

Global Industry Coalition
Submission of Information on Risk Assessment and Risk Management under the Cartagena
Protocol on Biosafety (Protocol)

SCBD/CPU/DC/MA/MW/87798 (2019-009)

15 March 2019

The Global Industry Coalition (GIC)¹ is pleased to submit the following information in response to the request in Notification 2019-02-01, Ref SCBD/CPU/DC/MA/MW/87798, to support the work of the Open-ended online forum and the *Ad Hoc* Technical Expert Group (AHTEG) on Risk Assessment and Risk Management.

I. **Introduction and Summary**

Development of additional guidance under the Protocol on specific topics of risk assessment

The GIC has contributed to the discussion on risk assessment under the Protocol since its inception. We remain of the view that the risk assessment framework set out in Annex III of the Protocol, including its principles and methodology, is broadly applicable to all existing and realistically foreseeable living modified organisms (LMOs). In making this assertion, we point to the accumulated knowledge and experience in implementing risk assessment and risk management for different types of LMOs for different uses, and the resulting corpus of resources, including sources of “guidance”, that is available to Parties and other Governments.

The GIC strongly supports the decision by the Parties to establish and use a process for the identification and prioritization of specific issues regarding risk assessment that may warrant the development of additional guidance. We hope that this will promote a more thorough examination and consideration of the experience and body of existing relevant materials than past activities on this topic and also the sharing of information by Parties and other governments. The GIC recommends that the criteria for identification and selection of issues outlined in Annex I of Decision CBD/CP/MOP/DEC/9/13 are strengthened and refined by the Parties following the outcomes of the current exercise on engineered gene drives and LM fish. We further

¹ The Global Industry Coalition (GIC) for the Cartagena Protocol on Biosafety receives input and direction from trade associations representing thousands of companies from all over the world. Participants include associations representing and companies engaged in a variety of industrial sectors such as plant science, seeds, agricultural biotechnology, food production, animal agriculture, human and animal health care, and the environment.

recommend that any future work on developing specific guidance is deferred until there is clear and objective evidence for the need, identified by the above-mentioned process.

The GIC notes that the subject of guidance for LMO risk assessment, and the need for additional guidance on specific topics, has been under continuous discussion by the Parties since their second meeting in 2004. A clear divergence of views is evident among Parties and other Governments on the utility of such materials and whether or not additional or specific guidance is “needed”.² Gaps in existing guidance materials are identified by only some Parties, while others consider to have sufficient basis for supporting case-by-case risk assessment of LMOs. This situation primarily reflects differences in experience in conducting risk assessment by Parties, with the need for guidance largely having a basis in a need for capacity building in risk assessment generally. Other arguments in support of developing guidance have been connected to the “newness” of technologies and/or the resulting LMOs, and assumptions that this must correspond to a need for “new” approaches to risk assessment. However, for more than two decades, many Parties and other Governments have been conducting risk assessments for LMOs to be released into the environment, and they have developed specialist knowledge and a solid foundation that enables adaptation of risk assessment approaches on a case-by-case basis to “new” LMOs. From this experience, a large body of example risk assessments and decisions (or “case studies”), scientific publications, and other “guidance” materials have been generated. Given the information above, the development of additional guidance documents is unlikely to add value to the existing relevant body of work or resolve the divide between experienced risk assessors and those with theoretical or limited hands-on experience. The GIC believes that Parties and other Governments with experience in LMO risk assessment should increase efforts to share experiences with Parties needing capacity building. Such exchange of information is consistent with Article 22 of the Protocol and the Convention on Biological Diversity.

With this introduction as background, the GIC is pleased to provide information below on the three elements specifically noted in the Notification.

II. **Information in response to Notification 2019-02-01, Ref SCBD/CPU/DC/MA/MW/87798**

- A. **Experience in undertaking risk assessment of living modified organisms containing engineered gene drives and living modified fish (detailing how and for which cases); or else, lack of experience in doing so;**

² CBD/CP/MOP/DEC/9/13.

i. LMOs Containing Engineered Gene Drives

The term “gene drive” refers to genetic mechanisms that lead to the transmission of a specific allele (gene variant) with a frequency of greater than 50% to the next generation. *In theory*, an engineered gene drive could lead to the preferential increase in the frequency of a specific genotype over many generations, and an entire population could eventually have that genotype.³ The GIC⁴ and others⁵ have provided detailed background information on gene drives in recent submissions to the Executive Secretary⁶ in response to their request for “information and supporting documentation” on “synthetic biology”.⁷

To date, **research on engineered gene drives has only been conducted in the laboratory and is restricted to a very small number of species.** Successful proof-of-concept laboratory experiments with engineered gene drives have been reported for yeast (*Saccharomyces cerevisiae*⁸), two species of mosquitos (*Anopheles gambiae*⁹ and *A. stephensi*¹⁰), the fruit fly (*Drosophila melanogaster*¹¹), and the crop pest spotted wing *Drosophila* (*Drosophila suzukii*¹²). The first engineered gene drive in rodents (mice) was reported in 2019.¹³ This research was not a proof-of-concept, but it served to identify a myriad of technical challenges. Therefore, the prospect of environmental release of such organisms containing gene drives for the control of populations of invasive species remains several years away. Other concepts have been proposed including agricultural applications involving the control of insect or weed pests, however these proposals are theoretical

³ Australian Academy of Science (2017) Discussion Paper: Synthetic gene drives in Australia – Implications of emerging technologies.

⁴ See GIC submission (Feb 2019), available at: <https://bch.cbd.int/database/record.shtml?documentid=114285>.

⁵ E.g. see the Outreach Network for Gene Drive Research submission (Feb 2019), available at: <https://bch.cbd.int/database/record.shtml?documentid=114306>.

⁶ Notification SCBD/CP/DC/MA/MW/87791 of 14-December-2018.

⁷ All submissions are available at: <https://bch.cbd.int/synbio/submissions/>.

⁸ DiCarlo JE, Chavez A, Dietz SL, Esvelt KM, Church GM (2015) Safeguarding CRISPR-Cas9 gene drives in yeast. *Nature Biotechnology* 33: 1250–1255.

