OUTREACH NETWORK FOR
GENE DRIVE RESEARCH

Submission of information pursuant to paragraph 7 of decision CP-10/10[1]

Part I. Endorsement of submission

Name of Country/Organization: Outreach Network for Gene Drive Research

Name of Cartagena Protocol Focal point/Head of Organization endorsing: Isabelle Coche, Coordinator, Secretariat to the Outreach Network for Gene Drive Research

Signature of the Cartagena Protocol Focal Point/ Head of Organization:

Date: March 15, 2023

Part II. Submission of information

Paragraph 1(c) of the annex to decision CP-10/10 calls for the AHTEG to "Develop additional voluntary guidance materials for conducting case-by-case risk assessments of living modified organisms containing engineered gene drives in accordance with annex III of the Protocol. A specific focus of this material should be engineered gene drive mosquitos taking into account the current experience with the organism, the type of gene drive and specific issues of risk assessment, identified in annex I to decision CP-9/13, including existing reports, general considerations of living modified organisms containing engineered gene drives, and existing national and regional risk assessment experiences".

Based on this, please submit information on the following areas:

1) General considerations of living modified organisms containing engineered gene drives that may be useful for risk assessment

There are many different types of gene drive constructs being considered or under development, for many potential different uses and contexts. They are at many different stages of the research and development process and none are ready yet for field use. Risks and benefits associated with each gene drive approach will primarily depend on the objective targeted, the type of modification made, the species it is applied to, and the ecosystem and geography where the organism with the drive system will be used, rather than on the gene drive mechanism itself. Therefore, gene drive risk assessments must be science-based and consistent with the principle of case-by-case assessment. Current guidance for risk assessment of living modified organisms (LMOs) under the Cartagena Protocol and from other sources are broadly adequate for organisms containing engineered gene drives. Relevant Publications include:

- Guidance Framework for Testing of Genetically Modified Mosquitoes (WHO, 2021)
- Gene Drives on The Horizon: Advancing Science, Navigating Uncertainty, And Aligning Research with Public Values (US National Academy of Sciences, Engineering and Medicine (NASEM), 2016)
- Adequacy and Sufficiency Evaluation of Existing EFSA Guidelines For The Molecular Characterisation, Environmental Risk Assessment And Post-Market Environmental Monitoring Of

[1] Who can submit information: Parties, other Governments, indigenous peoples and local communities, and relevant organizations.

Genetically Modified Insects Containing Engineered Gene Drives (European Food Safety Authority (EFSA), 2020)

- Synthetic Gene Drives in Australia: Implications of Emerging Technologies (Australian Academy of Science, 2017)

In order to ensure that the new CBD guidance adds value, the materials should focus on issues that are clearly specific to organisms containing engineered gene drives (rather than generally relevant to LMOs). These would include issues related to the temporal and spatial spread of those organisms (persistence, spread, predictability and transboundary movements), molecular characterization, and monitoring efforts. As much as possible the guidelines should be useful for risk assessment for all types of organisms containing engineered gene drives, as research is advancing in other areas, such as gene drive systems for the control of mice that are invasive alien species.

Many Parties already expressed the concern that they lack the adequate resources and/or expertise (legal, scientific, procedural, or otherwise) to implement existing guidelines. Therefore, the development of new guidelines should not overshadow the need to support Parties to build their biosafety expertise and increase others' ability to take part in, and benefit from, innovative research. This dovetails with the broader need to ensure implementation of the Cartagena Protocol for all LMOs, not just gene-drive organisms. Equal weight should be placed on fostering and strengthening information sharing as learning from other countries' approaches and experience can be an effective approach to improve capacity and preparedness – the Biosafety Clearing House (BCH) plays a vital role in this regard.

