Draft Outline

"Additional Voluntary Guidance Materials on Risk Assessment of Living Modified Organisms (LMOs) Containing Engineered Gene Drives (EGDs)"

Comments by the Outreach Network for Gene Drive Research
August 2023

In decision CP-10/10, the Conference of the Parties serving as a meeting of the Parties to the Cartagena Protocol on Biosafety (COP-MOP) agreed to develop additional voluntary guidance materials to support case-by-case risk assessment of living modified organisms (LMOs) containing engineered gene drives (EGDs) in accordance with Annex III of the Cartagena Protocol. To support its development, the COP-MOP requested the Executive Secretary to commission the preparation of a detailed outline to be reviewed by the online forum and serve as a base for the work of the Ad Hoc Technical and Expert Group (AHTEG). This document compiles the views of the members of the Outreach Network for Gene Drive Research of the draft outline for the "Additional Voluntary Guidance Materials on Risk Assessment of Living Modified Organisms (LMOs) Containing Engineered Gene Drives (EGDs)".

SECTIONS 1 to 3

PARAGRAPH & TEXT REFERENCE		COMMENTS
1.0	**Objective and scope of these additional voluntary guidance materials** • Decision CP-10/10	• CBD's guidance should complement existing guidelines and focus on items that are novel for gene drive organisms compared to other LMOs. • The guidance should be science-based and in accordance with the principle of case-by-case assessments. It should align with paragraph 11 of CBD decision 14/19 on the necessary conditions for the experimental release of organisms containing engineered gene drives.
2.0	**Introduction** • Annex III of Cartagena Protocol on Biosafety • Previous guidance under the Cartagena Protocol • Relevant guidance from other processes	• CBD's guidance should draw upon experiences from other LMOs and other fields, such as biocontrol, reflecting these existing resources where possible. • Relevant guidance from the World Health Organization (WHO) and national authorities should also be considered to ensure coherence and compatibility with the CBD's guidance. **Relevant references:** • Technical evaluation of a potential release of OX513A *Aedes aegypti* mosquitoes on the island of Saba (National Institute of Public Health and the Environment (RIVM), 2017) • Risk associated with the release of *Wolbachia*-infected *aedes aegypti* mosquitoes into the environment in an effort to control dengue (Murray et al., 2016) • Requirements for market entry of gene drive-modified mosquitoes for control of vector-borne diseases: analogies to other biologic and biotechnology products (James et al., 2023) • Guidance framework for testing of genetically modified mosquitoes (WHO, 2021) • Adequacy and sufficiency evaluation of existing EFSA guidelines for the molecular characterisation, environmental risk assessment and post-market environmental monitoring of genetically modified insects containing engineered gene drives (EFSA, 2020) • Regulatory requirements for contained research with GMOs containing engineered gene drives (Office of the Gene Technology Regulator, 2019)