⁹ Hammond A, Galizi R, Kyrou K, Simoni A, Siniscalchi C, Katsanos D, Gribble M, Baker D, Marois E, Russell S, Burt A, Windbichler N, Crisanti A, Nolan T (2016) A CRISPR-Cas9 gene drive system targeting female reproduction in the malaria mosquito vector *Anopheles gambiae*. *Nature Biotechnology* 34: 78–83.

¹⁰ Gantz VM, Jasinskiene N, Tatarenkova O, Fazekas A, Macias VM, Bier E, James AA (2015) Highly efficient Cas9-mediated gene drive for population modification of the malaria vector mosquito *Anopheles stephensi*. *Proceedings of the National Academy of Sciences USA* 112: E6736-E6743.

¹¹ Gantz VM, Bier E (2015) Genome editing. The mutagenic chain reaction: a method for converting heterozygous to homozygous mutations. *Science* 348: 442–444.

¹² Buchman A, Marshall JM, Ostrovski D, Yang T, Akbari OS (2018) Synthetically engineered Medea gene drive system in the worldwide crop pest *Drosophila suzukii*. *Proceedings of the National Academy of Sciences USA* 115: 4725-4730.

¹³ Grunwald HA, Gantz VM, Poplawski G, Xiang-Ru XS, Bier E, Cooper KL (2019) Super-Mendelian inheritance mediated by CRISPR–Cas9 in the female mouse germline. *Nature* 566: 105–109.

and speculative¹⁴ and do not reflect current or near future possibilities and are thus not addressed in our information submission.

The most realistically foreseeable application of gene drives to be released into the environment is mosquitoes designed to control malaria-carrying populations. LM mosquitoes¹⁵, and other LM insects (e.g. *Plutella xylostella*^{16,17}, *Ceratitis capitata*¹⁸), have been developed for release into the environment previously, but these should not be confused with LM insects containing engineered gene drives. It is expected that LM mosquitoes containing engineered gene drives will not be ready for field testing for at least another five years. Moreover, the technology will require testing for several years thereafter to determine their suitability for a vector control strategy.¹⁹ Regardless, several technical challenges (e.g., fitness costs in organisms carrying the drive, and the evolution of resistance that inactivates the drive²⁰) first must be overcome prior to considering environmental release of LMOs for control of wild populations.

Presently, practical experience in undertaking risk assessment for an environmental release of a LM mosquito carrying an engineered gene drive is limited. **However, this limited practical experience should not be**

¹⁴ Neve P. (2018) Gene drive systems: do they have a place in agricultural weed management? *Pest Manag Sci.* 74(12):2671-2679.

¹⁵ See: Harris AF, McKemey AR, Nimmo D, Curtis Z, Black I, Morgan SA, Oviedo MN, Lacroix R, Naish N, Morrison NI, Collado A, Stevenson J, Scaife S, Dafa'alla T, Guoliang F, Phillips C, Miles A, Raduan N, Kelly N, Beech C, Donnelly CA, Petrie WD, Alphey L (2012) Successful suppression of a field mosquito population by sustained release of engineered male mosquitoes. *Nature Biotechnology* 30: 828–830; Winskill P, Carvalho DO, Capurro ML, Alphey L, Donnelly CA, McKemey AR (2015) Dispersal of engineered male *Aedes aegypti* mosquitoes. *PLoS Neglected Tropical Diseases* 9: e0004156; Brazilian CTNBio decision on open field release of GM mosquitoes: <http://www.jusbrasil.com.br/diarios/23935599/dou-secao-1-17-12-2010-pg-48>.

¹⁶ See USDA APHIS 2016. Proposal to permit the field release of genetically engineered diamondback moth in New York, Environmental assessment, available at: https://www.aphis.usda.gov/brs/aphisdocs/16_076101r_pea.pdf.

¹⁷ Harvey-Samuel T, Morrison NI, Walker AS, Marubbi T, Yao J, Collins HL, Gorman K, Davies TGE, Alphey N, Warner S, Shelton AM, Alphey L (2015) Pest control and resistance management through release of insects carrying a male-selecting transgene. *BMC Biology* 13:49.

¹⁸ Leftwich PT, Koukidou M, Rempoulakis P, Gong H-F, Zacharopoulou A, Fu G, Chapman T, Economopoulos A, Vontas J, Alphey L (2014) Genetic elimination of field-cage populations of Mediterranean fruit flies. *Proceedings of the Royal Society B: Biological Sciences* 281: 20141372.

¹⁹ Target Malaria (2016) Open Letter on Gene Drive Technology, available at: <https://targetmalaria.org/open-letter/>; Outreach Network for Gene Drive Research submission on synthetic biology to the CBD (Feb 2019), available at: <https://bch.cbd.int/database/record.shtml?documentid=114306>.

²⁰ Champer J, Liu J, Oh SY, Reeves R, Luthra A, Oakes N, Clark AG, Messer PW (2018) Reducing resistance allele formation in CRISPR gene drive. *Proceedings of the National Academy of Sciences USA* 115: 5522-5527; Callaway E (2017) Gene drives meet the resistance. *Nature* 542: 15; Drury DW, Dapper AL, Siniard DJ, Zentner GE, Wade MJ (2017) CRISPR/Cas9 gene drives in genetically variable and nonrandomly mating wild populations. *Science Advances* 3: e1601910 DOI: 10.1126/sciadv.1601910.

Noble C, Olejarz J, Esvelt KM, Church GM, Nowak MA (2017) Evolutionary dynamics of CRISPR gene drives. *Science Advances* 3: e1601964; Unckless RL, Clark AG, Messer PW (2017) Evolution of resistance against CRISPR/Cas9 gene drive. *Genetics* 205: 827-841; Australian Academy of Science (2017) Discussion Paper: Synthetic gene drives in Australia – Implications of emerging technologies.

interpreted as a regulatory gap that requires support in the form of additional guidance. Review of the relevant experience accumulated with LM mosquito releases in different parts of the world, materials and guidance available for LM mosquitoes, and the growing body of work on LM mosquitoes containing engineered gene drives in containment (see below) demonstrates a precautionary, step-wise and scientifically-sound approach that involves the research community, international expert bodies, and national regulatory authorities. This approach is the same as that taken for the first LMOs released into the environment – LM crops – which were similarly surrounded by concerns about uncertainties. The GIC supports the step-wise approach being taken, which experience has shown to be successful.

