their resulting phenotypic changes and effects on the environment *(see "Step 1", "Point to consider (e)" in the Roadmap)*

Rationale:

It is possible that the crossing of two or more LMOs resulting in stacked events may influence the expression level of the transgenes or of endogenous genes through *trans-regulation*.

Changes in gene expression that may be specifically attributable to stacked events are most likely to occur if the transgenes or regulatory elements from the two parental LMOs bear similar genetic elements among themselves or to an endogenous sequence (e.g. same binding sites for transcriptional factors) and are localized in the same intracellular compartment (e.g. nucleus, chloroplast).

There may also be interactions between the expressed products of two or more transgenes and endogenous genes. This is most likely to occur if the gene products belong to the same metabolic pathway or physiological process.

Some of the interactions may lead to changes that can be detected during the phenotypic characterization of the stacked LM plant, whereas other interactions may not be detectable through a typical phenotypic characterization. Therefore, in addition to information about the characteristics of the parental LMOs, specific information on potential for interactions between the altered or inserted genes and DNA elements (e.g. promoters and other regulatory elements), proteins, metabolites or modified traits and endogenous genes and their products in the stacked LM plant should be considered and assessed.

For example, it should be assessed whether the different transgenes belong to the same biochemical pathways or physiological processes.

Points to consider:

(a) Effects of the parental LMOs on the environment;

(b) Information on transcriptional and post-transcriptional regulation of genes and their products that may be predictive of interactions between the novel and endogenous genes and/or DNA elements in the stacked LM plant;

(c) Whether transgenes of similar functions or belonging to the same metabolic pathways were stacked.

(d) Levels of expression of the transgenes compared to the parental LMOs and to the non-modified recipient organisms.

Combinatorial and cumulative effects *(see "Step 1", "Point to consider (d) and (o)", "Step 2", "Point to consider (d)" and "Step 3", "Point to consider (b)" in the Roadmap)*

Rationale:

Assessment of combinatorial and cumulative effects[21] is based on the environmental risk assessment data for the stacked event LMO in comparison to the closely related non-modified recipient organism(s) and the parental LMOs in the likely receiving environment, taking into consideration the results of the genotypic and phenotypic assessments outlined above.

Proteins and metabolites produced due to the insertion of multiple transgenes in the same stacked LM plant can interact between themselves as well as with endogenous genes and metabolic pathways. These interactions could lead to unpredicted combinatorial effects. For example, the impact on non-target organisms could be broader than the sum of the individual parental LMOs, or the evolution of resistance in target organisms (e.g. insect pests) could happen faster than in the case of single event LMOs.

Possible interactions on DNA- or RNA-level and/or between proteins and metabolites could be investigated and the potential adverse effects arising from them may be thoroughly assessed. An assessment of potential combinatorial and cumulative effects may be performed, for instance, by conducting phenotypic and compositional analyses, toxicity tests on non-target organisms and any other study that integrate these multiple and interacting factors to predict the adverse effects. Also, indirect effects due to changed agricultural management procedures, combined with the use of the transgenic stacked event LMOs, may be taken into consideration.

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 stacked event through the above analysis of possible interactions, additional supporting data on the stacked event may be required.

Points to consider:

(a) Effects of the use of pesticides, other chemicals or agricultural practices commonly used in the cultivation of the parental LMOs;

(b) Phenotypic characteristics compared to the parent LMOs and to the non-modified recipient organisms;

(c) Interactions between the stacked transgenes or their products, or interactions between the physiological pathways in which the transgenes are involved. Considerations on how these could result in potentially harmful substances (e.g. anti-nutritional factors). The possibility of persistence and accumulation of these substances in the environment, such as in the food chain;

(d) Combinatorial and cumulative effects arising from the presence of two or more insecticidal traits in the environment that could result in a broadened target range or increased toxicity.

Crossing and segregation of transgenes *(see "Step 1", "Point to consider (k)", "Step 2", "Point to consider (g)", "Step 3", "Point to consider (d)" in the Roadmap)*

Rationale:

A set of new stacked LMOs may arise in the environment through crossings between the stacked event LMOs and other LM plants or sexually-compatible non-modified relatives in the receiving environment. These crossings can be controlled (i.e. mediated by man) or uncontrolled (i.e. natural outcrossings

[21] See definition of combinatorial and cumulative effects in the "Use of Terms" section.

through pollination) and, depending on the segregation patterns, the new stacked LMOs could contain new and/or different combinations of transgenes and DNA fragments that could result in cumulative effects.

The higher the number of different sexually-compatible stacked LMOs being cultivated in the same environment, the more possible variations of new stacked events arising which contain different combinations of transgenes and DNA fragments, and the higher the probability of new unintentional stacking occurring. The considerations above should be taken into account in the context of establishing plausible risk scenarios or risk hypotheses.

Points to consider:

(a) Presence of sexually-compatible non-modified relatives and their ecological function;

(b) Presence of other single-event and stacked LMOs of the same species;

(c) Possible new combinations of transgenes and/or DNA fragments should the stacked event under consideration cross, intentionally or unintentionally, with other LMOs, stacked or not, or with non-modified relatives;

(d) Possible impacts of the new stacked events on non-target organisms or a change in the range of non-target organisms;

(e) Scientifically plausible risk scenarios or risk hypotheses involving the stacked events with different combinations of transgenes and DNA fragments.

Methods for distinguishing the combined transgenes in a stacked event from the parental LMOs *(see "Step 5", "Point to consider (f)" in the Roadmap)*

Rationale:

In the context of paragraphs 8(f) and 9(f) of Annex III of the Protocol, some of the risk management strategies for stacked events may involve methods for the detection and identification of these LM plants 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.

Several of the current PCR-based detection methods are designed to be specific for a single transformation event. While these methods may be used to detect and identify single transformation events, when the detection analysis is done in bulk (i.e. mixing material collected from various test individuals), these methods are not sensitive or specific enough to differentiate between single transformation events and a stacked event arising from a cross between these single transformation events. As such, in a bulk analysis of seeds, for example, it is not possible to tell apart a sample containing material from different transformation LMOs from another sample containing one or more stacked LM plants.

PCR-based detection methods that are specific to a single transformation event often rely on the amplification of DNA sequences that flank the insertion sites and that are unique for a single transformation event. In the future, it may become a challenge to detect single transformation events produced through site-specific insertions since the flanking sequences could be the same among different LMOs. This could become challenging particularly in cases where the stacked event contains multiple transformation cassettes with similar DNA sequences.

Based on the considerations above, the detection of each and all individual transgenes in a stacked event, if needed or required, may become a challenge and need special consideration.

Points to consider:

(a) Level of similarity/difference between different transformation constructs in the stacked LM plant;

(b) Availability and specificity of detection methods;

(c) Whether environmental monitoring strategies will be recommended at the end of the risk assessment.

BIBLIOGRAPHIC REFERENCES

See references relevant to "*Risk Assessment of LM Plants with Stacked Genes or Traits*": http://bch.cbd.int/onlineconferences/stackedref_ahteg_ra.shtml

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

BACKGROUND

This guidance should be considered in the context of the Cartagena Protocol on Biosafety. The elements of Article 15 and Annex III of the Protocol also apply to LM plants with tolerance to abiotic stress. Accordingly, the methodology and points to consider[22] contained in Annex III are also applicable to this type of LMO.

The considerations in this guidance complement the Roadmap for Risk Assessment of LMOs and aim at providing a general overview of issues that may be relevant when assessing the risks of LM plants with tolerance to abiotic stress(es).

