**Draft guidance document on Risk Assessment and Risk Management
of living modified Mosquitoes**

***Prepared by the Ad Hoc Technical Expert Group on
Risk Assessment and Risk Management***

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**OBJECTIVE**

The Ad Hoc Technical Expert Group (AHTEG) on Risk Assessment and Risk Management has developed a Roadmap for Risk Assessment which sets out the necessary steps to conduct a risk assessment in accordance with Annex III to the Cartagena Protocol on Biosafety[[1]](#footnote-1).

The present document, prepared by the AHTEG Sub-working Group on Living Modified (LM) Mosquitoes aims at complementing the Roadmap on specific issues that may need special consideration for the environmental releases of LM mosquitoes. It focuses mainly on Paragraphs 8 (a) and (e) of Annex III.

The present Guidance Document also provides additional information that may contribute to better understanding the issue and help regulators in their decision-making process in relation to the environmental release of LM mosquitoes.

For each topic of this document, reference will be made to which step of Annex III it refers to. Suggestions for supporting bibliographies are also provided through links to web pages in the Biosafety Clearing House.

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

**Introduction**

LM mosquitoes are being developed for use to reduce incidence of disease caused by pathogens transmitted by the insects, particularly malaria and dengue. Various strategies are being developed to control the population of vectors by suppressing their population or reducing their vector competence. In addition, there is a serious market for LM mosquitoes that would reduce populations of pestiferous mosquitoes independent of the likelihood of disease, or justified based on potential, rather than actual, transmission of pathogens.

The biology and ecology of mosquitoes, and their importance to public health as vectors of human pathogens, pose new considerations and challenges to the risk assessment and risk management of LMOs, which have mainly dealt with LM crop plants.

These challenges arise, for example, from the lack of (i) a clear regulatory framework in many countries, (ii) a limited number of risk-assessment/decision documents either completed (US EPA environmental assessment with finding of no significant effects for the pink bollworm pest of cotton) or in process (tephritid fruit flies, pests of many orchard crops; and the New World screwworm fly, pest of wildlife, livestock, and humans); and (iii) limited experience in regulatory agencies to address the deployment of recombinant DNA strategies to combat vector related diseases. The technical requirements for efficient environmental and health impact assessments need to be taken into consideration. While the various approaches to combat vector borne pathogens using LM mosquitoes may have many issues in common, it is recognized that there may be different sets of challenges to address the specific strategies. Control of pestiferous mosquitoes raises a different set of concerns.

**Scope**

This document focuses on the risk assessment and risk management of LM mosquitoes developed for use in vector control of human diseases such as malaria, dengue, chikungunya and yellow fever. However, much of the market and benefit from successful application of integrated vector management of mosquitoes results from the public's desire to reduce the discomfort caused by mosquito bites.

**POTENCIAL ADVERSE EFFECTS**

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

A specific and complete list of potential adverse effects of a particular LM mosquito, taking into account the molecular mechanisms of gene insertion, the LM trait, the mosquito species and the intended environment for release, should consider, for instance, but not be limited to: (a) the kinds of possible adverse effects that result from scientifically established natural phenomena [analyzed by considering (a) the species and ecological processes that could be affected by the introduction of the LM mosquitoes; (b) a conceptual link between the identified environmental protection goals and the introduction of the LM mosquito into the environment; and (c) an evaluation of the likelihood and consequences of the identified possible adverse effects]; and the environmental and public health protection goals of the country where the LM mosquitoes will be introduced.

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

*Rationale:*

The release of LM mosquitoes may have a negative impact on the target and other species, such as:

*Failure of efficacy:* Whether the intention of the LM mosquito release is reduction of vector competence, sterile male inundation of the population, or other strategies for reduction of the population, the program's ultimate practical success will depend on careful implementation and, in most cases, integration with other methods. The risk would be dependence on the LM mosquito technique without assurance that the program would be as effective as another available method.

*Harm to or loss of other species*. Ecological effects might result from competitive release if the target mosquito is reduced or from trophic consequences of species that rely on mosquitoes for food during some specific time of the year, though other effective methods of mosquito control could have the same effect. The reduction in damage caused by the mosquito as a vector could have unintended consequences, such as the initial human population increase resulting from dramatic reduction in childhood mortality following malaria control. More subtly, cessation of transmisson 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, favoring increases in their numbers.

*Disruption of ecological communities and ecosystem processes*. Under some circumstances, mosquitoes are significant pollinators, therefore mosquito control of any kind might either reduce pollination of some species of plants 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:*

1. The ecological significance of the target species.
2. The potential for control of the mosquito species outside of the target geographic range.
3. Endemicity of target species.
4. Significance of the target species to pollination.

**Gene Flow**

*Rationale:*

Gene flow in regard to biosafety refers to the transfer of transgenes or genetic elements from the LMO to non-modified organisms. It can occur via cross-hybridization or independent movement of the transgenes or genetic elements. Whether gene flow occurs and what adverse effects it might have depend on various factors such as the LM technology used, the trait or traits carried by the mosquitoes, the receiving environment, etc.