A non-exhaustive list of materials developed by international organizations and expert bodies relevant to work with LM mosquitoes containing engineered gene drives, both in contained use and in field trials, is provided below.

World Health Organisation (WHO) guidance and recommendations²¹ issued in line with the Vector Control Advisory Group Guidance

- *The Guidance Framework for testing genetically modified mosquitoes²²*: aims to foster quality and consistency among processes for testing and regulating new genetic technologies by proposing standards of efficacy and safety testing comparable to those used for trials of other new public health tools.
- *Recommendations for efficacy-testing of traps for control of Aedes spp. mosquito vectors²³*: supports product developers, programmes and testing institutions to generate robust entomological evidence of the efficacy of vector traps for control and, for a first-in-class vector trap, evidence of the public health impact in reducing arboviral disease.
- *Guidance and recommendations on designing vector control efficacy trials, phase III vector control field trial design²⁴*: supports designing and conducting phase III epidemiological field trials of new vector control interventions; sets out a framework of steps to take and concerns to be considered when designing and

²¹ See: <https://www.who.int/vector-control/vcag/guidance/en/>.

²² World Health Organisation Special Programme for Research and Training in Tropical Diseases (WHO-TDR) and Foundation for the National Institutes of Health (FNIH) (2014) Guidance framework for testing genetically modified mosquitoes.

²³ World Health Organisation/Department of control of neglected tropical diseases (2018) Efficacy-testing of traps for control of *Aedes* spp. Mosquito vectors. Vector Control Advisory Group WHO/HTM/NTD/VEM/2018.06.

²⁴ World Health Organisation/Department of control of neglected tropical diseases (2017) How to design vector control efficacy trials. Guidance on phase III vector control field trial design. Vector Control Advisory Group WHO/HTM/NTD/VEM/2017.03; World Health Organisation/Department of control of neglected tropical diseases (2017) Design of epidemiological trials for vector control products, Report of a WHO Expert Advisory Panel. WHO/HTM/NTD/VEM/2017.04.

conducting an epidemiological trial to assess the public health value of a new vector control intervention; these steps include defining the research question, choosing the study's design, randomizing the interventions, and calculating the sample size.

- *Data requirements and methods to support the evaluation of new vector control products*²⁵: WHO reviewed data requirements associated with the evaluation of new vector control interventions. The aim is to ensure that these can be deployed as soon as possible, while also ensuring that policy recommendations to guide deployment remain evidence-based.
- *Considerations of ethical issues associated with vector-borne diseases*²⁶: maps ethical issues associated with vector borne diseases highlighting environmental and social determinants of health, the ethics of vector control (including new technologies), relevant aspects of ethics in surveillance and research, and the ethics of mass public health interventions.

The American Committee of Medical Entomology of the American Society of Tropical Medicine and Hygiene

- *Arthropod Containment Guidelines*, Version 3.2²⁷ of the guidelines provide a reference for research laboratories to assess risk and establish protocols for the safe handling of arthropod vectors of human and animal disease agents. The guidelines were originally published in 2004 and have been updated to reflect the spectrum of vector taxa under investigation, and the demands of working with vector arthropods in the context of the Select Agent Rule.

Institute of Safety in Technology and Research (ISTR) UK

- *Safe working with arthropods: Containment and control for work with uninfected, infected and transgenic animals in research*²⁸ covers research work with exotic and UK native species of arthropods (mosquitoes, biting midges and ticks) and GM insects that are vectors of virus diseases affecting animals (such as bluetongue or African horse sickness virus), and humans (such as Zika or dengue fever virus)

French High Council for Biotechnology (HCB)

²⁵ World Health Organisation (2017) Data requirements and methods to support the evaluation of new vector control products. WHO/HTM/GMP/2017.14.

²⁶ World Health Organisation/Department of control of neglected tropical diseases (2017) Ethical issues associated with vector-borne diseases. WHO/HTM/NTD/VEM/2017.07.

²⁷ American Committee of Medical Entomology, American Society of Tropical Medicine and Hygiene (2019) Arthropod Containment Guidelines, Version 3.2. *Vector-Borne and Zoonotic Diseases* 19: 152-173.

²⁸ See:

https://istr.org.uk/resources/Documents/ISTR_Guidance_on_the_Containment_of_Infected_Arthropods_V1_2017.pdf

- *Scientific opinion concerning use of genetically modified mosquitoes for vector control*²⁹ provides review on gene drive research and considerations for risk assessment and management.

Commonwealth Scientific and Industrial Research Organisation (CSIRO)

- *Risk assessment for controlling mosquito vectors with engineered nucleases: Controlled field release for sterile male construct*³⁰: assessed the human health and environmental risks associated with a proposed field release of transgenic Dominant Sterile Male *Anopheles gambiae* mosquitoes from insectaries in Western Africa.

Office of the Gene Technology Regulator (Australia)

- *Regulatory requirements for contained research with GMOs containing engineered gene drives*³¹: provides guidance for Institutional Biosafety Committees and researchers on notification, licensing and physical containment requirements.

European Food Safety Authority

- *Guidance on the environmental risk assessment of genetically modified animals*³² includes recommendations for the environmental risk assessment (ERA) of animals, including insects. Recommends assessing potential effects of GM animals on animal and human health and the environment and the rationales for data requirements for a comprehensive ERA. The document underlines that ERA should be carried out on a case-by-case basis, following a step-by-step assessment approach and highlights the six sequential steps for the assessment (1) problem formulation including hazard and exposure identification; (2) hazard characterisation; (3) exposure characterisation; (4) risk characterisation; (5) risk management strategies; and (6) an overall risk evaluation.