For the purpose of this guidance, "abiotic stresses" are responses to non-living environmental factors which 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). Increased tolerance to abiotic stress has long been a target of plant breeders working towards improved crops.

INTRODUCTION

While the same general principles used in the risk assessments of other types of LMOs also apply to LM plants 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 plants tolerant to abiotic stresses.

As outlined in the section on "Context and scope" and in Step 1 of the Roadmap, identifying protection goals, assessment endpoints and establishing scientifically plausible risk scenarios are some of the first actions to be taken during a risk assessment.

A major difficulty in performing a risk assessment of an LM plant with tolerance to abiotic stress via comparative approach is the multiple interactions between the new trait and the receiving environment and the challenge to design the proper controlled field experiment.

In plants, any gene or gene combinations providing increased tolerance to some abiotic stress may have *pleiotropic effects* on the stress physiology of the plant, e.g. drought, temperature and salt stress are interconnected and plant responses to these stresses share multiple components and genes. Such pleiotropic effects may be classified as "unintended predicted effects" (see the Roadmap, step 1) and may be inferred during the risk assessment by examining the crosstalk between different stress responses of the plant and assessing if the identified changes may cause adverse effects.

The stress tolerance of the LM plant should be assessed with respect to a set of environmental conditions, capturing an appropriate range of variations that will likely be experienced, including for example the duration and periodicity of the stressor (e.g. drought, flood, suboptimal temperatures, salt or other toxic ions, etc.). These variations pose difficulties in (i) controlling/measuring these conditions in field experiments to analyze the phenotype of the LM plant and generate data for the risk assessment, and (ii) defining the phenotype of the LM plant itself, which in many cases may not be an unequivocal attribute of the LM plant but a complex relationship between external and physiological parameters.

In this context, questions that may be relevant to the risk assessment of LM plants with tolerance to abiotic stress in connection with the intended use and receiving environment include:

- Does the tolerance trait have the potential to affect other tolerance and/or resistance mechanisms of the LM plant, for example, via pleiotropic effects?
- Does the tolerance trait have the potential to increase the invasiveness, persistence or weediness

[22] Paragraphs 8 and 9 of Annex III, respectively.

of the LM plant that causes adverse effects to other organisms, food webs or habitats?

- Does an LM plant arising from outcrossing with the abiotic stress tolerant LM plant have the potential to change or colonize a habitat or ecosystem beyond the targeted receiving environment?
- Does a LM plant expressing tolerance to a particular abiotic stress have other advantages in the targeted receiving environment that could cause adverse effects?

Some of the potential adverse effects to be evaluated in the risk assessment, from the introduction of LM plants tolerant to abiotic stress into the environment may include, for example: a) increased selective advantage(s) other than the intended tolerance trait that may lead to potential adverse effects; b) increased persistence in agricultural areas and increased invasiveness in natural habitats; c) adverse effects on organisms exposed to the LM plant; and d) adverse consequences of potential gene flow to wild or conventional relatives. While these potential adverse effects may exist regardless of whether the tolerant plant is a product of modern biotechnology or conventional breeding, some specific issues may be more relevant in the case of abiotic stress tolerant LM plants.

The following sections elaborate on specific issues that may be taken into account, on a case-by-case basis, when assessing the risks of LM plants tolerant to abiotic stress and the potential adverse effects to biodiversity.

PLANNING PHASE OF THE RISK ASSESSMENT

The choice of comparators *(see "Planning Phase of the Risk Assessment", "The choice of comparators" in the Roadmap)*

Rationale:

As outlined in the Roadmap, 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 plant that may have adverse effects on biodiversity in the likely receiving environment, taking into account risks to human health.

The identification of genotypic and phenotypic changes in the abiotic stress tolerant LM plant, either intended or unintended, is typically done in comparison with the non-modified recipient organism. 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 plant. Comparisons with the observed range of changes in the non-modified plant in different environments, also provides baseline information.

The choice of the appropriate comparator(s) for the risk assessment of LM plants tolerant to abiotic stress may be challenging due to the need to evaluate the expression of the new trait(s) in a range of environmental conditions with different stressor intensities and durations.

While the comparative approach should be used to assess whether the LM plants with tolerance to abiotic stress have increased fitness advantages under non-stress conditions, additional approaches (and comparators) for risk assessment need to be implemented for assessing potential adverse effects under abiotic stress.

Challenges with respect to experimental design: LM plants with tolerance to abiotic stress may present unique challenges in the experimental designing for the 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 plant species. In such conditions, choosing appropriate comparators is challenging but an important element for characterizing LM plants tolerant to abiotic stress in the likely receiving environments.

Another important consideration is whether the experimental design is properly controlled for the effect of the abiotic stress trait. In the extreme case, when the non-modified plant cannot be 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 plant, a comparative approach between the LM plant and the non-modified plant will need to be adjusted. In such cases, non-modified varieties or distant relatives that are tolerant to abiotic stress may become useful comparators.

It is noted however that, in situations where the non-modified recipient organism, or (near-)isogenic or closely related lines cannot be used for a comparative risk assessment, the use of non-isogenic lines or distant relatives as comparators can make it more difficult to identify statistically meaningful differences.

In situations where a suitable comparator is not available to allow for a meaningful comparison to be carried out, a characterization of the abiotic stress tolerant LM plant 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 phenotypic and compositional changes (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 plant under the abiotic stress and non-stress conditions and under different stresses, if applicable; and

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

CONDUCTING THE RISK ASSESSMENT

Unintended characteristics including crosstalk between stress responses *(see "Step 1" in the Roadmap)*

Rationale:

The abiotic-stress-tolerant LM plant may have characteristics such as various levels of tolerances to other types of biotic and abiotic stresses (i.e. crosstalk), which could lead to a selective advantage of these plants under stress conditions other than that related to the modified trait. For instance, plants modified to become tolerant to drought or salinity may be able to compete better than their counterparts at lower and higher growing temperatures. These include changes to the biology of the plant species (e.g. if the genes alter multiple characteristics of the plant) or to its distribution range in relation to the likely potential receiving environment (e.g. if the plant can grow where it has not grown before) that may cause adverse effects.

It is also possible the LM plants with enhanced tolerance to an abiotic stress could have changes in seed dormancy, viability, and/or germination rates under other types of stresses. Particularly in cases where genes involved in abiotic stress are also involved in crucial steps in physiology, modifications involving these genes may have pleiotropic effects. If the stress tolerance trait leads to an increased physiological fitness, introgression of the transgenes for stress tolerance may occur at higher frequencies than observed among non-modified plants.

The response mechanisms to abiotic and biotic stresses in plants have interactions and cross-talk. For that reason, a LM plant modified to acquire drought or salinity tolerance may, for example, also acquire a changed tolerance to biotic stresses, which could result in changes in interactions with their herbivores, parasitoids and pathogens. Such crosstalk between the different types of stress-response mechanisms could, 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 plant 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 plant; and

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

Testing the LM plant in representative environments *(see "Step 1" in the Roadmap)*

Rationale:

Since LM plants with tolerance to abiotic stress are intended to be cultivated under abiotic stress conditions, it is important to consider the importance of regional aspects for the evaluation of specific characteristics and the environmental behaviour of this type of LMO as well as of its interactions with the environment. Therefore, in accordance with the general principles of Annex III to the Protocol that risk assessments should be carried out on a case-by-case basis, it is of particular importance that the assessment of potential adverse effects of LM plants with tolerance to abiotic stress be conducted in relation to the 'likely potential receiving environment' of the LM plant under consideration.