3.0	**Overarching issues in the risk assessment process on EGD-LMOs** • Engineered gene drive terminology, types and general characteristics	• "Gene drive" is an umbrella term covering various possible constructs and approaches. The guidance should acknowledge this diversity when defining what constitutes "gene drive" LMOs. This is essential because the specifics of the construct and the target species will have significant implications when analysing risks and benefits, and this underscores the need for case-by-case assessments. **Relevant references:** • Standardizing the definition of gene drive (Alphey et al., 2020) • Gene drives: evolved and synthetic (Burt A, Crisanti A, 2018) • A gene drive is a gene drive: the debate over lumping or splitting definitions (James et al., 2023)
3.1	**Protection goals, assessment endpoints and measurement endpoints** • Descriptions of relevant concepts	• Defining the target organism of an intervention is a critical element of the risk assessment process. However, because of some of the characteristics of gene drive approaches (such as temporal persistence and spatial spread), the definition of the target organism may differ for gene drive organisms compared to other LMOs – especially in cases where the organism is part of a species complex where not all species are relevant. • In the case of malaria, for example, not all species in the *Anopheles* sensu lato species complex are vectors of human malaria. This raises questions about the definition of the target organism – such as whether it should be extended to all species within the species complex or restricted to those which are vectors of human malaria. • As suggested by Connolly et al (2022a, 2022b), the target organism should be defined according to the intended outcomes of the gene drive application, which may be different from how target organisms have been defined for other LMOs to date. • As a result, and as noted by EFSA (2020), target organisms might include an individual population, a single species, or a species complex defined as a set of partially reproductively connected species. • While there may be differences in how target organisms will be defined for gene drive organisms, protection goals are expected to be broadly similar to those usually identified for other LMOs. **Relevant references:** • Recommendations for environmental risk assessment of gene drive applications for malaria vector control (Connolly et al., 2022a) • Adequacy and sufficiency evaluation of existing EFSA guidelines for the molecular characterisation, environmental risk assessment and post-market environmental monitoring of genetically modified insects containing engineered gene drives (EFSA, 2020) • Gene drive in species complexes: defining target organisms (Connolly et al., 2022b) • Problem formulation for gene drive mosquitoes designed to reduce malaria transmission in Africa: results from four regional consultations 2016–2018 (Teem et al., 2019)
3.2	**Quality and relevance of information** • Criteria for the quality of scientific information • Sources and relevance of information for the risk assessment	• Risk assessments for gene drive organisms need to be drawn from various sources. They will likely combine probabilistic (quantitative) and qualitative information elicited through various methods – from stakeholder interviews to literature reviews and laboratory studies. • Probabilistic risk assessments use quantitative modelling approaches to represent a probability distribution for a range of potential outcomes for a particular event. On the other hand, qualitative risk assessments categorize, in a structured and systematic way, the likelihoods and consequences of outcomes into a limited number of ordered classes to give a categorical

		indication of relative risk, such as 'high', 'moderate', 'low' or 'negligible'. Where feasible, such qualitative terms should preferably be defined as precisely as possible in a quantitative form (Connolly et al., 2022). Both types of assessments involve seeking expert opinion to determine the likelihood and possible outcomes of certain events. • In addition, some methodologies support assessing and considering different information relevant to risk assessment ("weight of evidence"). For example, the WHO and other institutions use the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) methodology. This is a widely endorsed and used approach to assess evidence and develop recommendations. **Relevant references:** • Recommendations for environmental risk assessment of gene drive applications for malaria vector control (Connolly et al., 2022) • WHO handbook for guideline development (WHO, 2012) • Application of weight of evidence and precaution in risk assessment (Government of Canada, 1999) • Guidance on the use of the weight of evidence approach in scientific assessments (EFSA, 2017) • GRADE working group • What is GRADE? BMJ Best Practices • Bayesian networks in environmental risk assessment: a review (Kaikkonen et al., 2021)
3.3	**Identification and consideration of uncertainty** • Categories of uncertainty • Consideration and treatment of uncertainty • Uncertainty and the potential use and role of modelling	• Uncertainty is not a concept unique to gene drive, and as for other LMOs, the quality of data will correlate with the level of confidence and reduce uncertainty. • Modelling, as noted by EFSA and others, can play a helpful role in reducing uncertainty, as sensitivity analysis can help identify which components influence outcomes. • It is important to recognize that the existence of uncertainties does not preclude taking a decision. This view is compatible with a precautionary approach, which states that where there is a threat of significant reduction or loss of biological diversity, the lack of complete scientific certainty should not be used as a reason for postponing measures to avoid or minimize such a threat. **Relevant references:** • Adequacy and sufficiency evaluation of existing EFSA guidelines for the molecular characterisation, environmental risk assessment and post-market environmental monitoring of genetically modified insects containing engineered gene drives. (EFSA, 2020) • Guidance on uncertainty analysis in scientific assessments (EFSA, 2018) • Risk assessment for controlling mosquito vectors with engineered nucleases: Controlled field release for sterile male construct (CSIRO, 2018) • Recommendations for environmental risk assessment of gene drive applications for malaria vector control (Connolly et al., 2022) • Modelling the potential of genetic control of malaria mosquitoes at national scale (North et al., 2019) • Review of gene drive modelling and implications for risk assessment of gene drive organisms (Frieß et al., 2023) • Gene drive dynamics in natural populations: the importance of density dependence, space, and sex (Dhole et al., 2020)

