EVENT REPORT

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Stakeholder workshop "Problem formulation for the environmental risk assessment of gene drive modified insects" (15 May 2019, Brussels)

European Food Safety Authority (EFSA),
Yann Devos, Barbara Gallani and Leslie G Firbank

Abstract

Recent advances in molecular and synthetic biology are enabling the engineering of gene drives that spread genes of interest through interbreeding populations at a frequency greater than the rate expected by simple Mendelian inheritance. At present, insects represent the most likely cases of gene drive modified organisms for deliberate release into the environment. Through an open workshop, the European Food Safety Authority (EFSA) aimed to engage with stakeholders to discuss potential environmental risks associated with the deliberate release into the environment of gene drive modified insects. Workshop participants were invited to contribute to an example problem formulation to: (1) identify relevant broad protection goals and make them operational for use in environmental risk assessment; (2) formally devise examples of plausible pathways to harm that describe how the deployment of gene drive modified insects could be harmful; (3) formulate example risk hypotheses about the likelihood and severity of such events; (4) identify possible information that would be useful to test these risk hypotheses; and (5) identify how to acquire new data for hypothesis testing when existing information is deemed insufficient for regulatory decision-making. The problem formulation exercise was run for two hypothetical case studies (i.e. self-sustaining low threshold gene drives to control disease-spreading mosquitoes (*Aedes albopictus,* the Asian tiger mosquito) and agricultural pests (*Drosophila suzukii,* the spotted-wing *Drosophila*)). Points raised by the workshop participants reveal different often contrasting opinions/perspectives toward gene drive and their risk assessment. Overall, there was agreement that the problem formulation process is fit-for-purpose for the environmental risk assessment of gene drive modified insects, but it was acknowledged that practical challenges may be encountered. Points raised by the workshop participants, on defining protection goals, formulating specific pathways to harm and on structuring risks, have been considered by EFSA's Panel on genetically modified organisms during its deliberations.

Key words: Deliberate release, harm, pathway to harm, protection goal, replacement, risk hypothesis, self-limiting gene drive, self-sustaining gene drive, suppression

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Correspondence: Any enquires related to this output should be addressed to gmo@efsa.europa.eu

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Summary

Through an open workshop, the European Food Safety Authority (EFSA) aimed to engage with stakeholders to discuss potential environmental risks associated with the deliberate release into the environment of gene drive modified insects.[1]

Workshop participants were invited to contribute to an example problem formulation to: (1) identify relevant broad protection goals and make them operational for use in environmental risk assessment; (2) formally devise examples of plausible pathways to harm that describe how the deployment of gene drive modified insects could be harmful; (3) formulate example risk hypotheses about the likelihood and severity of such events; (4) identify possible information that would be useful to test these risk hypotheses; and (5) identify how to acquire new data for hypothesis testing when existing information is deemed insufficient for regulatory decision-making. The problem formulation exercise was run for two hypothetical case studies (i.e. self-sustaining low threshold gene drives to control disease-spreading mosquitoes (*Aedes albopictus,* the Asian tiger mosquito) and agricultural pests (*Drosophila suzukii,* the spotted-wing *Drosophila*)).

The goal of the workshop was to familiarise the participants with the problem formulation process and its function in environmental risk assessment, and to gather feedback on this approach, instead of producing a comprehensive and detailed environmental risk assessment of the two case studies of gene drive modified insects.

Points raised by the workshop participants reveal different often contrasting opinions/perspectives toward gene drive and their risk assessment. They have been organised according to the following topics: (1) gene drive strategies; (2) potential novel hazards/risks; (3) risk assessment paradigm; (4) familiarity with/experience from existing insect vector/pest control strategies; (5) problem formulation; (6) potential harms; (7) comparators; (8) receiving environments; (9) risk management; and (10) post-market environmental monitoring.

Overall, there was agreement among the workshop participants that the problem formulation process is fit-for-purpose for the environmental risk assessment of gene drive modified insects, but it was acknowledged that practical challenges may be encountered.

Points raised by the workshop participants, on defining protection goals, formulating specific pathways to harm and on structuring risks, have been considered by EFSA's Panel on genetically modified organisms during its deliberations.

[1] This event report focuses on insect pest species, in particular disease-transmitting mosquitoes and agricultural pests for deliberate release into the environment

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1. Introduction

Recent advances in molecular and synthetic biology are enabling the engineering of gene drives that spread genes of interest through interbreeding populations at a frequency greater than the rate expected by simple Mendelian inheritance. The ability to engineer gene drives has sparked both enthusiasm and concerns among scientists and citizens. While engineered gene drives could be used to control agricultural pests and invasive species, rescue endangered species or supress disease vectors, there is concern that they may also have unintended effects and alter ecosystems in an irreversible manner.