Hence, regionally differing factors that may influence the characteristics and the behaviour of the LM plant as well as its interactions with the environment should be taken into account during the risk assessment procedure. Regions and locations selected to collect data or conduct field trials should represent the range of agricultural, plant health and environmental conditions the LM plant is expected to encounter if and when a decision is taken to allow its commercial cultivation.

Different environments may be defined, for example, by the differences in flora and fauna, soil property/chemistry, agricultural practices, climatic and geographic conditions, etc. Such relevant factors of a specific region or location should be determined at the start of the risk assessment, and calls for a broad and integrative concept. This is important as these factors may lead to differences in potential adverse environmental effects which only become evident if assessed on a regional level.

Points to consider:

(a) The likely potential receiving environment where exposure to the LM plant may occur and its characteristics such as information on the location, its geographical, climatic and ecological characteristics, including relevant information on biological diversity and centres of origin;

(b) Regionally differing factors that may influence the characteristics and the behaviour of the LM plant with tolerance to abiotic stress including, for example, differences in occurrence or in the number of generations of target organisms, different agricultural practices and agronomic structures (e.g. input of nitrogen fertilizers), different cultivation systems (e.g. low-tillage farming), different crop rotation practices, different climatic conditions, different occurrence of non-target organisms as well as other abiotic and biotic conditions;

(c) Locations where field trials have been conducted to generate data for the risk assessment, if applicable, and how the conditions of the field trials represent the regionally differing factors of the likely potential receiving environment(s);

(d) Relatives which can crossbreed with the LM plant in the likely receiving environment and the possible consequences of introgressing the abiotic stress tolerance traits into these species.

Increased persistence in agricultural areas and invasiveness of natural habitats *(see "Step 1", "Step 3" and "Step 5" in the Roadmap)*

Rationale:

Climate conditions, water availability and soil salinity are examples of factors that limit the growth, productivity, spread or persistence of a plant species. Expression of the genes for abiotic stress tolerance could result in increased persistence of the modified plant in agricultural areas. Expression of these genes may also alter the capacity of LM plants to spread to and establish in climatic and geographic zones beyond those initially considered as the likely 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 plant, 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 LM plant may acquire the potential to persist better than its non-modified counterpart under different abiotic-stress conditions.

Most tolerance traits can be expected to have a "metabolic cost" associated with them – usually an energy cost which may impact the potential for the plant to persist under conditions of low selection pressure (i.e. low abiotic stress). The metabolic cost can have a significant impact on the potential of the LM plant to survive and persist in an environment over time and should be taken into account when assessing the potential of the LM plant to persist in agricultural areas and natural habitats.

Points to consider:

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

(b) Need for and the feasibility of control measures if the abiotic stress-tolerant LM plant shows a higher potential for persistence 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 plant in comparison to the non modified plant.

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

Effects on the abiotic environment and ecosystem *(see "Step 3" in the Roadmap)*

Rationale:

The cultivation of LMOs may lead to changes in the abiotic characteristics of the receiving environment, such as climate, abiotic soil fractions or gases. Changes of the abiotic environment by the use of LMOs will depend largely on the introduced trait, and may be relevant for LMOs with altered tolerance of certain environmental conditions.

The development of LM plants with tolerance to abiotic stress(es) may allow for an expansion of arable lands and cultivation of these plants in natural environments. The increase in the area of land for food

production may be harmful to the natural environment and the consequences to biodiversity should be assessed.

The cultivation of LM plants with tolerance to abiotic stress may also lead to changes in the ecosystem, for example, by allowing certain accompanying pests to breed in different ecosystems than before.

Points to consider:

(a) Changes in the geography and extension of arable lands;

(b) Agricultural practices related to the LM plant and how these may alter the abiotic environment and ecosystem;

(c) Availability of modelling tools to predict how the changes in agricultural practices due to the LM plant may affect the abiotic environment.

BIBLIOGRAPHIC REFERENCES

See references relevant to "*Risk Assessment of LM plants with Tolerance to Abiotic Stress*": http://bch.cbd.int/onlineconferences/abioticref_ahteg_ra.shtml

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 and reduction of such diseases, is a recognized public health goal. The impacts of such diseases on human health are staggering. For instance, in 2008, there were 247 million cases of malaria and nearly one million deaths.[23] Therefore, specific and comprehensive considerations should be undertaken with regard to the potential benefits and adverse effects of LM mosquitoes.

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, taking into account that virtually all these have sylvatic zoonotic reservoirs, pose specific considerations and challenges during the risk assessment process.

Two strategies of modern biotechnology, namely self-limiting and self-propagating strategies, are being developed to produce LM mosquitoes to control vector-borne diseases.

Self-limiting strategies are being developed to control mosquito vectors by suppressing their population or reducing their competence by developing LM mosquitoes that are unable to produce viable offspring.

LM mosquitoes that are developed under self-limiting strategies are intended to prevent the passage of the modified trait to subsequent generations, e.g. by interrupting larval development. Modern biotechnology techniques for the development of self-limiting LM mosquitoes populations (e.g. "Release of Insects carrying a Dominant Lethal" or RIDL) are different from those based on the use of irradiation to induce male sterility since they target behavioural sterility of female populations. Other self-limiting strategies target metabolic processes of the mosquito vectors and aim at lowering their fitness and reducing their populations.

Self-propagating strategies, also known as self-sustaining, rely on *gene-drive systems* that promote the spread and persistence of the transgene through populations of the same mosquito species. As opposed to the self-limiting strategy, the modifications in the LM mosquitoes produced through self-propagating strategies are intended to be heritable and to spread through the target population and, thus, to persist in the ecosystem at least in the medium term. The objective of the self-propagating strategies is, hence, population replacement of the non-modified mosquitoes by the LM mosquitoes.

Another strategy, the so-called paratransgenesis, is under development to control, reduce or eliminate the capacity of the mosquitoes to transmit pathogens mainly, but not exclusively, by blocking the development of the pathogen in the vector. Paratransgenesis focuses on utilizing LM symbionts of insects to express molecules within the vector that are deleterious to the pathogens they transmit. So rather than genetically modifying the mosquitoes, the focus of paratransgenesis is on the genetic modification of microorganisms that inhabit the mosquito midgut. Such microorganisms may have a specific, symbiotic relationship with the mosquito, or it may be commonly associated with the mosquito but not have an obligate relationship. Paratransgenesis can be used as a self-limiting strategy for population suppression or as a limited self-propagating strategy for population replacement (see above). It is noted that although in the case of paratransgenesis the mosquito itself will not be genetically modified, the symbionts or parasites will most likely be the product of modern biotechnology, and therefore this type of strategy is also being mentioned here.

The mosquitoes developed through the different strategies will differ, for example, in their ability to persist in the environment and to spread the inserted transgenes into the local mosquito population, or even into other organisms. Therefore, the risk assessment needs and criteria will depend on the specific characteristics of the LMO and the strategy used.

[23] WHO (2010) Malaria fact sheet. Available at http://www.who.int/mediacentre/factsheets/fs094/en/.

Since this guidance is not focused on one particular type of technology or genetic mechanism, additional and more specific guidance may be necessary when conducting the risk assessment of a particular LM mosquito depending, among other things, of the strategy used. The risk assessment of LM mosquitoes performed on a case-by-case basis may also benefit from a broader approach using laboratory and confined field tests together with mathematical modelling.