SECTIONS 4 TO 6

PARAGRAPH & TEXT REFERENCE		COMMENTS
4.0	**Planning phase of the risk assessment of EGD-LMOs**	
4.1	**Establishing the context and scope** • Relevant considerations (e.g. legislation, guidelines, national requirements, protection goals, experience, available information) • Stakeholder engagement	• Engagement should be an essential element in the development of guidance on Environment Risk Assessment (ERA) of gene drive applications. It allows assessors to draw on a wide variety of technical and non-technical expertise. • The importance of engagement is recognized and emphasized in many of the frameworks guiding gene drive research, including those published by the WHO. However, how to engage for risk assessment purposes has not been further defined, and this can pose challenges for developers and regulatory authorities. • For example, while Article 23 of the Cartagena Protocol on "Public awareness and participation" includes an obligation for national governments to engage with 'the public' on GMO applications, it does not set out specifics and the engagement may be only in the form of a period of public comment. • The additional guidance should recognize the importance of engagement and encourage governments to clearly set their expectations for engagement activities in the risk assessment process. • It is also relevant to note that other processes carried out independently from ERA – such as Strategic Environmental Assessments (SEA) and Environmental and Social Impact Assessments (ESIA), also sometimes known as Environmental, Social and Health Impact Assessments (ESHIA) – can offer opportunities to gather information and views on possible risks and benefits at different scales and inform the ERA process. SEA and/or ES(H)IA may be required in some countries but not in all. Considerations of how these elements can be leveraged to support the establishment of the context and scope, and more generally, of the risk assessment could be noted in the new guidance. **Relevant references:** • Recommendations for environmental risk assessment of gene drive applications for malaria vector control (Connolly et al., 2022) • Considering the case of gene drive technologies through social science theories on stakeholder engagement (Gene Drive Research Forum, 2021) • Environmental impact assessment and strategic environmental assessment: towards an integrated approach (UNEP, 2004) • International principles for social impact assessment (Vanclay, 2003) • Principles of environmental impact assessment best practice (International Association for Impact Assessment, 1999)
4.2	**Problem formulation** • Pathways to harm • Analysis plan	• The methodology for problem formulation for a gene drive LMO is the same as for other LMOs. Therefore, previous experience should be relevant and existing guidance can be re-used. **Relevant references:** • Systematic identification of plausible pathways to potential harm via problem formulation for investigational releases of a population suppression gene drive to control the human malaria vector *Anopheles gambiae* in West Africa (Connolly et al., 2021) • Problem formulation for gene drive mosquitoes designed to reduce malaria transmission in Africa: results from four regional consultations 2016–2018 (Teem et al., 2019) • Problem formulation and hypothesis testing for environmental risk assessments of genetically modified crops (Raybould, 2006)