As potential future applications for the placement of genetically modified organisms on the EU market (including public use) may include the deliberate release into the environment of genetically modified organisms with engineered gene drives, the European Food Safety Authority (EFSA) has been requested by the European Commission to assess, through a problem formulation exercise, whether:

(1) the deliberate release of gene drive modified organisms could pose potential new hazards and risks to human/animal health and the environment, considering relevant comparators;

(2) the scientific considerations/requirements given in its previously published guidelines for the risk assessment of genetically modified animals (EFSA, 2012, 2013) are adequate for the molecular characterisation and environmental risk assessment of gene drive modified organisms;

(3) there is a need for updated guidance in relation to previous documents.

This advice is expected to support the EU in its work under the Convention on Biological Diversity[2] and the Cartagena Protocol on Biosafety.[3] The Cartagena Protocol and its Nagoya–Kuala Lumpur Supplementary Protocol on Liability and Redress[4] aim to ensure safe handing, transport, and use of living modified organisms resulting from modern biotechnology that may have adverse effects on biodiversity, also taking into account risks to human health. These multinational agreements bear direct relevance for the governance of gene drive modified organisms.

2. Stakeholder workshop

Through an open workshop, EFSA aimed to engage with stakeholders to discuss potential environmental risks associated with the deliberate release into the environment of gene drive modified insects. At present, insects represent the most likely cases of gene drive modified organisms for deliberate release into the environment.

To focus the discussions, workshop participants were invited to contribute to an example problem formulation to:

(1) Identify relevant broad protection goals and make them operational for use in environmental risk assessment;

(2) Formally devise examples of plausible pathways to harm that describe how the deployment of gene drive modified insects could be harmful;

(3) Formulate example risk hypotheses about the likelihood and severity of such events;

(4) Identify possible information that would be useful to test these risk hypotheses;

(5) Identify how to acquire new data for hypothesis testing when existing information is deemed insufficient for regulatory decision-making.

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2 The Convention on Biological Diversity is a multilateral treaty under the auspices of the United Nations Environment Program. Its major goals are the conservation of biodiversity, sustainable use of the components of biodiversity, and fair and equitable sharing of benefits arising from genetic resources stemming from biodiversity

3 The Cartagena Protocol on Biosafety to the Convention on Biological Diversity was adopted on 29 January 2000, and entered into force on 11 September 2003. The Cartagena Protocol presently has 171 contracting parties, excluding large LMO exporters such as Argentina, Canada and the United States

4 The Nagoya–Kuala Lumpur Supplementary Protocol on Liability and Redress to the Cartagena Protocol on Biosafety was adopted on 15 October 2010, and entered into force on 5 March 2018 The Supplementary Protocol presently has 43 contracting parties, chiefly from the European and African regions

The problem formulation exercise was run for two hypothetical case studies in two separate discussion groups (see Section 3):

(1) Self-sustaining low threshold gene drives to control disease-spreading mosquitoes (*Aedes albopictus,* the Asian tiger mosquito);

(2) Self-sustaining low threshold gene drives to control agricultural pests (*Drosophila suzukii,* the spotted-wing *Drosophila*).

The two case studies were selected representing species relevant for the EU.

(1) *Aedes albopictus*, the Asian tiger mosquito, is an aggressive biting mosquito native to Asia that has colonised all continents, except Antarctica, during the last ~30-40 years. The species is of great public health concern as it can transmit several arboviruses, including dengue, chikungunya and Zika viruses. With climate change, the *Ae. albopictus* transmission potential is likely to increase substantially for most of Europe even in the short term;

(2) *Drosophila suzukii*, commonly known as the spotted-wing *Drosophila*, is a highly invasive pest that has recently and rapidly expanded out of its native range, in Southeast Asia, to Europe and both North and South America, where it causes significant economic damage to the fruit sector. Females lay eggs inside ripening soft-skinned fruits, and larvae feed inside the fruit, which becomes soft and rots.

The outcomes of the two discussion groups were presented and further developed in a final plenary session, during which the conclusions of the workshop were drawn.

The goal of the workshop was not to produce a comprehensive and detailed environmental risk assessment of the two case studies of gene drive modified insects, but rather to familiarise the participants with the problem formulation process and its function in environmental risk assessment, and to gather feedback on this approach.

Any points raised by workshop participants should not necessarily be interpreted as comprising substantiated hazards or risks associated with the two hypothetical case studies of gene drive modified insects that are supported by evidence from the scientific literature.