OBJECTIVE AND SCOPE

The objective of this document is to give additional guidance on the risk assessment of LM mosquitoes in accordance with Annex III to the Cartagena Protocol on Biosafety.[24] Accordingly, it complements the Roadmap for Risk Assessment of LMOs on specific issues that may need special consideration for the environmental release of LM mosquitoes.

This document focuses on the risk assessment of LM mosquitoes developed through self-limiting and self-propagating strategies to be used in the control of human and zoonotic diseases such as malaria, dengue, chikungunya, yellow fever and West Nile. Paratransgenesis is not in the scope of this guidance.

PLANNING PHASE OF THE RISK ASSESSMENT

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 and unintended receiving environment, and the objective and scale of the intended release. These considerations should focus on, for instance: (a) the kinds of possible adverse effects for which there are scientifically plausible scenarios; (b) the species as well as ecological and epidemiological processes that could be affected by the introduction of the LM mosquitoes; (c) the protection goals of the country where the LM mosquitoes will be introduced; and (d) 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 rather well known in many regions of the world. However, in certain regions and in the environment where LM mosquitoes are likely to 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.

The choice of a comparator: The line/strain used as recipient organism for transformation may serve as a comparator for the risk assessment of LM mosquitoes. The approach of using a (near-)isogenic line may be a challenge. In successive passages of the development of the LM mosquito, the parental LM strain may be an additional comparator.

[24] 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.

CONDUCTING THE RISK ASSESSMENT

Characterization of the LM mosquito *(See "Step 1" in the Roadmap)*

Rationale:

Description of the mosquito species should include its sub-species and strains, including their bio-geographical distribution, ecological niche, and capacity to transmit the pathogen and may include the use of reliable molecular markers.

Points to consider:

(a) The instability of the transgene and its spread to other organisms, or increased susceptibility of LM mosquitoes to infection by vector-borne disease pathogens.

(b) Description of the genetic modification, and the molecular characterization associated with the relevant technologies with particular attention to sequences which might influence the mobility of the insert in the mosquito (such as transposable elements);

(c) The likelihood of mutations in the transgene(s) and changes in the insertion site(s) (in the case of mobile DNAs) in response to selection in the receiving environment.

Effects on biological diversity (species, habitats, ecosystems, and ecosystem function and services) (*See "Step 2" in the Roadmap*)

Rationale:

The role of mosquitoes in natural ecosystems should be assessed, as the release of LM mosquitoes may have a negative impact on the target vector and pathogen[25] and other non-target 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 due to gene silencing or undetected failures in the development of self-limiting LM mosquitoes, which could result in the release of sexually competent mosquitoes and thus increase the vector population or disease transmission; (ii) mosquito species are currently able to transmit several pathogens from viruses to filaria to human beings and animals. An LM mosquito, in which the capacity of transmission of one of these pathogens has been modified, may have a positive effect on the transmission of other pathogens. This point should also be taken into consideration; (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 may become pests; (v) the released LM mosquitoes may cause other pests to become more serious, including agricultural pests and other pests that affect human activities. For example, the replacement of *Aedes aegypti* by *Aedes albopictus* could happen as the result of a release. Such risks should be monitored through time and at the appropriate geographical scale.

Harm to or loss of other species: The released LM mosquitoes might cause other species (for instance, birds, bats or 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 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 target pathogen's abundance is reduced or eliminated and

[25] 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.

this may affect other organisms that interact with it, for example, by altering the population of another animal that hosts the pathogen.

Mosquitoes, like other insects, typically have strong reproductive isolating mechanisms that will not allow interspecific gene flow. However, if interspecific mating between released LM mosquitoes and other mosquito species occurs, it could disrupt the population dynamics of these other 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) The natural dispersal range and seasonality of the host mosquito;

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

(c) 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;

(d) The effect of the transgene on the fitness of the LM mosquito in the receiving environment, including the areas to which the LM mosquito may spread, in particular if a self-sustaining technology is implemented;

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

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

(g) Whether the mosquito is a member of a species complex in which inter-specific mating occurs;

(h) 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;

(i) The consequences of likely mutations resulting from the mosquito interactions with other organisms in the environment and any potential changes in its response to abiotic stresses;

(j) Whether the LM mosquitoes are likely to affect other interacting organisms, e.g. predators of mosquitoes, and whether that could lead to an adverse effect, e.g. on the food chain;

(k) Whether, in the absence of the target mosquito, niche displacement by other disease vector species may occur, and if so, whether it can result in an increased incidence of the target disease or other diseases in humans or animals;

(l) Whether the transgenic mosquito has potential for natural long-distance transboundary dispersal or transport by anthropogenic activities (used tires, aircraft, ships);

(m) Whether changes in land management in the receiving environment (e.g. wetland drainage, irrigation practices) associated with the release of LM mosquitoes would result from the release of LM mosquitoes and what consequences these changes could have on biodiversity.

Vertical gene transfer (*See "Step 2" and "Step 3" in the Roadmap*)

Rationale:

For self-propagating LM mosquitoes, gene-drive systems for moving genes into wild populations may be the initial focus when assessing the risks of vertical gene transfer from LM mosquitoes to non-LM mosquitoes through cross-fertilization. The risk of vertical gene transfer in self-limiting LM mosquitoes is likely to be smaller but should nevertheless be assessed on a case-by-case basis (see below). Various factors may influence gene flow and any associated adverse effects, such as, the strategy, the transgenes, the gene-drive system and the stability of the trait(s) carried by the mosquito over generations, as well as the receiving environment, etc.

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. The likelihood and consequences of this hazard can be gauged by assessing the fitness of the transgene should the self-limiting mechanism fail to prevent spread of the transgene.

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 (dis)advantage conferred by the introduced trait to the LM mosquito and frequency of the introduction of the LM mosquito into the environment will affect its population size as well as the likelihood and rate of spread of the transgenes or genetic elements.

For self-sustaining strategies, the initial numbers of LM mosquitoes released may be small, however their persistence in the environment will provide continuing opportunities for novel interactions and mutations that may not be detected in limited trials. Although sexual sterility (cytoplasmic incompatibility) may prevent the transfer of the microorganism to some species, the risks due to rare exceptions to the normal mating pattern should 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 if so, the occurrence of any potential undesirable consequences;

(b) Whether LM mosquitoes have the potential to induce undesirable characteristics, functions or behaviour within the target mosquito species or sexually compatible species complex.

Horizontal gene transfer

Rationale:

LM mosquitoes may be associated with symbionts and/or parasites, such as microorganisms. In particular, potential adverse effects as a result of the interaction between LM mosquitoes and *Wolbachia* could be given attention because mosquitoes are currently infested by these bacteria. Horizontal gene transfer between mosquitoes and *Wolbachia* appears to occur, and *Wolbachia* seems to reduce host fitness and to hamper virus transmission, such as for the Dengue viruses. Therefore, potential adverse effects to the *Wolbachia* could change the capacity of the mosquitoes to transmit diseases.

Points to consider:

(a) Presence of symbionts and parasites in the LM mosquitoes and whether there may be exchange of genetic information between the host and the microorganism;

(b) Whether LM mosquitoes have the potential to induce undesirable characteristics, functions, or behaviour to other organisms, in particular to bacteria living in symbiosis;

(c) Nucleic acid sequences in the LM mosquito which might influence the mobility of the insert and transgenes (such as mobile elements) and that share homology with sequences in the microorganism.

Persistence of the transgene in the ecosystem (*See "Step 2", "Point to consider (f)" and "Step 3", "Point to consider (a)(iii)" and "Point to consider (b)" in the Roadmap*)

Rationale:

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 ecosystem need to be considered.