Computer simulation modelling is one of the key areas that deserves attention in terms of disciplines requiring further capacity building and in increasing understanding of its use. In a risk assessment context, modelling helps predicts "behaviour based on the properties and assumptions of the transgenic modification that may be helpful in assessing the likelihood of events", as noted in:

- Guidance framework for testing of genetically modified mosquitoes (WHO, 2021)

Other relevant publications that illustrate the importance of modelling for gene drive assessment are:

- Engineered reproductively isolated species drive reversible population replacement (Buchman et al., 2021)

- Recommendations for environmental risk assessment of gene drive applications for malaria vector control (Connolly et al., 2022)

It should be noted that as no releases of organisms containing engineered gene drives have taken place, or are planned to take place in the near future, the information and expertise directly related to risk assessment for releases that is available is limited. However, many scientists, regulators, and other experts have extensive experience with conducting risk assessments for lab-contained use of organisms containing engineered gene drives, which can inform the risk assessment of an eventual environmental release. There is also a plentiful body of knowledge related to risk assessment of the deliberate release of (non-gene drive) organisms designed to propagate for the purpose of biocontrol, which can also be a source of useful information.

Risk assessments should consider the perspectives of different stakeholders, as their expertise, concerns and priorities can help identify and assess potential benefits and harms. For example, in a series of workshops, experts identified relevant environmental and health protection goals for an environmental risk assessment of a suppression gene drive for malaria vector control in West Africa, helping scientists to identify potentially harmful effects from these simulated releases:

- 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)

This process built on previous work on problem formulation for gene drive mosquitoes conducted in consultation with African regulators through a series of workshops organized by the New Partnership for Africa's Development (NEPAD):

- Problem formulation for gene drive mosquitoes designed to reduce malaria transmission in Africa: results from four regional consultations 2016–2018 (Teem et al., 2019)

Consultation with communities which may be directly affected by any release will also be crucial to conducting effective risk assessment of any proposed release, to ensure their knowledge and insight is taken into account. For a discussion of good practices and challenges with regards to community consultation for gene drive research in Africa, please see:

- 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)

Further publications which contain useful information regarding aspects of, and experiences with, organisms containing engineered gene drives that may be useful for risk assessment include:

- Report on the experience of Member States with Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms for the period 2019 – 2021 (European Commission, 2023)

- Lessons learned from the introduction of genetically engineered crops: relevance to gene drive deployment in Africa (Quemada, 2022)

- Larval mosquito management and risk to aquatic ecosystems: A comparative approach including current tactics and gene-drive Anopheles techniques (Peterson & Rolston, 2022)

- 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)

- Monitoring Needs for Gene Drive Mosquito Projects: Lessons From Vector Control Field Trials and Invasive Species (Rasic et al., 2021)

2) Types of engineered gene drives that are or could be used in mosquitos, including whenever possible specificities of the type of engineered gene drives that should be considered for risk assessment

Gene drive is a term that covers a variety of approaches and typologies. Many different types of gene drive systems have been discussed as suitable for use in mosquitoes and other species. Lists and brief descriptions of the approaches which have garnered the greatest interest to date can be found in the studies below. While there is no set definition of what "gene drive" is, there are broad categories that can help describe how the different approaches and results that would come under the umbrella term of "gene drive". The paper by Alphey et al (2020) offers a useful description of these categories.

- Gene drives to fight malaria: current state and future directions (Hammond & Galizi, 2017)
- 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 (European Food Safety Authority (EFSA), 2020)
- Standardizing the definition of gene drive (Alphey et al., 2020)
- Combating mosquito-borne diseases using genetic control technologies (Wang et al., 2021)
- Engineering the Composition and Fate of Wild Populations with Gene Drive (Hay et al., 2021)
- Can CRISPR-Based Gene Drive Be Confined in the Wild? A Question for Molecular and Population Biology (Marshall & Akbari, 2018)