4.3	**The choice of comparators** • Selection of appropriate comparators • Alternative approaches	• In most LMOs, the comparator has usually been the non-modified/non-transgenic version of the organism (for example, LMO soybeans versus non-transgenic soybeans). • In the case of gene drives, the choice of comparators could be different and broadened to other methods with similar effects, like insecticides and suppression gene drives for malaria control. • This is noted in the EFSA study: "*The selection of suitable comparators […] should include the intended outcome of engineered gene drive applications in insects, and put more emphasis on the purpose of the risk assessment studies conducted and thus purpose of comparisons. As a GDMI progresses through the phased testing and release pathway, the range of risk assessment studies and their purpose change (Hayes et al., 2018). Consequently, there will often not be a single comparator for a given proposed deliberate release into the environment of a GDMI, but a range of comparators that can inform ERA and contextualise risks (HCB, 2017).*" **Relevant references:** • Adequacy and sufficiency evaluation of existing EFSA guidelines for the molecular characterisation, environmental risk assessment and post-market environmental monitoring of genetically modified insects containing engineered gene drives (EFSA, 2020, p.53) • Pathway to deployment of gene drive mosquitoes as a potential biocontrol tool for elimination of malaria in Sub-Saharan Africa: recommendations of a scientific working group (James et al., 2018) • Guidance framework for testing of genetically modified mosquitoes, second edition (WHO, 2021)
5.0	**Conducting the risk assessment** • Annex III of the Cartagena Protocol on Biosafety • Application of the Roadmap for risk assessment of living modified organisms	• The Roadmap for Risk Assessment of Living Modified Organisms was not officially endorsed by CBD parties; hence it should be made expressly clear why it is referenced here.
5.1	**Step 1. Identification of any novel genotypic and phenotypic characteristics associated with the EGD-LMO that may have adverse effects on biological diversity in the likely potential receiving environment, taking also into account risks to human health** • Identification of plausible risk hypotheses and clear pathways to harm • Elements for consideration of the EGD-LMO (e.g. non-modified/parental organism, characteristics of the donor organism, transformation method, molecular characteristics of the engineered gene drive, genotypic and phenotypic changes in the LMO) • Elements for consideration for the intended use and in the receiving environment (e.g. availability of data on the receiving environment, spatial scale, duration, containment, characteristics of the receiving environment, pests of pathogen resistance) • Elements for consideration regarding potential adverse effects resulting from the interaction between EGD-LMO and the receiving environment (e.g. characteristics of the EGD-LMO in the receiving environment, considerations for unmanaged and managed ecosystems, dispersal of EGD-LMO, potential for outcrossing, horizontal gene transfer, effects on non-target organisms, cumulative effects with other EGD- LMOs in the environment) • Illustrative examples	• The risk assessment methodology for gene drives is not different from other LMOs. However, differences may arise when considering gene drives' impacts due to the temporal persistence and spatial spread of gene drive constructs. • It is worth noting that containment refers to a physical structure, which is not applicable in this CBD's guidance, as the document must focus on risk assessment for releasing LMOs containing engineered gene drives. It is important to clarify why the outline includes containment among the elements for consideration; otherwise, the mention should be removed. • In addition, "unmanaged and managed ecosystems" seems to be a concept mostly relevant to agriculture. Therefore, it is unclear how this would apply to the context of gene drive organisms. **Relevant references:** • Results from the workshop "Problem Formulation for the Use of Gene Drive in Mosquitoes" (Roberts et al., 2017)

5.2	**Step 2. Evaluation of the likelihood of adverse effects being realised, taking into account the level and kind of exposure of the likely potential receiving environment to the living modified organism** • Risk, likelihood and exposure characterization • Elements for consideration (e.g. relevant characteristics in the receiving environment, expression in the EGD-LMO and persistence and accumulation in the environment, geographic and biogeographic information on the location of release, factors affecting spread of the EGD-LMO, likelihood of outcrossing, persistence of transgene in the environment, expected type and level of exposure) • Illustrative examples	• The risk assessment methodology for gene drives is not different from other LMOs. However, differences may arise in the consideration of gene drive's adverse effects once it is necessary to consider the temporal and spatial dimension of gene drive constructs.
5.3	**Step 3. Evaluation of the consequences should these adverse effects be realized** • Hazard characterization • Evaluation of consequences • Elements for consideration (e.g. pathways for dissemination, potential adverse effects from combinatorial or cumulative effects in the receiving environment, relevant knowledge and experience with LMOs or organisms with similar traits, results from laboratory experiments, results from field trials, potential adverse effects from outcrossing) • Illustrative examples	• As for Steps 1 and 2, Step 3 is not specific to gene drives organisms. CBD guidance should acknowledge that having a gene drive in the environment is not *a priori* a hazard. In other words, exposure does not equal hazard. • It would also be worth recognizing that cumulative impacts are also evaluated through the Economic Social (and Health) Impact Assessments (ESIA/ESHIA), which will help inform the environmental risk assessment (ERA). **Relevant references:** • Environmental and social impact assessment (ESIA) (IUCN, 2020)
	Step 4. 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 • Risk characterization • Elements for consideration (e.g. individual risk and possible interactions between them, risk management, broader considerations based on ecosystems services approach)	• Considerations of "overall" risk should encompass the risk of inaction – the risk of doing nothing, not adopting a specific course of action and the risk of alternatives. It is worth highlighting that the risk of inaction is also considered in the ESIA/ESHIA's analysis of alternatives. **Relevant references:** • Defining the no-action alternative for national environmental policy act analyses of continuing actions (McCold L, Saulsbury J, 1998) • Criteria for determining alternatives in eia, integrated environmental management, information series 11 (South Africa Department of Environmental Affairs and Tourism, 2004) • Improving alternatives for environmental impact assessment (Steinemann, 2000)
	Step 5. Recommendation as to whether or not the risks are acceptable or manageable, including, where necessary, identification of strategies to manage these risks • Acceptability of risks • Monitoring • Recommendations • Elements for consideration related to risk management (e.g. existing management practices, methods to detect and identify EGD-LMO, management options and their feasibility, methods for evaluating proposed risk management and monitoring strategies) • Elements for consideration related to acceptability of risks (e.g. established criteria, protection goals, assessment endpoints, relevant experience with non-	• As for Steps 1 to 4, Step 5 is not specific to gene drive organisms. Risks will need to be evaluated in comparison to alternatives – the risk of inaction and risk posed by other approaches – to contextualize the assessment. • Regarding mitigation strategies, there are no single answers to this question despite ongoing and active research on this topic. However, mitigation strategies will depend on the risks identified, the construct, the species etc. In other words, it will need to be considered case-by-case. • The issues outlined in Step 5 are also being considered in the context of biological control agents. Although these are not LMOs, their spatial and temporal dimensions are similar to gene drive and could offer valuable points of comparison. **Relevant references:** • Risk management recommendations for environmental releases of gene drive modified insects (Devos et al., 2022)

