**Draft guidance document on Risk Assessment and Risk Management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 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 to conduct risk assessment in the particular case of the environmental release of LM mosquitoes.

Reference will be made for each topic of this document to which step of Annex III it refers. 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. A similar sentence should be added in the other guidance documents.

**Introduction**

LM mosquitoes are being developed to control the population of vectors in order to reduce transmission of vector-borne human diseases, especially malaria and dengue. Control, including eradication, of such diseases is a widely-recognized public health goal.

Various strategies are being developed to control the population of vectors by either suppressing their population or reducing their vector competence. Furthermore, these strategies can be subcategorized according to the technology involved and the method of implementation. Some are sterile or self-limiting (unable to pass the modification on indefinitely through subsequent generations), and thus depend on continued releases of male mosquitoes. Others are self-sustaining (heritable modifications intended to spread through the target population) and would depend on small and infrequent releases. Thus, the strategy under consideration is an important factor in the risk assessment process.

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

These challenges arise, for example, from the lack of (i) a clear regulatory framework in many countries, (ii) guidance documents (with the exception of some public environmental impact assessments done for LM fruit fly and LM pink bollworm, which are both agricultural pests); and (iii) 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 diseases 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.

**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.

**POTENTIAL ADVERSE EFFECTS**

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

A consideration that we frequently encounter (but more in estimating potential risks of, for instance, LM *Plasmodium*, is potential extension of the habitat of a vector due to climate change. Is that relevant here too, e.g. in point to consider (c) in line 101, or in line 156 (ecosystem effects)?

A specific and complete list should be provided 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 be not limited to: (a) the kinds of possible adverse effects where there is solid scientific evidence; (b) the protection goals of the country where the LM mosquitoes will be introduced; (c) the species and ecological processes that could be affected by the introduction of the LM mosquitoes; (d) a conceptual link between the identified environmental protection goals and the introduction of the LM mosquito into the environment; and (e) an evaluation of the likelihood and consequences of the identified possible adverse effects .

**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:

*New or more vigorous pests, especially those that have adverse effects on human health:* (i) The released LM mosquitoes may not function as expected. Gene silencing or production failures could result in the release of non-sterile or competent mosquitoes and thus increase the vector population or disease transmission. (ii) The released LM mosquitoes could transmit another disease more efficiently. Such diseases might include yellow fever, chikungunya, etc. (iii) Suppression of the target mosquito might enable another vector species to increase and result in higher levels of the target disease or a new disease in humans. These include other mosquito vectors of diseases. (iv) The released LM mosquitoes might become nuisance pests. (v) The released LM mosquitoes might cause other pest problems to become more serious, including agricultural pests and other pests that affect other valued human activities.

*Harm to or loss of other species*. The released LM mosquitoes might cause other valued non-pest species (for instance fishes the mechanism how this could come about is not immediately clear) to become less abundant. These include species of economic, cultural, and/or social importance such as wild foods, iconic species and endangered 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. Effects might also occur if (i) the target mosquito was also transmitting a disease to another animal species, (ii) the released LM mosquitoes transmit a disease of another animal species more efficiently, or (iii) a vector of an animal disease was released from ecological control by the reduction of the target mosquito. Sterile interspecific matings between released LM mosquitoes and other mosquito species could disrupt the population dynamics of these other species leading to harm or loss of valued ecological species.

*Disruption of ecological communities and ecosystem processes*. The ecological communities in the ephemeral, small aquatic habitats occupied by the vector mosquitoes targeted with LM mosquitoes are unlikely to be greatly disrupted beyond the possibilities already addressed above under “harm to or loss of other species.” However, if the released LM mosquitoes were to inhabit more natural habitats, such as 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 processes may be culturally or socially specific.

*Points to consider:*

1. What is the impact of the strategy under consideration on the target mosquitoes?
2. May the LM mosquitoes have an adverse effect on other species becoming agricultural, aquacultural, public health, or environmental pests or produce nuisances or health hazards?
3. What is the habitat range of the target species (see above, line 50)?
4. Is the target species native / invasive in a given area?
5. Will the release affect mosquito species that are pollinators or otherwise are known to participate in valued ecosystem processes?
6. What species do the target mosquitoes typically interact with in the environment?
7. May the LM mosquitoes have an adverse effect on other interacting organisms?

**Gene Flow**

*Rationale:*

Gene flow in regard to biosafety refers to the transfer of transgenes or modified 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 host 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 do 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 why, are there examples where HGT has been observed, or are there plausible ways that HGT might occur?. Gene drive systems for moving genes into wild populations should be one of the initial foci 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 pass their modified traits to non-related organisms? If so, what may be 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:*

Any strong ecological effect also exerts an evolutionary selection pressure. The main evolutionary effects are those that could result in a breakdown in the technology and the resumption of previous disease levels. Other evolutionary effects could be hypothesized but they would first require the occurrence of some adverse effect on a species, community or ecosystem effect (see line 50 above). Therefore, consideration of secondary evolutionary effects can be postponed until such effects are identified and found to be significant.

*Points to consider:*

1. Does the mosquito vector have the potential to evolve to avoid population suppression, regain vector competency or acquire new or enhanced competency of another disease agent? If so, what may be the undesirable consequences?
2. Does the trait have the potential to evolve to lose effectiveness or the pathogen to overcome the limitation posed by the genetic modification? If so, what may be the undesirable consequences?

**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 been found through the risk assessment process to have the potential to cause adverse effects to the biological diversity, taking also into account human health, methods to reduce the persistence of the transgene in the environment 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 monitoring is NOT a risk management strategy! during and after the environmental release of LM mosquitoes to follow the spread of the trait in the local population.. Operational management processes should carefully follow the design criteria for implementation of the risk management strategies laid out in the risk assessment;
2. Monitoring the potential evolutionary breakdown of the mosquito technology (monitoring for transgene intactness and proper function over time),
3. Monitoring the efficacy and effectiveness of mosquito technology;
4. Monitoring strategies for managing the dispersal and to ensure that the LM mosquitoes do not establish themselves beyond the intended receiving environment;
5. Halting the releases if unanticipated effects occur; and/or
6. Mitigations, such as an alternative set of control 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.

**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)*”.*

Add

[Female-specific flightless phenotype for mosquito control.](http://www.ncbi.nlm.nih.gov/pubmed/20176967)

Fu G, Lees RS, Nimmo D, Aw D, Jin L, Gray P, Berendonk TU, White-Cooper H, Scaife S, Kim Phuc H, Marinotti O, Jasinskiene N, James AA, Alphey L.

Proc Natl Acad Sci U S A. 2010 Mar 9;107(10):4550-4.

Also, a more recent version of the WHO report stemming from the May, 2009, meeting is now available from Dr. Yeya Toure.

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)