Organisation for Economic Co-operation and Development (OECD)

- Biology consensus documents by the OECD: a biology consensus document for the mosquito *Aedes aegypti*³³ was published in 2018 and another for *Anopheles gambiae* is in development. OECD biology documents are routinely used by regulators in environmental risk assessments of LMOs as they provide

²⁹ HCB Scientific Committee (2017) Scientific Opinion of the High Council for Biotechnology concerning use of genetically modified mosquitoes for vector control in response to the referral of 12 October 2015 (Ref. HCB-2017.06.07). Available at: <http://www.hautconseildesbiotechnologies.fr>.

³⁰ Hayes KR, Hosack GR, Ickowicz A, Foster S, Peel D, Ford J, Thresher R (2018) Risk assessment for controlling mosquito vectors with engineered nucleases: Controlled field release for sterile male construct. CSIRO Health and Biosecurity. Available at: <https://targetmalaria.org/wp-content/uploads/target-malaria-independent-ecological-risk-assement-small-scale-release-sterile-male-executive-summary.pdf>.

³¹ See:

[http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/53139D205A98A3B3CA257D4F00811F97/\\$File/OGTR%20guidance%20on%20gene%20drives.pdf](http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/53139D205A98A3B3CA257D4F00811F97/$File/OGTR%20guidance%20on%20gene%20drives.pdf).

³² European Food Safety Authority (2013) Guidance on the environmental risk assessment of genetically modified animals. *EFSA Journal* 11: 3200.

³³ OECD (2018), Safety Assessment of Transgenic Organisms in the Environment, Volume 8: OECD Consensus Document of the Biology of Mosquito *Aedes aegypti*, Harmonisation of Regulatory Oversight in Biotechnology, OECD Publishing, Paris, <https://doi.org/10.1787/9789264302235-en>.

scientific information on characteristics of the organism such as taxonomy, morphology, life cycle, reproductive biology, genetics, ecology, and interactions with other species and the environment.

CTNBio, Brazil's National Technical Commission on Biosafety

- In April 2014, CTNBio assessed the potential risks of the release in Brazil of the transgenic OX513A strain of *Aedes aegypti* and concluded that such a release would be safe for unconstrained release.³⁴

The GIC highlights that biosafety and containment measures are being carefully reviewed by regulatory bodies and/or by biosafety experts from institutions conducting gene drive research with mosquitoes. Based on the process of gathering information from well-designed experiments, recommendations for adapting standard operating procedures^{35,36} were developed building on established practices for work with mosquitoes in containment. Similarly, a risk assessment framework and methods for risk assessment of activities involving organisms containing engineered gene drives under contained use^{37,38} was recently published in support of gene drive research. Experts concluded that no special risk assessment methodology was judged to be needed aside from considerations reflecting the possibility of genetic spread in the absence of selective advantage to the organism. The main recommendations deemed necessary to safely conduct contained use experiments of organisms containing gene drives are summarized as follows³⁹:

- establish standard operating procedures;
- knowledge of the organisms that are engineered and the gene drive system used is needed in order to establish adequate containment measures;
- use measures that are proportionate to the estimated risk of an establishment of the LMO in the environment in case of an accidental release; and
- consider alternative pathways to meet the needed containment standards.

³⁴ Technical opinion no. 3964/2014. Brasília: National Technical Biosafety Commission; (2014). Available at: <http://bch.cbd.int/database/attachment/?id=14514>.

³⁵ Adelman ZN, Pledger D, Myles KM (2017) Developing standard operating procedures for gene drive research in disease vector mosquitoes. *Pathogens and Global Health* 111: 436-447.

³⁶ Benedict M, Burt A, Capurro M, De Barro P, Handler A, Hayes K, Marshall J, Tabachnick W, Adelman Z (2018) Recommendations for laboratory containment and management of gene drive systems in arthropods. *Vector-Borne and Zoonotic Diseases* 18: 1.

³⁷ van der Vlugt C, van den Akker E, Roesink CH, Westra J (2018) Risk assessment method for activities involving organisms with a gene drive under contained use. RIVM (National Institute for Public Health and the Environment) Letter report 2018-0090.

³⁸ van der Vlugt CJB, Brown DD, Lehmann K, Leunda A, Willemarck N (2018) A framework for the risk assessment and risk management of gene drive technology in contained use. *Applied Biosafety* 23: 25-31.

³⁹ See refs 35-38

Using a deliberative and adaptive approach, conditions for future environmental releases (field trials) of mosquitoes containing engineered gene drives are being developed. They are building on experience with work with insects, pathogenic organisms, pests, LM insects, modeling of spread of natural gene drives⁴⁰, but importantly they are based on established principles found in Annex III of the Protocol. Guidance for contained field trials⁴¹ of LM vector mosquitoes engineered to contain a gene drive system was first proposed in 2008, followed more recently by recommendations for their safe and ethical testing⁴², and considerations for problem formulation for environmental risk assessment.⁴³

It is evident in the scientific literature and the growing body of experimental work on LM mosquitoes containing engineered gene drives that there is consensus regarding the need to take a phased-testing pathway. This is aimed at understanding, on a case-by-case basis, the target organism, its relationship with its environment, and potential unintended consequences. This also represents a precautionary approach, with evaluation at each phase in the pathway informing the next phase, and checkpoints to determine whether the research progresses to the next phase.⁴⁴ For example, the phased-testing pathway described in the WHO *Guidance Framework for testing genetically modified mosquitoes* is reproduced below.⁴⁵

⁴⁰ Cha SJ, Mori A, Chadee DD, Severson DW (2006) Cage trials using an endogenous meiotic drive gene in the mosquito *Aedes aegypti* to promote population replacement. *American Journal of Tropical Medicine and Hygiene* 74: 62–68/