modified recipient organisms, benefit analysis, ability to manage adverse effects)	• Points to consider in seeking biosafety approval for research, testing, and environmental release of experimental genetically modified biocontrol products during research and development (Tonui et al., 2022)
• Related issues • Socioeconomic considerations (e.g. Voluntary Guidance on the Assessment of Socio- Economic Considerations in the Context of Article 26 of the Cartagena Protocol on Biosafety) • Issues related to Indigenous Peoples and Local Communities (IPLCs) • Risks vs. benefits • Sources and nature of uncertainty that could not be previously addressed	• It is crucial to acknowledge that there are well-established methodologies for considering socioeconomic aspects. In addition, other assessment methodologies, notably ESIA/ESHIA and SEA, will also address these aspects. • As discussed in Step 5, gene drive risk assessment should consider risks, benefits and the impact of alternative paths of action. • Monitoring gene drive organisms and other LMOs is vital and should be based on the key risks identified in the risk assessment process. Health aspects of monitoring for some gene drive applications may be greater than for other LMOs – like gene drive constructs seeking to reduce malaria transmission. **Relevant references:** • Assessment tools for decision making for area wide malaria vector control using gene-drive approaches – perspectives on evaluation of socio-economic considerations (Turner, 2023) • Environmental impact assessment and strategic environmental assessment: towards an integrated approach (UNEP, 2004) • Environmental and social impact assessment (ESIA) (IUCN, 2020) • Evaluating methods for analyzing economic impacts in environmental assessment (Gunton et al., 2020) • International principles for social impact assessment (Vanclay, 2003)

SECTIONS 7 TO 9

PARAGRAPH & TEXT REFERENCE	COMMENTS
7.0 Introduction • Case study of an *Anopheles* mosquito	• Overall, comments provided on the previous sections also apply to the following sections focused on mosquitoes containing engineered gene drives. Some additional references are provided below.
8.0 Objective and scope	
9.0 Planning phase of the risk assessment of EGD in *Anopheles* **9.1 The choice of comparators** • Non-modified strains, comparator activities	**Relevant references:** • Recommendations for environmental risk assessment of gene drive applications for malaria vector control (Connolly et al., 2022) • Refractory gene drive risk assessment: Scoping and hazard analysis for UCMI (CSIRO, UCMI, 2022) • Problem formulation for gene drive mosquitoes designed to reduce malaria transmission in Africa: results from four regional consultations 2016–2018 (Teem et al., 2019) • Toward the definition of efficacy and safety criteria for advancing gene drive-modified mosquitoes to field testing (James et al., 2020)