Experimental gene drives have been developed for use in lab settings for several different species of mosquitoes, including species from genus *Aedes* and genus *Anopheles* as these are vectors for some of the most devastating diseases affecting humans. For further details on some of the mosquito gene drives that already exist, see below (the list is not comprehensive). It is important to note that gene drive research is ongoing and advancing in other species, notably rodents and in these cases different types of drives are being developed:

- A multiplexed, confinable CRISPR/Cas9 gene drive propagates in caged *Aedes aegypti* populations (Anderson et al., PREPRINT)
- Development of a confinable gene drive system in the human disease vector *Aedes aegypti* (Li et al., 2020)
- A male-biased sex-distorter gene drive for the human malaria vector *Anopheles gambiae* (Simoni et al., 2020)
- Efficient population modification gene-drive rescue system in the malaria mosquito *Anopheles stephensi* (Adolfi et al., 2020)
- A CRISPR-Cas9 gene drive system targeting female reproduction in the malaria mosquito vector *Anopheles gambiae* (Hammond et al., 2016)
- Highly efficient Cas9-mediated gene drive for population modification of the malaria vector mosquito *Anopheles stephensi* (Gantz et al., 2015)
- Gene drive designs for efficient and localisable population suppression using Y-linked editors (Geti et al. 2022)
- Driving down malaria transmission with engineered gene drives (Garrood et al. 2022)
- A synthetic sex ratio distortion system for the control of the human malaria mosquito. (Galizi et al., 2014)
- A CRISPR-Cas9 sex-ratio distortion system for genetic control (Galizi et al., 2016)

- Double drives and private alleles for localised population genetic control (Willis & Burt, 2021)

- Next-generation gene drive for population modification of the malaria vector mosquito, *Anopheles gambiae*. (Carballar-Lejarazu et al., 2020)

- Gene drives gaining speed (Bier, 2022)

- Closing the gap to effective gene drive in Aedes aegypti by exploiting germline regulatory elements (Anderson et al., 2023)

- The Challenges in Developing Efficient and Robust Synthetic Homing Endonuclease Gene Drives (Verkuijl et al., 2022)

2) Gene drive mosquitoes can aid malaria elimination by retarding Plasmodium sporogonic development (Hoermann et al., 2022)

3) General information about the host organism

Gene drive research is to a large extent currently focused on vectors of malaria, but other mosquito-borne diseases such as dengue and chikungunya could also be candidates for gene drive tools. In the case of human malaria, the *Anopheles* genus is the only mosquito that can transmit the disease. Several species can carry the malaria parasite, including *Anopheles gambiae, Anopheles arabiensis, Anopheles coluzzii, Anopheles funestus* and *Anopheles stephensi*.

Malaria, dengue, chikungunya and the insect vectors of the agents that cause these diseases have been the subject of study for a long time. Their host organisms are well known, and their biology is well characterized. There are ongoing efforts to compile available information to facilitate the work of regulatory authorities and policymakers. Supporting initiatives such as the OECD Consensus Document of the Biology of Mosquito *Aedes aegypti* is crucial. The report provides an overview of current information on this host organism to help national authorities and scientists evaluate the safety of genetically engineered mosquitoes when released into the environment:

- Safety Assessment of Transgenic Organisms in the Environment, Volume 8: OECD Consensus Document of the Biology of Mosquito *Aedes aegypti* (Organization for Economic Co-operation and Development (OECD), 2018)

A similar exercise is underway for *Anopheles gambiae* and it would be critical to have a similar report on other species, including *Anopheles stephensi.* A malaria vector in South-East Asia and large parts of the Arabian Peninsula, it is now spreading to Africa as an invasive alien species, threatening gains previously made in the region towards malaria eradication.