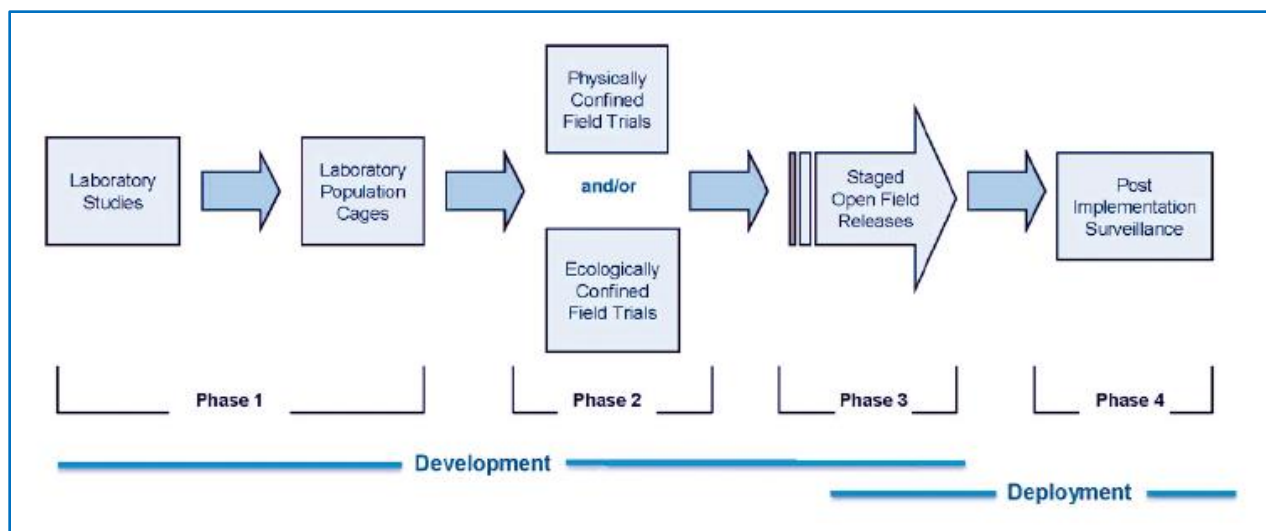
⁴¹ Benedict M, D’Abbs P, Dobson P, Gottlieb M, Harrington L, Higgs S, James A, James S, Knols B, Lavery J, O’Neill S, Scott T, Takken W, Toure Y (2008) Guidance for contained field trials of vector mosquitoes engineered to contain a gene drive system: Recommendations of a scientific working group. *Vector-Borne and Zoonotic Diseases* 8: 127-166.

⁴² James S, Collins FH, Welkhoff PA, Emerson C, Godfray CJ, Gottlieb M, Greenwood B, Lindsay SW, Mbogo CM, Okumu FO, Quemada H, Savadogo M, Singh JA, Tountas KH, Touré Y (2018) 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. *American Journal of Tropical Medicine and Hygiene* 98: 1-49.

⁴³ Roberts A, Andrade PP, Okumu F, Quemada H, Savadogo M, Singh JA, James S (2017) Results from the Workshop “Problem Formulation for the Use of Gene Drive in Mosquitoes”. *American Journal of Tropical Medicine and Hygiene* 96: 530-533.

⁴⁴ National Academies of Sciences Engineering and Medicine (2016) Gene drives on the horizon: Advancing science, navigating uncertainty, and aligning research with public values. Washington, DC: The National Academies Press. doi: 10.17226/23405.

⁴⁵ World Health Organisation Special Programme for Research and Training in Tropical Diseases (WHO-TDR) and Foundation for the National Institutes of Health (FNIH) (2014) Guidance framework for testing genetically modified mosquitoes.



In the pathway above, the Phases consist of, for example:⁴⁶

1. Laboratory testing under highly controlled conditions to obtain preliminary assessment of desired biological and functional characteristics.
2. Confined testing in a more natural setting but under conditions that limit release into the environment.
3. Series of sequential trials of increasing size, duration and complexity, at a single or multiple site, to assess performance under various conditions.
4. Ongoing surveillance to assess effectiveness under operational conditions.

As we have noted above, research with organisms containing engineered gene drives is in the early stages, which corresponds to the laboratory-based work in phase 1 of the pathway illustrated above, and field testing is at least five years away. Another area of work where there is broad consensus among the scientific community is the need for multiple confinement and containment strategies to reduce the potential for unintended releases during gene drive research and development, with stringent physical, reproductive, ecological and molecular barriers recommended for the early phases of testing⁴⁷ (discussed further under

⁴⁶ From: Carter SR, Friedman RM (2016) Policy and regulatory issues for gene drives in insect, Workshop Report. See also: Hayes KR, Hosack GR, Dana GV, Foster SD, Ford JH, Thresher R, Ickowicz A, Peel D, Tizard M, De Barro P, Strive T, Dambacher JM (2018) Identifying and detecting potentially adverse ecological outcomes associated with the release of gene drive organisms. *Journal of Responsible Innovation* DOI: doi.org/10.1080/23299460.2017.1415585.

⁴⁷ Akbari OS, Bellen HJ, Bier E, Bullock SL, Burt A, Church GM, Cook KR, Duchek P, Edwards OR, Esvelt KM, Gantz VM, Golic KG, Gratz SJ, Harrison MM, Hayes KR, James AA, Kaufman TC, Knoblich J, Malik HS, Matthews KA, O'Conner-Giles KM, Parks AL, Perrimon N, Port F, Russell S, Ueda R, Wildonger J (2015) Safeguarding gene drive experiments in the laboratory – Multiple stringent confinement strategies should be used whenever possible. *Science* 349: 927-929; National Academies of Sciences Engineering and Medicine (2016) Gene drives on the horizon: Advancing

Topic B). We note that a similar approach was taken with the early development of LM crops, now long-established with commercial releases throughout the world, and such an approach is recommended for any “new” LMO.⁴⁸