Point to consider:

(a) Any undesirable consequence should the transgene persist in the ecosystem;

(b) Methods to reduce the persistence of the transgene.

Evolutionary responses (especially in target mosquito vectors or pathogens of humans and animals) (*See "Step 1" in the Roadmap*)

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 additional 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.

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.

Unintentional transboundary movement

Rationale:

Mosquitoes, being LM or not, have very broad dissemination spectra and geographical distribution. Ensuring the containment of the LM mosquitoes to a particular receiving environment or to a country is thus unlikely. It is much more likely that the release of LM mosquitoes will result in unintentional transboundary movements between countries.

The risk of dispersal due to anthropogenic activities, such as transport and trade of potential source of breeding sites such as tyres or lucky bamboos should be considered. The consequences of water management practices, such as irrigation, sewage water treatment, on the introduced LM mosquito strains and on possible effect on the genotype and phenotype of the LM mosquito introduced should also be taken into account.

Risk management strategies (*See "Step 5" in the Roadmap*)

Rationale:

Risk assessors may consider risk management strategies such as monitoring the LM mosquitoes to ensure that the technology is functioning as intended and for monitoring the environment for potential unintended adverse effects. Strategies for halting the release and recalling the LM mosquitoes as well as mitigation methods if an unanticipated effect occurs should be considered. Careful implementation of the technology including the availability of mitigation 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.

Commonly the segregation of male mosquitoes against female mosquitoes is done at the pupal stage, according to the size of pupae. Some self-limiting strategies rely on releasing male LM mosquitoes only and require that no female LM mosquitoes are released. Understanding and measuring the reliability and failure rate of this segregation process and having quality control measures in place will be important in such cases.

Points to consider:

(a) Availability of monitoring methods to:

(i) Measure the efficacy and effectiveness of LM mosquito technology, including gene-drive systems and segregation of male LM mosquitoes;

(ii) Detect the transgene and other markers that distinguish the LM mosquito from non-LM mosquitoes in the receiving environment;

(iii) Detect the spread of the transgenes into mosquitoes strains other than the target strain, e.g. by using reliable molecular markers to distinguish the strains;

(iv) Assess the potential evolutionary long-term effects of the LM mosquito technology (monitoring for transgene stability and proper function over time);

(v) 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 or contain 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) Effectiveness and availability of conventional methods of mosquito control (e.g. insecticides, larval site destruction, trapping) to control LM and paratransgenic mosquito strains as compared to the non-modified strain;

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

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

(f) Whether the release of a LM mosquito would affect pest control activities, such as the use of personal protection and insecticides that control other vectors.

RELATED ISSUES

There are other issues 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 use of LM mosquitoes. LM mosquitoes will require broader considerations of how target-disease risk affects human behaviour, veterinary medicine, public health practices and national health priorities.

BIBLIOGRAPHIC REFERENCES

See references relevant to "*Risk Assessment of LM Mosquitoes*":

http://bch.cbd.int/onlineconferences/mosquitoesref_ahteg_ra.shtml

Annex

USE OF TERMS

This section provides a working glossary of key terms used in this document. An attempt was made to adapt definitions that are used in internationally accepted risk assessment guidances to the context of this document.

Assessment endpoint – An explicit expression of the environmental value or human condition that is to be protected, operationally defined by an entity (such as salmon or honeybees) and its attributes (such as their abundance and distribution) (adapted from IPCS, 2001, Integrated Risk Assessment, http://www.who.int/ipcs/publications/new_issues/ira/en/). [back to the text]

Baseline – A baseline consists of a measurement of the existing conditions of the environment and ecosystems prior to the introduction of the LMO under consideration and serves as a starting point for the risk assessment and as a basis to which all following measurements are compared. [back to the text]

Case-by-case – A case-by-case approach is one where each release of an LMO is considered relative to the environment in which the release is to occur, and/or to the intended use of the LMO in question (IUCN, 2003, An Explanatory Guide to the Cartagena Protocol on Biosafety, http://bch.cbd.int/database/record-v4.shtml?documentid=41476). [back to the text]

Combinatorial effects – Effects that may arise from the interactions between two (or more) genes, including epistatic interactions. 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 (see also "Cumulative effects"). [back to the text]

Consequence (of the adverse effect) – Severity of adverse effects associated with exposure to an LMO or its products. [back to the text]

Conventional – Not involving the use of modern biotechnology. [back to the text]

Cumulative effects – Effects that occur due to the presence of multiple LMOs in the receiving environment (see also "Combinatorial effects"). [back to the text]

EC50 (median effective concentration) – A concentration that is statistically or graphically estimated to cause a specified effect in 50% of a group of test organisms under specified experimental conditions (IPCS, 2001, Integrated Risk Assessment, www.who.int/ipcs/publications/new_issues/ira/en/). [back to the text]

Ecological function (or "ecological services") – Refers to the role of an 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. [back to the text]

Exposure – The contact or co-occurrence of an LMO or its products to the target- or non target-organisms and the receiving environment (adapted from IPCS, 2001, Integrated Risk Assessment, www.who.int/ipcs/publications/new_issues/ira/en/). [back to the text]

Gene-drive system – Method for introducing a desired gene into a mosquito population (Hood E, 2008, Selfish DNA versus Vector-Borne Disease, Environmental Health Perspectives 116: A69; www.ncbi.nlm.nih.gov/pmc/articles/PMC2235231/pdf/ehp0116-a00066.pdf. [back to the text]

Gene flow – For the use of this term in the context of this Guidance, see "Vertical gene transfer". [back to the text]

Gene product – The RNA or protein that results from the expression of a gene. [back to the text]

Genotypic (characteristics) – Relating to "genotype" as all or part of the genetic constitution of an organism. [back to the text]

Hazard – The potential of an organism to cause harm to human health and/or the environment (UNEP, 1995, International Technical Guidelines for Safety in Biotechnology, www.unep.org/biosafety/Documents/Techguidelines.pdf). [back to the text]

Horizontal gene transfer – Movement of genetic information from one organism to another through means other than sexual transmission. Also referred to as "horizontal gene flow" or "lateral gene transfer". [back to the text]

Introgression – Introduction of genetic elements from an organism into the genetic pool of organism of another species, sub-species or population occurring when mating between the two produce fertile hybrids. [back to the text]

LD50 (median lethal dose) – A statistically or graphically estimated dose that is expected to be lethal to 50% of a group of organisms under specified conditions. [back to the text]

Likelihood (of the adverse effect) – Probability, possibility or chance of the adverse effect to occur. [back to the text]

Management strategies – Appropriate mechanisms and measures to regulate, manage and control risks identified in the risk assessment. [back to the text]

"Omics" technologies – A collection of high-throughput techniques to study an organism or group of organisms at the level of the genome, gene transcripts, proteins or metabolites, which depending on the level are specifically called "genomics", "transcriptomics", "proteomics" and "metabolomics", respectively. [back to the text]

Outbreeding – The breeding of stocks or individuals that are not closely related. [back to the text]

Outcrossing – The transmission of genetic elements from one group of individuals (e.g. population, crop variety) to another. In plants, outcrossing most commonly results from cross-pollination (adapted from GMO Compass, www.gmo-compass.org/eng/glossary). [back to the text]

Potential receiving environment – An ecosystem or habitat, including humans and animals, which is likely to come in contact with a released organism (UNEP, 1995, International Technical Guidelines for Safety in Biotechnology, www.unep.org/biosafety/Documents/Techguidelines.pdf). [back to the text]