When carrying out risk assessments, clear understanding of what is being defined as the target organism is a key consideration. How target organisms are defined will impact assessment of how the genetic modification may spread and of the impact of the organism in the ecosystem. Mosquitoes that transmit malaria can belong to species complexes that contain both vector and non-vector species, and the answer to this question can vary significantly. Environmental risk assessment of organisms containing engineered gene drives invites more nuanced considerations of target and non-target organisms than for transgenes not intended to increase in frequency in target populations. This is discussed at length in the papers:

- 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)
- Gene drive in species complexes: defining target organisms (Connolly et al., 2022)

The latter proposes introducing the concept of target species complexes, as it offers more flexibility when assessing the potential impacts of gene drives. It also highlights that the approach used to define a target organism most likely needs to be made on a case-by-case basis, considering the nature of the species complex, the extent of harm it causes, and its ratio of vector to non-vector species. The issue of how to define target organisms is also relevant for organisms containing engineered gene drives other than mosquitoes.

The risk assessment process should also take into consideration how a particular species may be spread by human activities. Disease vector species may sometimes expand their range due to accidental or intentional introduction to new areas by humans.

4) Experience with risk assessment of mosquitos, including if any, direct experience with engineered gene drive mosquitos

No organisms containing engineered gene drives have been proposed for release yet; hence regulatory authorities have never evaluated a risk assessment for the release of gene drive mosquitoes (for field evaluation or use). However, work is already under way to develop risk assessment methodologies and procedures. For example, Target Malaria, a not-for-profit research consortium that aims to develop and share new, cost-effective and sustainable genetic technologies to modify mosquitoes and reduce malaria transmission which is working on a population suppression approach for the main malaria vector in Africa, published its work last year on starting to identify and assess plausible pathways to harm**.** The outcomes from this work provide an overview of the issues currently under consideration for future gene drive risk assessments. In addition, they further published a series of recommendations for environmental risk assessments. See both publications below:

- 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)

- Recommendations for environmental risk assessment of gene drive applications for malaria vector control. (Connolly et al., 2022)

It is also possible to build from previous experiences with other genetically modified (non-gene drive) mosquitoes. For example, Oxitec, a biotechnology company, has been using genetically modified mosquitoes to suppress wild populations of *Aedes aegypti*. When released, genetically modified male mosquitoes search for wild females to mate with, and their offspring inherit a self-limiting gene that causes them to die before reaching functional adulthood. The genetically modified mosquitoes die along with their offspring; hence, they do not persist in the environment. In 2017, the National Institute of Public Health and the Environment (RIVM) in the Netherlands carried out a biosafety evaluation of Oxitec's self-limiting mosquito technology following the guidance for risk assessment of genetically modified animals by the European Food Safety Authority (EFSA). More information about the assessment is available in the publications:

- 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)

- OX513A Technical Dossier Saba (Oxitec, 2016)

Target Malaria has also documented useful information for this topic. In 2019, the consortium proceeded with the small-scale release of non-gene drive, genetically modified, sterile male mosquitoes in the village of Bana, in Burkina Faso, as part of its research pathway to develop gene drive mosquitoes. Target Malaria released approximately 6,400 non gene drive genetically modified sterile male mosquitoes of the *Anopheles gambiae* species and approximately 8,500 non-modified mosquitoes in the framework of a comparative study. The independent risk assessment carried out by CSIRO prior to the releases and more reports containing information about the experience can be found below. The national biosafety agency of Burkina Faso also conducted a risk assessment of this release, and although their report has not been made publicly available, they may be contacted for further information about their experience.

- Risk Assessment for Controlling Mosquito Vectors with Engineered Nucleases: Controlled field release for Sterile Male Construct Risk assessment final report (Hayes et al., 2018)

- Mark-release-recapture experiment in Burkina Faso demonstrates reduced fitness and dispersal of genetically-modified sterile malaria mosquitoes (Yao et al., 2022)

- Operationalizing stakeholder engagement for gene drive research in malaria elimination in Africa—translating guidance into practice (Pare Toe et al., 2022)

- Small-scale release of non-gene drive mosquitoes in Burkina Faso: from engagement implementation to assessment, a learning journey (Pare Toe et al., 2021)