In addition to technical guidance on biosafety considerations and risk assessment for gene drives, broader policy assessments have also been developed at national levels. For example, the Netherlands Government Gene drives Policy report⁴⁹ provides recommendations on adjustments to the existing risk assessment provisions to account for the potential for spread of the gene drive, and to prevent inadvertent creation of gene drives by researchers in the lab. It also highlights the need for international approaches considering the potential for spread of gene drive organisms. In 2016, the National Academies of Sciences Engineering and Medicine (NASEM) published a review of the science and considerations for responsible use of the technology that highlighted areas for further research as well as recommending a phased testing pathway as discussed above.⁵⁰ The gene drive research community responded to the 2016 NASEM publication by developing a set of “Principles for Gene Drive Research”.⁵¹ These are intended to be guiding principles for sponsors and supporters of gene drive research, and they include: advancing quality science to promote the public good; promoting stewardship, safety and good governance; demonstrating transparency and accountability; thoughtful engagement with affected communities, stakeholders and the public; and fostering opportunities to strengthen capacity and education.

ii. LM Fish

Risk assessment strategies for fish modified by the addition of a gene construct have been available for over twenty years. The Environmental Risk Assessment of Genetically Modified Organisms, Volume 3, Methodologies for Transgenic Fish was published in 2007, and presents a comprehensive risk assessment framework and methodologies for assessing risk for this class of organisms. Many of the methods described in this volume have been applied in the review and approval of a genetically modified Atlantic Salmon in the

science, navigating uncertainty, and aligning research with public values. Washington, DC: The National Academies Press. doi: 10.17226/23405.

⁴⁸ Hayes KR, Hosack GR, Dana GV, Foster SD, Ford JH, Thresher R, Ickowicz A, Peel D, Tizard M, De Barro P, Strive T, Dambacher JM (2018) Identifying and detecting potentially adverse ecological outcomes associated with the release of gene drive organisms. *Journal of Responsible Innovation* DOI: doi.org/10.1080/23299460.2017.1415585.

⁴⁹ Westra J, van der Vlugt CJB, Roesink CH, Hogervorst PAM, Glandorf DCM (2016) Gene drives Policy report. RIVM Letter report 2016-0023.

⁵⁰ National Academies of Sciences Engineering and Medicine (2016) Gene drives on the horizon: Advancing science, navigating uncertainty, and aligning research with public values. Washington, DC: The National Academies Press. DOI: 10.17226/2340.

⁵¹ Emerson C, James S, Littler K, Randazzo F (2017) Principles for gene drive research. *Science* 358: 1135-1136.

United States and Canada (approved as AquAdvantage Salmon, NADA # 141-454 in the United States, and as AquAdvantage Salmon, a novel food, in Canada).

In the review and approval of AquAdvantage Salmon in the United States (approved as NADA 141-454 on November 19, 2015), the United States Food and Drug Administration (US-FDA) considered the safety of the modified fish itself, the safety of the food derived from it for humans and the safety of the production of the fish to the environment. Based on the multiple forms of physical and biological containment proposed by AquaBounty Technologies in their first and supplemental application, the US-FDA found that an approval of the applications related to AquAdvantage Salmon would not have a significant impact on the environment of the United States. The overall process is described on the Center for Veterinary Medicine website (www.fda.gov/AnimalVeterinary) and the resulting approvals and supporting documents, including the environmental risk assessment (“Risk Assessment and the Finding of No Significant Impact”)⁵², are available on the FDA website.⁵³ The risk assessment conducted by the US-FDA considered all life stages and all zygosity and ploidy levels required for the production of AquAdvantage, as well as the conditions for use of the product, being grown in physically contained facilities. The assessment, based on extensive knowledge of the characteristics of the conventional organism, considered the likelihood of escape, the likelihood of survival, dispersion and reproduction in the event of an escape from containment. Lastly, the assessment considered the potential consequences or effects on the environment should AquAdvantage be introduced into the environment. The conclusions of the review determined that the conditions for use included the appropriate controls, genetic, physical, and procedural controls, to mitigate any perceived risk of environmental impact, further leading to a Finding of No Significant Impact (FONSI). Detailed information on the US-FDA website provides information on the AquAdvantage product, its conditions of use, the studies considered for its regulatory approval, and the rationale of the various risk assessments conducted by the US-FDA during its review of the application.

In Canada, LM fish products such as AquAdvantage are regulated by Environment and Climate Change Canada (ECCC) under the New Substances Notification Regulations (Organisms) [NSNR(Organisms)] of the Canadian Environmental Protection Act, 1999 (CEPA). CEPA is administered by both ECCC and Health Canada (HC). For applications involving fish, ECCC and HC have executed a Memorandum of

⁵² ⁵² Available at:

<https://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/BiotechnologyProductsatCVMAnimalsandAnimalFood/AnimalswithIntentionalGenomicAlterations/ucm280853.htm>.

⁵³ The link to the full Environmental Assessment for AquAdvantage is located at:

<https://www.fda.gov/downloads/AnimalVeterinary/DevelopmentApprovalProcess/BiotechnologyProductsatCVMAnimalsandAnimalFood/AnimalswithIntentionalGenomicAlterations/UCM605680.pdf>.

Understanding (MOU) with the Department of Fisheries and Oceans (DFO) to provide additional expertise in assessing environmental and indirect human health risks associated with LM fish. The assessment considered the potential for acute or chronic release of AquAdvantage, the potential for release during transit of life forms, and the potential environmental impact of such releases. The conclusions of the assessment panel were peer reviewed by a panel of scientific experts from DFO, HC, ECCC, and external scientists with relevant expertise. A summary of the risk assessment and its conclusions may be found on DFO's website on Aquatic Biotechnology Regulation,⁵⁴ and published in Science Response 2013/023, November 2013.