SECTIONS 10 TO 13

PARAGRAPH & TEXT REFERENCE		COMMENTS
10.0	**Conducting the risk assessment of EGD-LM *Anopheles***	• This section is presented as a case study; hence, it should not be considered guidance per se for any particular case of a gene drive containing *Anopheles* mosquito.
10.1	**Step 1. Characterization of the EGD-LM mosquito** • Biology and relationship with environment of *Anopheles* mosquito • Molecular characterisation of the EGD-LM Mosquitos	• Each gene drive LMO will need to be considered case-by-case, as there is a great variety of approaches being proposed to reduce the burden of mosquito-borne diseases. • Depending on the species target, the disease, the approach and the construct, the relevant aspects in terms of characterization could change. **Relevant references:** • Consensus document on the biology of mosquito Aedes aegypti (OECD, 2018) • OECD – Consensus document on the biology of mosquito *Anopheles* gambiae (forthcoming) • Mosquitoes of the world (Wilkerson et al., 2021)
10.2	**Step 2. Unintended effects on biological diversity (species, habitats, ecosystems, and ecosystem function and services)** • Vertical gene transfer • Horizontal gene transfer • Persistence of the transgene in the ecosystem • Evolutionary response • Unintentional transboundary movements	• The assessment of unintended effects on biological diversity is relevant to gene drive organisms and to all other LMOs. • While these issues are not specific to gene drives, how applicable or relevant each dimension is will need to be assessed on a case-by-case basis. It is difficult to generalize considerations, but as mentioned before, the spatial and temporal dimension of the proposed gene drive LMO may render the consideration of these issues somewhat different to another LMO.
10.3	**Step 4. and Step 5. Risk management strategies** • Detection and identification • Monitoring • Mechanisms to eliminate EGD-LMO • Effectiveness and availability of conventional mosquito control methods • Availability of methods for managing potential development of resistance • Containment of the EGD-LM mosquito	• The current outline does not include Step 3 for mosquitoes. Since the document aims to layout a process, it should clarify the reason for skipping this particular step. • As noted under Step 1 (part 5), it is unclear why the outline mentions containment. Containment refers to a physical structure, which is not applicable in this context once – CBD's guidance is focused on risk assessment for releasing gene drive organisms. The meaning or purpose of this mention should be clarified. • As noted in Step 5 regarding mitigation strategies, there is no single answer to this question despite ongoing and active research on this topic. Mitigation strategies will depend on the risks identified, the construct, the species, etc. Therefore, they will need to be considered on a case-by-case basis. • Resistance issues need to be part of the assessment for efficacy as well as risk. However, this also affects other tools currently used as alternatives to gene drive technologies. When considering resistance issues, the assessor should also take into account the susceptibility to resistance of alternative approaches. **Relevant references:** • Containment practices for arthropods modified with engineered transgenes capable of gene drive addendum 1 to the arthropod containment guidelines, version 3.2 (American Committee of Medical Entomology and American Society of Tropical Medicine and Hygiene, 2022) • Guidance for IBCs: Regulatory requirements for contained research with GMOs containing engineered gene drives (Office of the Gene Technology Regulator, Australian Government, 2019)

11.0	**Monitoring EGD-LM *Anopheles* released in the environment** • Pre-release monitoring, monitoring during release, post-release monitoring	• The term "pre-release monitoring" should be clarified, as it is unclear how to monitor the impact of an organism on the environment prior to its release.
12.0	**Related Issues**	• Stakeholder engagement during the research and risk assessment processes, particularly during the problem formulation phase, is critical. Many efforts have been underway in this regard, including for the develop of best practices that can inform future research. **Relevant references:** • Operationalizing stakeholder engagement for gene drive research in malaria elimination in Africa—translating guidance into practice (Pare Toe et al., 2022) • Guidance on stakeholder engagement practices to inform the development of area-wide vector control methods (Thizy et al., 2019) • Proceedings of an expert workshop on community agreement for gene drive research in Africa (Thizy et al., 2021) • Sustainable innovation in vector control requires strong partnerships with communities (Bartumeus et al., 2019)

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