Experiences with other organisms can also be helpful, such as non-mosquito LMOs or insects released as part of biocontrol initiatives. One such case is the Australian release of *Wolbachia*-infected *Aedes aegypti* mosquitoes, a primary dengue vector. *Wolbachia* is a type of bacteria which can reduce dengue virus transmission as well as the expected lifespan of an infected mosquito. The results of the risks analysis conducted to evaluate the hazards associated with the release are available in the publications:

- Risk Analysis on the Australian release of *Aedes aegypti* (L.) (Diptera: Culicidae) containing *Wolbachia* (Murphy et al., 2010)

- Risk Associated with the Release of *Wolbachia*-Infected *Aedes aegypti* Mosquitoes into the Environment in an Effort to Control Dengue (Murray et al., 2016)

5) Specific issues of risk assessment identified with the use of annex I to decision CP-9/13, including existing reports, general considerations of living modified organisms containing engineered gene drives, and existing national and regional risk assessment experiences

New guidance materials should take into account and be complimentary to the existing CBD Guidance on Risk Assessment of LMOs - UNEP/CBD/ BS/COP-MOP/6/13/Add.1

It should also be complementary to existing materials outside of CBD, such as the body of expertise and analysis already developed in many countries, as well as efforts specifically focused on organisms containing engineered gene drives already undertaken by other international organizations:

- Guidance framework for testing of genetically modified mosquitoes (WHO, 2021)

- Evaluation of genetically modified mosquitoes for the control of vector-borne diseases (WHO, 2020)

- Ethics and vector-borne diseases: WHO guidance (WHO, 2020)

- Gene Drives on The Horizon: Advancing Science, Navigating Uncertainty, And Aligning Research with Public Values (US National Academy of Sciences, Engineering and Medicine (NASEM), 2016)

- 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 (European Food Safety Authority (EFSA), 2020)

- Synthetic Gene Drives in Australia: Implications of Emerging Technologies (Australian Academy of Science, 2017)

- Regulatory requirements for contained research with GMOs containing engineered gene drives (Office of the Gene Technology Regulator, 2019)

- Recommendations for environmental risk assessment of gene drive applications for malaria vector control (Connolly et al., 2022)

- Report on the experience of Member States with Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms for the period 2019 – 2021 (European Commission, 2023)

- 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)

- Gene drives: Policy Report (National Institute of Public Health and the Environment (RIVM), 2016)

- Study on Risk Assessment Application of annex I of decision CP 9/13 to living modified organisms containing engineered gene drives (Smets & Rudelsheim, 2019)

6) **Any other information that may be relevant for the development of additional voluntary guidance materials for conducting case-by-case risk assessments of living modified organisms containing engineered gene drives in accordance with annex III of the Protocol.**

With regards to biorisks and dual-use research, WHO's Global guidance framework for the responsible use of the life sciences: mitigating biorisks and governing dual-use research provides values and principles, tools and mechanisms to support countries and key stakeholders to mitigate and prevent biorisks and govern dual-use research:

- Global guidance framework for the responsible use of the life sciences: mitigating biorisks and governing dual-use research (WHO, 2022)

Although not part of an environmental risk assessment (ERA), taking into account the socio-economic aspects and potential impacts of a potential release is vital for decision-making. These aspects can be considered in other additional assessment processes, such as the Environmental, Social, and Health Impact Assessment (ESHIA), complementing the ERA and supporting the decision-making process.

Both empirical and probabilistic methods are useful in conducting risk assessments, and can be used in conjunction in complementary fashion. Probabilistic approaches, such as simulation modelling, are fundamental to evaluating how organisms containing engineered gene drives could spread in the environment and interact with the ecosystem. For further details, see:

- Engineered reproductively isolated species drive reversible population replacement (Buchman et al., 2021)
- Recommendations for environmental risk assessment of gene drive applications for malaria vector control (Connolly et al., 2022)

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