Based on the existing knowledge on the ecology and biology of mosquito species that transmit malaria and dengue, it may not be likely that other species will be affected by LM mosquitoes. More information is needed in cases involving other mosquito species and the environments where the LM mosquitoes are likely to be released. 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 parasites and pathogens respond to the introduction of new vectors etc. Such information may be needed in order to successfully apply the LM technology. Additionally, methods for the identification of specific ecological or environmental hazards are also needed.

*Gene flow through cross-hybridization:* Some LM mosquitoes are being designed to spread a trait rapidly through the target mosquito population. For instance, for *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, thus, spread of the transgenes or genetic elements in the target mosquito population is not expected. . For such technologies, the potential for an unexpected spread of the transgenic trait should be considered by focusing on the ways that any management strategy to limit the spread could fail. Gene flow between different species should be considered for all of the LM mosquito technologies. Mosquitoes, like other insects, typically have strong reproductive isolating mechanisms that will not allow interspecific gene flow. Identifying the key reproductive isolating mechanisms and the conditions leading to their breakdown could be a focus of this assessment. In addition, the fitness conferred by the transgenic trait and the size and frequency of the introduction of the LM mosquito into the environment will also determine the likelihood and rate of spread of the transgenes or genetic elements.

*Independent movement of the transgenes or genetic elements:* This is commonly referred to as “horizontal gene flow”, which is the movement of genetic information from one organism to another through means other than sexual transmission. The risk associated with horizontal gene flow in LM mosquitoes should still be considered. Gene drive systems for moving genes into wild populations should be one of the initial focus of the risk assessment. The risk of horizontal gene flow in LM mosquitoes that do not contain a gene drive system may be smaller but should nevertheless be assessed.

*Points to consider:*

1. Does the release of the LM mosquitoes have the potential to create new pests or pass their modified traits to wild populations and to non-related organisms? If so, what are the undesirable consequences?
2. Will the LM mosquitoes induce undesirable functions or behaviors within target species, other wild related species or non-related organisms?

**Evolutionary responses (especially in vector or pathogen)**

*Rationale:*

There is a danger that when modifying vector competence, the pathogen target might develop resistance to physiological mechanism. That resistance would not only harm the effectiveness of the disease control program, it might also create a population of pathogens that will be transmitted more easily by all populations of its vector. For example, *Anopheles* mosquitoes limit the population of *Plasmodium* parasites in an individual mosquito through a cytokine-nitric oxide pathway. Conceivably, genetic modification could enhance this pathway to create pathogen-incompetent vectors. However, if the pathogen developed resistance to this pathway, it would presumably be transmitted more frequently by all populations of the vector, whether or not the LM version.

*Points to consider:*

1. The mosquito vector might evolve to avoid population suppression, regain vector competency or acquire new or enhanced competency of another disease agent;
2. The trait may evolve to lose effectiveness; and
3. The disease agent might evolve to overcome the limitation posed by the genetic modification, and thus could become more virulent, overcome the noncompetency mechanism, or acquire new vector species.

**Persistence of the transgene in the environment**

*Rationale:*

Inserted transgene(s) may spread and persist in natural populations. Some of the transgenes in LM mosquitoes are designed not to persist whereas others are expected to spread rapidly through wild population. In cases where the LM mosquitoes have the potential to cause adverse effects to the biological diversity, taking also into account human health, methods to reduce the persistence of the transgene in the environment or to mitigate the expression of the transgene may be needed. Monitoring during and after the environmental release of the LM mosquitoes to address prompt detection of unexpected adverse effects may be recommended (see additional considerations on monitoring below).

**Risk Management strategies**

*(see Step 5 of the Roadmap for Risk Assessment)*

Risk assessors may want to consider the following risk management strategies for the release into the environment of LM mosquitoes:

1. Monitoring during and after the environmental release of LM mosquitoes to address species replacement before it becomes an irreversible problem. Operational management processes should carefully follow the design criteria for implementation of the risk management strategies laid out in the risk assessment;
2. monitoring for transgene intactness and proper function over timeMonitoring the efficacy and effectiveness of mosquito technology;
3. Monitoring strategies for managing the dispersal and to ensure that the LM mosquitoes do not establish themselves beyond the intended receiving environment;
4. Halting the releases if unanticipated effects occur; and/or
5. Mitigations, such as an alternative control set of measures should a problem occur.

**Other Issues**

There are other dimensions that should be taken into consideration in the decision for environmental releases of LM mosquitoes which are not governed by Annex III of the Protocol. They encompass among others: economic, health and social trade-offs associated with the technology application as well as social and cultural issues that are expected to influence the acceptance of these methods. In addition, the benefits should be estimated from effective use of LM mosquitoes for control of disease, vector species, or pestiferous mosquitoes.

**BIBLIOGRAPHIC REFERENCES**

*See references relevant to the “*[*Guidance Document on Risk Assessment and Risk Management of LM Mosquitoes*](http://bch.cbd.int/onlineconferences/mosquitoesref_ahteg_ra.shtml)*”.*

1. 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. [↑](#footnote-ref-1)