Phenotypic (characteristics) – Relating to "phenotype" as the observable physical or biochemical characteristics of an organism, as determined by both genetic makeup and environmental influence. [back to the text]

Pleiotropic effects – Effects of a single gene on multiple phenotypic traits. [back to the text]

Protection goal – A goal set out by a country that relates to desired environmental outcomes, and that guides the formulation of strategies for the management of human activities that may affect the environment. [back to the text]

Risk – The combination of the magnitude of the consequences of a hazard, if it occurs, and the likelihood that the consequences will occur (adapted from UNEP, 1995, International Technical Guidelines for Safety in Biotechnology, www.unep.org/biosafety/Documents/Techguidelines.pdf). [back to the text]

Risk assessment – The measures to estimate what risks may be associated with an LMO and what adverse effects may be caused, how likely the adverse effects are to occur, and what would the consequences be should they occur (adapted from UNEP, 1995, International Technical Guidelines for Safety in Biotechnology, www.unep.org/biosafety/Documents/Techguidelines.pdf). [back to the text]

Risk management – The measures to ensure that risks involved in the production and handling of an LMO are reduced (adapted from UNEP, 1995, International Technical Guidelines for Safety in Biotechnology, www.unep.org/biosafety/Documents/Techguidelines.pdf). [back to the text]

Risk threshold – The level of tolerance to a certain risk or the level of change in a particular variable beyond which a risk is considered unacceptable. Risk thresholds may be defined in the national legislation or in the decision-making process of each country. [back to the text]

Transformation cassette – A transformation cassette comprises a group of genetic elements (e.g. parts of a vector and one or more of the following: a promoter, the coding sequence of a gene and a terminator), which are physically linked and often originated from different donor organisms. The transformation cassette is integrated into the genome of a recipient organism through methods of modern biotechnology to produce an LMO. In some cases, a transformation cassette may also be called "expression cassette", "DNA cassette" or "gene construct". [back to the text]

Transformation event – An LMO resulting from the use of modern biotechnology applying *in vitro* nucleic acid techniques according to Article 3 (i) (a) of the Protocol. [back to the text]

Transgene – A genetic element or 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. [back to the text]

***Trans*-regulation –** Type of transcriptional regulation that is done by trans-regulatory elements which modify the expression of genes distant from the gene that was originally transcribed to create them. For example, a transcriptional factor transcribed in one chromosome may regulate the expression of a gene located in another chromosome. On the other hand, "*cis*-regulatory elements" are those that are physically linked to the genes that they regulate, e.g. promoters. [back to the text]

Unintended (effects) – Effects that appear in addition to or, in some cases, instead of the intended effects. Unintended effects can be divided into two categories: those that can be foreseen and those that are genuinely unanticipated. [back to the text]

Unintended gene product – Gene products that occur, for example, when the inserted gene construct suffers changes during the modification process, such as deletions, duplications, etc, that give rise to gene products (e.g. proteins or metabolites) which are different from those intended originally. [back to the text]

Unmanaged and managed ecosystems – An "unmanaged ecosystem" is an ecosystem that is free from significant human intervention, such as wetlands and nature preserves, as opposed to a "managed ecosystem", which is an ecosystem affected by varying degrees of human activities, such as farm lands, plantations, aquaculture sites and urban parks. [back to the text]

Vector – In the context of genetic modification, a vector is an organism or object used to assist the transfer of genetic material from a donor organism to a recipient organism (adapted from UNEP, 1995, International Technical Guidelines for Safety in Biotechnology, www.unep.org/biosafety/Documents/Techguidelines.pdf). In the context of epidemiology, a vector is an organism, often an invertebrate arthropod (e.g. mosquito), that transmits a pathogen (e.g. plasmodium) to a host (e.g. humans). [back to the text]

Vertical gene transfer – Transfer of genetic information from one organism to another organism via crossing or sexual recombination. [back to the text]

Annex II

DEVELOPMENT OF ADDITIONAL GUIDANCE

A. Composition of the sub-working groups and Bureau

Sub-working Group on "Post-release monitoring and long-term effects of LMOs released into the environment"

Chair:	David Quist
Core-group (Parties):	Ossama Abdel-kawy, Hans Bergmans, Michael DeShield, Eliana Fontes, Kok Gan Chan, Angela Lozan, Sol Ortiz García, Leticia Pastor Chirino, Wei Wei, Jelena Žafran Novak
Non-Parties and Observers:	Phil McDonald, Piet van der Meer, Esmeralda Prat

Sub-working Group on "Risk assessment of living modified trees"

Chair:	Beatrix Tappeser
Core-group (Parties):	Ossama Abdel-kawy, Rufus Ebegba, Mahaman Gado Zaki, Branka Javornik, Vilasini Pillai, Kazuo Watanabe
Non-Parties and Observers:	David Heron, Thomas Nickson, Ricarda Steinbrecher, Piet van der Meer

Bureau

The composition of the former Bureau was confirmed with the addition of the new sub-working group chairs.

B. Tentative outline for the development of additional guidance

The following are tentative outlines that were discussed by the sub-working groups as a basis for further work in the development of guidance:

Post-release monitoring and long-term effects of LMOs released into the environment:

I. Background (reason and need for this guidance)
   a. Reason for this guidance
   b. Relation to the Roadmap and Annex III/Risk Assessment other guidance

II. Introduction (outlining concepts and definitions)
   a. Why we monitor
      i. Detect adverse effect
      ii. Early warning
      iii. Evaluation of the assumptions of the risk assessment
      iv. Support biodiversity conservation
   b. Types of monitoring
      i. GS – scope (scale of release, scope of LMOs)

ii. CSM – (scale of release, scope of LMOs)

III. General considerations for PRM and long-term effects

a. Designing a monitoring scheme

i. General Surviellence (GS)

- Why (needs)
- What (scope)
- Where (site selection and converage)
- When (specific conditions)
- How (methods and approaches)
- How long – (Duration, consideration of long-term effects)

ii. Case Specific Monitoring (CSM)

- Why (needs)
- What (scope)
- Where (site selection and converage)
- When (specific conditions)
- How (methods and approaches)
- How long – (Duration, consideration of long-term effects)

IV. Scenarios guidance

a. Utilizing this guidance (guide to operationalization)

b. Specific scenarios (introduction)

c. Outcomes (expected outcomes)

V. Specific scenarios and issues I

a. Rationale (background and scheme)

b. Points to consider

c. Experiences (countries approaches, options and outcomes)

VI. Specific scenarios and issues II

a. Rationale (background and scheme)

b. Points to consider

c. Experiences (countries approaches, options and outcomes)

VII. Specific scenarios and issues III

a. Rationale (background and scheme)

b. Points to consider

c. Experiences (countries approaches, options and outcomes)

VIII. Annotations

a. Graphical representation of scenarios - Flowchart

IX. References

Risk assessment of living modified trees:

Notes: The guidance shall complement the Roadmap and will follow the overall structure. It will address generic questions and specifics for the chosen categories as far as possible.

Topics to be addressed in the common structure of rational and points to consider.