The workshop materials supplied by EFSA and speakers (i.e. agenda and briefing notes for participants, list of participating stakeholders and presentations) are available on EFSA's website.[5]

3. Scientific program

08:15-09:00	**Registration and welcome coffee**	
SESSION 1 | Plenary session Chair: Barbara Gallani, European Food Safety Authority (IT)		
09:00-09:15	**Welcome and introduction to the workshop**	Barbara Gallani, European Food Safety Authority (IT) and Leslie Firbank, University of Leeds (UK)
09:15-10:00	**Keynote: Gene drive modified insects – Hopes, fears, gene drive systems and problem formulation concepts** Questions	Fred Gould, North Carolina State University (US)
10:00-10:30	**Problem formulation consultations for gene drive modified mosquitoes designed to reduce malaria transmission in Africa** Questions	Stephanie James, Foundation for the National Institutes of Health (US)
10:30-10:45	**Coffee/Tea break**	

[5] https://www.efsa.europa.eu/en/events/event/190515

10:45-11:15	**Problem formulation for the environmental risk assessment of gene drive modified *Drosophila suzukii*** Questions	Jörg Romeis, Agroscope (CH)
11:15-11:55	**Experiences with gene drives and risk assessment implications: Opinion of the Netherlands Commission on Genetic Modification (COGEM)** Questions	Marjan Bovers, The Netherlands Commission on Genetic Modification (NL) and Patrick Rüdelsheim, Perseus (BE)
11:55-12:15	**Discussion**	
12:15-13:00	**Lunch break**	
SESSION 2A | Case study: Gene drive modified mosquitoes **Moderator: Fred Gould, North Carolina State University (US)**		**SESSION 2B | Case study: Gene drive modified agricultural pests** **Moderator: Leslie Firbank, University of Leeds (UK)**
13:00-15:30	**Discussion**	
15:30-15:45	**Coffee/Tea break**	
SESSION 3 | Plenary session **Chair: Barbara Gallani, European Food Safety Authority (IT)**		
15:45-15:55	**Reporting on discussion group 2A**	John Mumford, Imperial College London (UK)
15:55-16:05	**Reporting on discussion group 2B**	Michael Bonsall, University of Oxford (UK)
16:05-16:30	**Discussion**	
16:30-16:45	**Concluding remarks and closing of the workshop**	Barbara Gallani, European Food Safety Authority (IT) and Leslie Firbank, University of Leeds (UK)

4. Speakers' abstracts

4.1. Gene drive modified insects – Hopes, fears, gene drive systems and problem formulation concepts (by Fred Gould)

The field of insect genetic engineering, and more specifically, gene drive research has been advancing rapidly in laboratory settings. The advent of CRISPR-Cas technology is enabling broader access to tools needed for building strains that could spread genes into populations, even if those genes decrease the survival and/or reproduction of individuals that carry them. In this presentation, I will give a brief review of the history of genetic pest management over the past 60 years with emphasis on developments in the past 10 years. I will discuss the two dimensions that differentiate among gene drive strategies: (1) population suppression versus alteration; and (2) spatially unlimited drives versus those that only spread locally. This will be followed by an examination of case studies of two mosquito species that transmit human diseases and one example from agriculture and biodiversity conservation. I will use these case studies to demonstrate the great technical progress that has been made as well as the technical challenges ahead in each of the cases. This will lead into a discussion of the need for broad stakeholder engagement and environmental risk assessment well before a product is ready for release if we are to move the field of genetic pest management forward in a manner consistent with the concept of "Responsible Innovation".

4.2. Problem formulation consultations for gene drive modified mosquitoes designed to reduce malaria transmission in Africa (by Stephanie James, Andrew Roberts and Aggrey Ambali)

Scientists have speculated for decades about how naturally occurring gene drive mechanisms might be harnessed to insert beneficial traits into populations of insect vectors for controlling disease transmission. New techniques of modern molecular biology now have made this possible, and researchers are working to apply this technology for control of malaria in Africa. Before any releases of gene drive modified mosquitoes are contemplated, it is important to conduct a thorough risk assessment. To support the risk assessment process, a series of consultations were held in the US and four regions of Africa bringing together scientists, biotechnology regulators, health professionals and government policymakers to familiarise participants with the tool of problem formulation to identify protection goals and begin to consider potential hazards and pathways to harm associated with use of gene drive mosquitoes. A case study approach was utilised, providing examples of theoretical gene drive applications for reducing numbers of vector mosquitoes or reducing the mosquitoes' ability to transmit the malaria parasite. All groups identified human and animal health and biodiversity as relevant protection goals. Water quality also was identified by some. Soil quality, air quality, agriculture and natural resources largely were not considered pertinent. While a thorough consideration of possible causal pathways to harm was not possible within these brief workshops, participants were able to propose exemplary pathways and there was some consistency among the different workshops in the potential pathways most often raised. The results of these consultations should inform future environmental risk assessments of gene drive modified mosquitoes by identifying potential harms of broad concern to relevant stakeholders. Identification of common concerns also will be important to product developers to help them understand the data that will be required to decrease uncertainties about this new technology.