There are many publications relating to risk assessment of LM fish, as outlined in Annex I below. This knowledge base, in combination with the expertise of these two countries in conducting the risk assessments for LMOs, allowed for environmental risk assessments to be undertaken without any legitimate challenges identified, or any impediments resulting in delays in product development and commercialization. We also highlight that there is a great deal of knowledge about the conventional organism,⁵⁵ which lends itself to guiding the case-by-case assessment called for in Annex III of the Protocol. The most significant challenges in relation to risk assessment of LM fish are the concerns that the existing experience is somehow inadequate. Environmental risk assessment of LM fish is being conducted by multiple regulatory authorities, using well-established methodologies and principles, and with the background of extensive familiarity with the conventional organism. No novel challenges have been presented by this "new" (non-crop) organism, nor have any specific additional needs have been identified relevant to environmental risk assessment. Thus, the GIC will not be providing a response to Topic B (Challenges experienced or foreseen in undertaking risk assessment of living modified fish).

⁵⁴ <http://www.dfo-mpo.gc.ca/science/biotech-genom/regulation/index-eng.htm>

⁵⁵ E.g., see:

[http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono\(2017\)64&doclanguage=en](http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2017)64&doclanguage=en)

B. Challenges experienced or foreseen in undertaking risk assessment of living modified organisms containing engineered gene drives and living modified fish;

i. LMOs Containing Gene Drives

As noted above in topic A, research with LM mosquitoes containing engineered gene drives is in the early stages (phase 1) and direct experience with environmental risk assessments for these types of LMOs is limited compared to the experience that exists with “traditional” LMOs (e.g. LM crops) or LM mosquitoes. The gene drive research community is actively investigating questions about the behavior of engineered gene drives in wild populations using modelling⁵⁶ and information obtained from “lab releases”.⁵⁷ These data are supplemented by the large body of relevant guidance (listed above in topic A), and we also note that the existing scientific literature should not be overlooked. An investigation into the information available for a range of parameters for potential gene drive target species (for the control of invasive species in Australia) revealed the existence of information relevant to a LMO environmental risk assessment, e.g. biological information for the target species such as its mating system; ecological information such as its distribution, gene flow and interactions with other species in the receiving environment; and risk management options.⁵⁸ Additional considerations for further investigation that were identified included population dynamics of the target species, and implications for ecosystem food webs. This work indicates that gene drive target species are likely, due to their nature (e.g. where they are an environmental problem), to be well characterised, with information gaps and how to address them readily identifiable.

Parallel research by the scientific community includes investigation of mitigation strategies (i.e. risk management) in the event of unintended release or consequences, and mechanisms that have been proposed include molecular (e.g. separation of drive components) and physical confinement; geographical (e.g. trials in regions where there are no native populations of the target organisms), ecological or reproductive containment; the tandem use of immunization drives; the release of reversal drives to remove the initially

⁵⁶ See e.g. de Jong TJ (2017) Gene drives do not always increase in frequency: from genetic models to risk assessment. *Journal of Consumer Protection and Food Safety* 12: 299-307.

⁵⁷ See NPR (20 Feb 2019) Scientists release controversial genetically modified mosquitoes in high-security lab: <https://www.npr.org/sections/goatsandsoda/2019/02/20/693735499/scientists-release-controversial-genetically-modified-mosquitoes-in-high-security>.

introduced trait; and the use of drives designed to have limited spread (e.g. threshold dependent drives).⁵⁹ It is also proposed that the presence and prevalence of engineered gene drives could be monitored by targeted amplification or meta-genomic sequencing of environmental samples.⁶⁰ It is noteworthy that several mitigation strategies and combinations of these were also proposed for LM crops in the early years of commercialization in response to similar concerns.⁶¹

The GIC is of the view that perceived challenges to undertaking risk assessment of LMOs containing engineered gene drives are readily manageable following an approach similar to that which has been used in the development and environmental release of other LMOs.⁶² However, we note that for LMOs containing engineered gene drives, there exist accumulated prior knowledge, experienced risk assessors and regulators and a plethora of directly relevant resources. In addition, the scientific community has a high awareness of concerns about the technology and a willingness to work with regulators and other experts to ensure a transparent, precautionary, step-wise approach. We emphasise that a case-by-case approach is critical to undertaking a risk assessment and identifying information needs – and these needs must be separated from speculation and exaggerated claims.⁶³

Experience from the risk assessment of LM mosquitoes indicates that it is important to also take into account and compare proposed actions with the “no action” alternative or status quo^{64,65} and integrate these considerations in the decision-making process. Similar considerations would be equally relevant in relation to organisms containing engineered gene drives.

⁵⁹ Australian Academy of Science (2017) Discussion Paper: Synthetic gene drives in Australia – Implications of emerging technologies; Royal Society (2018) Statement: Gene drive research: why it matters. See also Akbari OS, Bellen HJ, Bier E, Bullock SL, Burt A, Church GM, Cook KR, Duchek P, Edwards OR, Esvelt KM, Gantz VM, Golic KG, Gratz SJ, Harrison MM, Hayes KR, James AA, Kaufman TC, Knoblich J, Malik HS, Matthews KA, O’Conner-Giles KM, Parks AL, Perrimon N, Port F, Russell S, Ueda R, Wildonger J (2015) Safeguarding gene drive experiments in the laboratory – Multiple stringent confinement strategies should be used whenever possible. *Science* 349: 927-929.

⁶⁰ Oye KA, Esvelt K, Appleton E, Catteruccia F, Church G, Kuiken T, Lightfoot SB-Y, McNamara J, Smidler A, Collins JP (2014) Regulating gene drives. *Science* DOI: 10.1126/science.1254287.

⁶¹ See e.g. Daniell H (2002) Molecular containment strategies for gene containment in transgenic crops. *Nature Biotechnology* 20:581-586.

⁶² Andrade PP, Aragão FJL, Colli W, Dellagostin OA, Finardi-Filho F, Hirata MH, Lira-Neto AC, Melo MA, Nepomuceno AL, Nóbrega FG, Sousa GD, Valicente FH, Zanettini MHB (2016) Use of transgenic *Aedes aegypti* in Brazil: risk perception and assessment. *Bulletin of the World Health Organisation* 94: 766-771.

⁶³ Panjwani A, Wilson A (2016) What is stopping the use of genetically modified insects for disease control? *PLoS Pathogens* 12: e1005830 DOI:10.1371/journal.ppat.1005830.