I. What is a tree?

II. What is it used for?
   a. Food
   b. Feed
   c. Fiber
   d. Recreational, industrial use

III. Different categories according to its uses
   a. Forest trees
   b. Plantation trees
   c. Fruit trees

IV. Differences between trees from temperate and tropical regions
   a. Short description what trees are engineered for
   b. Reference to transgenic trees in decisions of COP VIII and IX
   c. The need for additional guidance
      i. Uniqueness of trees (e.g. long lifespan, unique reproductive biology, high fecundity, seed dormancy and viability, large biomass, ecological and landscape architecture contribution, degree of domestication
      ii. Biodiversity aspects: role of trees in ecosystems – ecosystem functions/ecosystem services
      iii. Broad interaction with other organisms – trees as an ecosystem in itself

V. Scope (as decided by the Subworking Group)
   a. Forest trees/ Plantation trees/Fruit trees
   b. What is outside of the additional guidance (e.g. heritage trees)

VI. Planning Phase of a Risk Assessment of transgenic trees
   a. Overarching issues
      i. intentional and unintentional transboundary movement with reference to AIA requirements
      ii. intentional and unintentional movement of non-modified trees
   b. Comparative approach - what would the specifics be?
      i. Choice of comparator
      ii. Design and length of field trials- long life span of the trees
      iii. Detection of changes (more difficult in trees due to their long life cycle)

VII. Risk assessment

a. Transformation and propagation methods

b. Dispersal

i. Pollen dispersal

- Pollen viability and pollination specifics
- Possible spatial pollen distribution
- Diversity of hybridizing species

ii. Seed dispersal

- Via abiotic means (wind, water, floods etc.)
- Via animals including humans
- Via commodities
- Seed dormancy and viability
- …

iii. Vegetative dispersal

iv. Other/new dispersal pathways, e.g. seed dispersal via commodity fruits

c. Exposure

i. Receiving environment

ii. Persistence (e.g. life span)

iii. Spatial distribution of hybridizing species

iv. Interactions/Food webs

- with symbiotic microorganisms/mykorhiza
- insects
- birds
- …

d. Management strategies

i. Isolation distance of trees- is it possible to enforce

ii. Rotation period Degree of management

Annex III

ACTION PLAN

As an action plan for its work prior to the fourth meeting, the AHTEG agreed on the following tentative timeline for activities.

Timeframe	Revision of the Guidance on Risk Assessment of Living Modified Organisms	Revision of the list of background materials	Development of two new guidance documents	Main responsibility
4 – 10 June 2011	Finalization of the report of the third meeting of the AHTEG			*Chair and Rapporteur of the AHTEG in consultation with the Secretariat*
6 June – 8 July 2011			First draft of the guidance	*Chairs of the SWGs in consultation with the SWG*
6 June – 15 July 2011		Revision of the common format for submission of background materials to be linked to the Guidance		*Secretariat in consultation with the AHTEG Bureau*
18 – 25 June 2011	Online discussion on the Annex: Use of Terms			*AHTEG*
18 June – 2 July 2011	Consolidation of suggested amendments			*AHTEG Chair in consultation with the Bureau and Secretariat*
4 July 2011	Online circulation of the revised Chair's draft of the Guidance			*Secretariat*
11 July 2011			Online circulation of the draft guidance to the SWGs	*Secretariat*
15 July – 31 August 2011		Implementation of the changes to the common format for submission of documents to be linked to the Guidance		*Secretariat*
18 – 29 July 2011	Provision of concrete text proposals to the revised Chair's draft of the Guidance			*Open-ended Online Group and AHTEG*

Timeframe	Revision of the Guidance on Risk Assessment of Living Modified Organisms	Revision of the list of background materials	Development of two new guidance documents	Main responsibility
18 – 29 July 2011			Provision of comments to the draft guidance	*SWGs*
1 – 26 August 2011			Consolidation of comments	*Chairs of the SWGs*
1 August – 9 September 2011	Consolidation of suggested amendments			*AHTEG Chair in consultation with the Bureau and Secretariat*
29 August 2011			Online circulation of the 1st draft guidance	*Secretariat*
1 September 2011		Notification to national focal points, organizations and BCH users for submission of additional background materials to be linked to the Guidance		*Secretariat*
1 September – ongoing		Submission of background materials to be linked to the Guidance		*National Focal Points, organizations and BCH users*
1 September – ongoing		Assessment and validation of submitted background materials to be linked to the Guidance		*AHTEG Chair in consultation with the Bureau and Secretariat*
5 – 16 September 2011			Provision of comments to the 1st draft guidance	*Open-ended Online Group and AHTEG*
12 September 2011	Online circulation of the Revised Chair's draft of the Guidance			*Secretariat*
12 September – 15 Dec. 2011	Testing of the draft revised Guidance			*Secretariat, AHTEG, Parties*
19 September – 14 October 2011			Consolidation of comments	*Chairs of the SWGs in consultation with the SWGs*

Timeframe	Revision of the Guidance on Risk Assessment of Living Modified Organisms	Revision of the list of background materials	Development of two new guidance documents	Main responsibility
19 September – 15 Dec. 2011	Revision on the basis of the comments provided during the testing of the draft revised Guidance			*AHTEG Chair in consultation with the Bureau and Secretariat*
17 October 2011			Online circulation of 2nd draft guidance	*Secretariat*
24 October – 4 November 2011			Provision of concrete text proposals to the 2nd draft guidance	*Open-ended Online Group and AHTEG*
7 November – 13 January 2012			Consolidation of comments	*Chairs of the SWGs in consultation with the SWGs*
28 November – 2 Dec. 2011	Online exchange of experiences from the testing phase			*Open-ended Online Group and AHTEG*
2 – 15 Dec. 2011	Consolidation of suggested amendments			*AHTEG Chair in consultation with the Bureau and Secretariat*
16 December – 15 January 2012	Scientific editing			*Consultant*
16 January 2012	Online circulation of the draft revised Guidance		Online circulation of 3rd draft guidance	*Secretariat*
23 January – 3 February 2012	Online discussion			*Open-ended Online Group and AHTEG*
27 February – 30 March 2012	Real-time online regional conferences			*Open-ended Online Group and AHTEG*
7 – 11 May 2012	**Fourth meeting of the AHTEG**			***AHTEG***
14 June – 1 July 2012	Scientific editing			*Consultant under the supervision of the AHTEG Chair*

Annex IV

LIST OF PARTICIPANTS

A. Experts from Parties

Austria

1. Dr. Helmut Gaugitsch
Head of Unit
Landuse & Biosafety
Environment Agency Austria
Spittelauer Lände 5
Vienna A-1090
Austria
Tel.: +43 1 31 304 3133
Fax: +43 1 31 304 3700
E-Mail: helmut.gaugitsch@umweltbundesamt.at
Web: http://www.umweltbundesamt.at

Belize

2. Dr. Michael DeShield
Director
Food Safety Services
Belize Agricultural Health Authority
Central Investigation Laboratory
P.O. Box 181
Belize City
Belize
Tel.: +501 224 4794
Fax: +501 224 5230
E-Mail: foodsafety@btl.net; deshield@btl.net

Brazil

3. Dr. Eliana Maria Gouveia Fontes
Senior Scientist
Biological Control Unit /Ecology,
Semiochemicals & Biosafety
Laboratory
EMBRAPA-Cenargen
C.P. 02372
Brasilia, DF 71.510-230
Brazil
Tel.: +55 61 448 4793
Fax: +55 61 3448 4672
E-Mail: eliana@cnpq.br;
efontex551@gmail.com

China

4. Mr. Wei Wei
Institute of Botany
Chinese Academy of Sciences
20 Nanxincun, Xiangshan
Beijing 100093
China
Tel.: +86 10 6283 6275
Fax: +86 10 8259 6146
E-Mail: weiwei@ibcas.ac.cn