4.3. Problem formulation for the environmental risk assessment of gene drive modified *Drosophila suzukii* (by Jörg Romeis, Jana Collatz, Debora CM Glandorf and Michael B Bonsall)

Some insects are a threat to agricultural production and humans have thus always aimed at controlling or eradicating such species. This has been achieved by a variety of methods including the use of chemical or biological insecticides, resistant crop varieties (bred conventionally or by genetic modification, biological control (caused by predators, parasitoids, or entomopathogens), and genetic control methods such as the sterile insect technique or the incompatible insect technique that is based on the cytoplasmic incompatibility caused by *Wolbachia* endosymbionts.

The advent of molecular biology has allowed the development and adoption of synthetic gene drive constructs for insect pest management. Theoretically, this tool allows local or even global eradication of a target species. One of the potential applications of this technology is the management of invasive species that are causing increasing problems worldwide.

We will use the spotted-wing Drosophila (*D. suzukii*) as a case study. *D. suzukii* is of Asian origin but has established widely in Europe and the Americas during recent years. Since it can oviposit into undamaged, ripening fruit it causes serious damage. Recently, a *Medea* drive-system has been functionally developed for *D. suzukii.*

Using this case study, several pathways will be presented on how the release of such gene drive modified *D. suzukii* could cause harm to biodiversity. We will discuss this in the context of environmental risk assessment practices and experience with other insect pest control technologies that require the release of living insects. This includes the use of (exotic) biological control organisms in classical biocontrol programs, sterile genetically modified insects and the incompatible insect technique. We consider that existing risk assessment frameworks can be used to assess the potential adverse effects from insects carrying gene drives to control agricultural pests.

4.4. Experiences with gene drives and risk assessment implications: Opinion of the Netherlands Commission on Genetic Modification (COGEM) (by Marjan Bovers, Greet Smets and Patrick Rüdelsheim)

Gene drives are genetic mechanisms that may increase the frequency of a gene beyond the frequencies obtained by Mendelian inheritance. Recently, interest in gene drives has increased due to the possibilities offered by the CRISPR-Cas9 system. At the same time, concerns that the release of organisms with synthetic gene drives may irreversibly result in the suppression or the replacement of all wild-type alleles and/or individuals were raised. In order to gain insight on the potential consequences of a (accidental or intentional) release, The Netherlands Commission on Genetic Modification (COGEM) commissioned Perseus to map the experiences obtained with gene drive systems, both natural and synthetic.

Key findings include:

- Research on synthetic gene drives is so far limited to laboratory experiments and modelling;
- Field (cage) experiments and releases with modified naturally occurring gene drives are almost exclusively with mosquitoes;
- The potential spread of a gene drive is dependent on the biology of the host organism, population dynamics, the drive's efficacy, its fitness cost to the host, resistance development by the host and fitness cost of the "load";
- Homing endonucleases, such as CRISPR-Cas-based gene drives, are extremely sensitive to mutations or genetic variability in their recognition sites. This limits the spread of drives based on these mechanisms, at least for simple designs;
- Gene drives that bring a fitness cost are expected to accelerate resistance development;
- The experiments carried out so far suggest that an escape of a few individuals will not result in an invasion or transfer of the gene drive to non-intended populations.

Based on this state-of-the-art report, COGEM concludes that the concern that the release of organisms with gene drives will inevitably lead to the suppression or replacement of all wild-type individuals should be qualified.

5. Main points raised by workshop participants

5.1. Gene drive strategies

Participants addressed criteria to categorise gene drives, as gene drives are not all the same and encompass different molecular mechanisms. It was suggested to consider the following dimensions to categorise gene drives:

- Spread characteristics (temporally or spatially restricted *vs*. unrestricted gene drives);
- Impact (population replacement *vs*. suppression);
- Threshold dependency or not.

It was noted that gene drives can change from a category to another as they spread within a target population. Reference was made to a hypothetical example of a replacement gene drive that would change the host finding behaviour of the target insect. Theoretically, this could result in individuals feeding on another plant species, leading to population decline and thus suppression.