⁶⁴ Alphey L, Beech C (2012) Appropriate regulation of GM insects. *PLoS Neglected Tropical Diseases* 6(1): e1496.

⁶⁵ Turner G, Beech C, Roda L (2018) Means and ends of effective global risk assessments for genetic pest management. *BMC Proceedings* 12(Suppl 8): 13.

The GIC recognizes that differences in experience in undertaking risk assessment is a real and ongoing challenge for some Parties, but does not believe that this can be resolved by the development of additional guidance under the Protocol given the existing relevant body of work. Instead, greater effort should be focused on Parties and other Governments and relevant expert bodies with experience in LMO risk assessment sharing their experiences with Parties that need capacity building.

C. Specific needs (if any) to properly undertake risk assessment of living modified organisms containing engineered gene drives.

i. LMOs Containing Gene Drives

For LM mosquitoes containing engineered gene drives, the GIC is of the view that specific information should be gathered along the phased-testing pathway mentioned in A. This may include the generation of biological data for the target species, modelling of its environmental behavior, or the collection of data from releases of increasing scale. The outcomes of each phase of the testing pathway should facilitate and strengthen evidence-based risk assessments for increasing scales of release. We emphasise that the specific information (evidence) needed for undertaking risk assessment will vary on a case-by-case basis – e.g. depending on the target species, the area of environmental release, and the type of gene drive. A basis in sound science and a case-by-case approach are fundamental principles enshrined in Annex III of the Protocol, and these are applicable to any LMO. These have been applied to risk assessment of LMOs that have been released into the environment for more than 20 years in many parts of the world⁶⁶, without evidence for adverse impacts. Such an approach is necessary to promote the safe development and use of beneficial applications of technology and identify appropriate risk mitigation measures.

⁶⁶ Becker MP, Boari P, Burachik M, Cuadrado V, Junco M, Lede S, Lema MA, Lewi D, Maggi A, Meoniz I, Noe G, Roca C, Robredo C, Rubinstein C, Vicien C, Whelan A (2016) Development of a construct-based risk assessment framework for genetic engineered crops. *Transgenic Research* DOI 10.1007/s11248-016-9955-3.

Annex I
Peer-reviewed Publications Relevant to Environmental Risk Assessment
of LM Fish

ABRAC [Agricultural Biotechnology Research Advisory Committee] (1995). Performance standards for safely conducting research with genetically modified fish and shellfish. Document No. 95-04, Office of Agricultural Biotechnology, U.S. Department of Agriculture, 156 pp.

Abrahams, M.V., and A. Sutterlin (1999). The foraging and antipredator behaviour of growth enhanced transgenic Atlantic salmon. *Anim. Behav.* 58: 933–942.

Cnaani, A., E. McLean, and E.M. Hallerman. 2013. Effects of growth hormone transgene expression and triploidy on acute stress indicators in Atlantic salmon (*Salmo salar* L.). *Aquaculture* 412-413: 107–116.

Crossin, G.T., and R.A. Devlin (2017). Predation, metabolic priming and early life-history rearing environment affect the swimming abilities of growth hormone transgenic rainbow trout. *Biol. Lett.* 13:20170279.

Crossin, G.T., L.F. Sundström, W.E. Vandersteen, and R.H. Devlin (2015). Early life-history consequences of growth-hormone transgenesis in rainbow trout reared in stream ecosystem mesocosms. *PLoS ONE* 10(3): e0120173.

Cook, J.T., M.A. McNiven, and A.M. Sutterlin (2000a). Metabolic rate of pre-smolt growth enhanced transgenic Atlantic salmon (*Salmo salar*). *Aquaculture* 188: 33–45.

Cook, J.T., A.M. Sutterlin, and M.A. McNiven (2000b). Effect of food deprivation on oxygen consumption and body composition of growth-enhanced transgenic Atlantic salmon (*Salmo salar*). *Aquaculture* 188: 47–63.

Cook, J.T., M.A. McNiven, G.F. Richardson, et al. (2000c). Growth rate, body composition, and feed digestibility/conversion of growth-enhanced transgenic Atlantic salmon. *Aquaculture* 188: 15–32.

Cotter, D., V. O'Donovan, N. O'Maoiléidigh, et al. (2000). An evaluation of the use of triploid Atlantic salmon (*Salmo salar* L.) in minimizing the impact of escaped farmed salmon on wild populations. *Aquaculture* 186: 61–75.

Deitch, E.J., G.L. Fletcher, L.H. Petersen, et al. (2006). Cardiorespiratory modifications, and limitations, in post-smolt growth hormone transgenic Atlantic salmon *Salmo salar*. *J. Exp. Biol.* 209: 1310–1325.

Devlin, R.H., C.A. Biagi, and T.Y. Yesaki (2004a). Growth, viability and genetic characteristics of GH transgenic coho salmon strains. *Aquaculture* 236: 607–632.

Devlin, R.H., M. D'Andrade, M. Uh, et al. (2004b). Population effects of growth hormone transgenic coho salmon depend on food availability and genotype by environment interactions. *Proc. Natl. Acad. Sci. USA* 101: 9303–9308.

Devlin, R.H., J.I. Johnsson, D.E. Smailus, et al. (1999). Increased ability to compete for food by growth hormone-transgenic coho salmon *Oncorhynchus kisutch* (Walbaum). *Aquacult. Res.* 30: 479–482.

Devlin, R.H., L.F. Sundström, and R.A. Leggatt (2015). Assessing ecological and evolutionary consequences of growth-accelerated genetically engineered fishes. *BioScience* 65:685–700.

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- Devlin, R.H., T.Y. Yesaki, E.M. Donaldson, et al. (1995a). Production of germline transgenic Pacific salmonids with dramatically increased growth performance. *Can. J. Fish. Aquat. Sci.* 52: 1376–1384.
- Devlin, R.H., T.Y. Yesaki, E.M. Donaldson, et al. (1995b). Transmission and phenotypic effects of an antifreeze/GH gene construct in coho salmon (*Oncorhynchus kisutch*). *Aquaculture* 137: 161–169.
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