Croatia

5. Ms. Jelena Zafran Novak
Head of Laboratory
Laboratory for GMO Detection
Croatian National Institute of Public Health
Rockefellerova 7
Zagreb 10000
Croatia
Tel.: +385 1 4863207
Fax: +385 91 8996420
E-Mail: j.zafran-novak@hzjz.hr

Cuba

6. Prof. Leticia Pastor Chirino
Head
Department of Authorizations
National Centre for Biological Safety
Edif. 70c, apto 3. Zona 6 Alamar
Habana del este Ciudad Habana
Cuba
Tel.: +537 765 1202
Fax: +537 202 3255
E-Mail: leticiach@orasen.co.cu;
lpch06@yahoo.es

Egypt

7. Mr. Ossama Abdel-Kawy
Science Advisor
30 Maadi Zerae Road, 7th Floor
Maadi, Cairo
Egypt
Tel. +20 11 561 456
E-Mail: elkawyo@gmail.com;
abdkawy@yahoo.com

Germany

8. Dr. Beatrix Tappeser
Head of Division
Biosafety. GMO Regulation
Federal Agency for Nature Conservation
Konstantinstr. 110
Bonn D-53179
Germany
Tel.: +49 228 8491 1860
Fax: +49 227 8491 1869
E-Mail: TappeserB@bfn.de

Japan

9. Prof. Kazuo Watanabe
Gene Research Center
University of Tsukuba
1-1-1 Tennoudai
Tsukuba
Ibaraki 305-8572
Japan
Tel.: +81 29 853 4663
Fax: +81 29 853 7723
E-Mail: nabechan@gene.tsukuba.ac.jp

Malaysia

10. Dr. Chan Kok Gan
Senior Lecturer, Genetics & Molecular Biology
Faculty of Science
University of Malaya
Kuala Lumpur 50603
Malaysia
Tel.: +603 7967 5162
Fax: +603 7967 4509
E-Mail: kokgan@um.edu.my

11. Dr. Vilasini Pillai
Undersecretary
Secretariat of the National Science and Research Council
Ministry of Science, Technology and Innovation
Level 6, Block C5, Complex C,
Federal Government Administrative Centre
62662 Putrajaya
Malaysia
Tel.: +6 03 8885 8707
Fax: +6 03 8888 7710
E-Mail: vilasini@mosti.gov.my

Mexico

12. Dra. Sol Ortiz Garcia
Technical Director Public Policies and Regulation
Comisión Intersecretarial de Bioseguridad de los Organismos
Genéticamente Modificados
San Borja
938, esquina Heriberto Frías, Colonia del Valle,
Delegación Benito Juárez
México D.F. Distrito Federal - 03100
Mexico
Tel.: +52 55 5575 7618 ext 22
Fax: +52 55 5575 7618 ext 30
E-Mail: sortiz@conacyt.mx;
solortiz@conacyt.mx

Netherlands

13. Dr. Hans Bergmans
Senior Scientist
SEC/GMO Office
National Institute of Public Health and Environment
Antonie van Leeuwenhoeklaan 9, PO Box 1
Bilthoven 3720 BA
Netherlands
Tel.: +31 30 274 4195, +6 20 737792
Fax: +31 30 2744401
E-Mail: hans.bergmans@rivm.nl

Niger

14. Mr. Gado Zaki Mahaman
Point Focal National Biosécurité
Direction Générale de l'Environnement et des Eaux et Forêts
Ministère de L'Hydraulique et Environnement
P.O. Box 721
Niamey
Niger
Tel.: + 22796110415, +22720723755
Fax: +227 20723763
E-Mail: mahamane_gado@yahoo.fr

Nigeria

15. Mr. Rufus Ebegba
Assistant Director, BCH NFP, SBSTTA NFP
Biosafety Unit
Federal Ministry of Environment
Environment House, Independence Way (South)
Central Area, P.M.B. 468
Garki-Abuja
Nigeria
Tel.: +234 803 314 7778
E-Mail: rebegba@hotmail.com

Norway

16. Dr. David Quist
Senior Scientist
Genome Ecology Section
GenØk – Centre for Biosafety
Science Park, PO 6418
Tromso N-9294
Norway
Tel.: +47 77 646294
Fax: +47 77 646100
E-Mail: david.quist@uit.no

Republic of Moldova

17. Dr. Angela Lozan
Head of the Biosafety Office
Ministry of Ecology and Natural Resources
Str. Cosmonautiloz 9, Bir 526
Chisinou
Republic of Moldova
Tel.: +373 22 22 68 74
Fax: +373 22 22 68 74
E-Mail: angelalozan@yahoo.com

Slovenia

18. Dr. Branka Javornik
National Expert - Professor of Genetics & Biotechnology
Department of Agronomy, Biotechnical Faculty
University of Ljubljana
Jamnibarjeva 101
Ljubljana 1000
Slovenia
Tel.: +3861 320 360
Fax: +3861 423 1088
E-Mail: branka.javornik@bf.uni-lj.si

B. Observers from non-Parties

Canada

19. Mr. Philip Macdonald
National Manager
Plant and Biotechnology Risk Assessment Unit
Canadian Food Inspection Agency
1400 Merivale Rd
Ottawa, ON K1A 0Y9
Canada
Tel.: +613 773 5288
Fax: +613 773 5391
E-Mail: philip.macdonald@inspection.gc.ca

United States of America

20. Dr. David Heron
Assistant Director Policy Coordination,
Biotechnology Regulatory
Services
Animal and Plant Health Inspection Service (APHIS)
United States Department of Agriculture
4700 River Road
Riverdale MD 20737
United States of America
Tel.: +1 301 734 5295
Fax: +1 301 734 3135
E-Mail: david.s.heron@aphis.usda.gov

C. Non-Governmental Organizations

Federation of German Scientists

21. Dr. Ricarda Steinbrecher
Working group member
Working Group on Agriculture & Biodiversity
- incl. Biotechnology and Biosafety
Federation of German Scientists
P.O. Box 1455
Oxford Oxfordshire OX4 9BS
United Kingdom of Great Britain and Northern Ireland
Tel.: +44 1 865 725 194
E-Mail: r.steinbrecher@vdw-ev.de; r.steinbrecher@gn.apc.org

Public Research and Regulation Initiative

22. Prof. Mr. Drs. Piet van der Meer
Public Research and Regulation Initiative (PRRI)
c/o: Institute for Plant Biotechnology for Developing Countries (IPBO)
Faculty of Natural Sciences, Ghent University,
K.L. Ledeganckstraat 35
B-9000 Gent
Belgium
Tel: +32 2 652 1240
Fax: +32 2 652 3570
Email: info@pubresreg.org; pietvandermeer@gmail.com
Web: www.pubresreg.org

D. Business

Bayer Cropscience

23. Ms. Esmeralda Prat
Global Biosafety Manager
Regulatory Affairs
Bayer Cropscience
c/o Bayer Cropscience
Technologiepark 38
Gent B-9052
Belgium
Tel.: +32 9 243 0419
Fax: +32 9 224 0694
E-Mail: esmeralda.prat@bayercropscience.com

Monsanto Co.

24. Dr. Thomas Nickson
Regulatory Environmental Policy
Monsanto Co.
800 North Lindbergh Boulevard
Saint Louis Mo 63167
United States of America
Tel.: +314 694 2179
Fax: +314 694 2074
E-Mail: thomas.nickson@monsanto.com
Web: http://www.mosanto.com