There was discussion on whether the use of heritable microorganisms such as *Wolbachia* endosymbionts can be considered an engineered gene drive, as neither the host organism nor *Wolbachia* are genetically modified. It was mentioned that *Wolbachia* has a gene drive-like inheritance pattern that has been harnessed in replacement strategies to limit disease transmission in some mosquito populations.

5.2. Potential novel hazards/risks

Participants discussed potential novel hazards/risks associated with the deliberate release into the environment of gene drive modified insects.[6] The following points were raised:

- The deliberate release into the environment of gene drive modified insects would pose novel hazards/risks (in terms of their spatial and temporal scale, persistence, potential for self-replication, uncontrolled spread) with little or no opportunity for recall;
- Applications for gene drive modified insects differ from other applications with genetically modified organisms, as they deal with heterogeneous and diverse natural systems and non-managed species, instead of controlled environments (such as agroecosystems);
- Gene drives may eventually spread over entire continents and establish across national borders, raising issues of transboundary movements and international governance;
- Gene drive modified insects would not pose new harms compared with genetically modified insects, though such harms might be more likely due to their repeated cycles of reproduction, or might lead to more severe environmental effects;
- Concerns pertaining to the suppression of insect pest populations are not necessarily novel; such an effect is not unique to gene drive technology. Humans have aimed at controlling or eradicating insect pests through a variety of methods for many years. Consequently, environmental impacts of gene drive modified insects should be evaluated against those of alternative actions (i.e. sterile insect releases, classical biological control programmes), including no action. This experience is considered useful to inform the environmental risk assessment of gene drive modified insects and put risks in a broader perspective;
- The use of engineered gene drives should be seen as complementing the range of genetic methods of insect pest control.

5.3. Risk assessment paradigm

Participants had contrasting views on whether the existing framework for the risk assessment of genetically modified organisms would be sufficiently robust to assess the potential adverse effects associated with the deliberate release into the environment of gene drive modified insects. The following points were raised:

- The deliberate release into the environment of gene drive modified insects will challenge the current environmental risk assessment paradigm, as it will be difficult or impossible to predict their ecological impact, control any unintended effects, or to manage risks, especially with regard to potential long-term adverse effects;
- The classical methods used in risk assessment (such as the comparative and stepwise testing approach) would not be sufficient, as they are tailored to crop plants and animals that typically do not spread on their own in the environment. In contrast, engineered gene drives are intended to spread into interbreeding populations in the environment. Consequently, the current environmental risk assessment paradigm may be not generally appropriate for assessing gene drive modified insects;
- Judging the sufficiency of scientific knowledge and the extent to which uncertainty should be reduced for decision-making may be challenging for gene drive applications;
- The current environmental risk assessment frame, pending revisions, should remain appropriate for gene drive modified insects;
- The tiered-based testing, stepwise and weight of evidence approaches, and appropriately designed modelling and post-market environmental monitoring would provide the necessary

[6] This event report focuses on insect pest species, in particular disease-transmitting mosquitoes and agricultural pests for deliberate release into the environment. It does not address the use of engineered gene drives for biodiversity conservation purposes or the enhancement of agricultural production systems, as no concrete applications are currently in the pipeline for such purposes

safeguards to manage potential risks and uncertainty linked to the deliberate release into the environment of gene drive modified insects.

5.4. Familiarity with/experience from existing insect vector/pest control strategies

Similarities between the use of engineered gene drives for insect vector/pest control, some well-established insect vector/pest control strategies (e.g. biological or chemical insecticides, resistant crop varieties, biological control) and genetic control methods (such as the sterile insect technique or the incompatible insect technique) were addressed. The following points were raised:

- Existing vector/pest control methods (such as *Wolbachia* and the sterile insect technique) are unsuitable comparative systems to predict potential long-term effects associated with the deliberate release into the environment of gene drive modified insects;
- Substantial regulatory and environmental risk assessment experience has been gained, which can be used to identify information/data requirements for the environmental risk assessment of gene drive modified insects.

5.5. Problem formulation

The usefulness of problem formulation as an approach to frame the environmental risk assessment of gene drive modified insects was addressed. Overall, there was agreement that the problem formulation process is fit-for-purpose for the environmental risk assessment of gene drive modified insects, but it was acknowledged that practical challenges may be encountered. Moreover, it was noted that it is complicated to apply problem formulation to a technology in a generic manner; instead, it may be easier to apply problem formulation to concrete/specific cases.

The following points on the identification of relevant broad protection goals and how to make them operational were raised:

- Policy goals are defined broadly. Consequently, there is a need to translate policy goals into operational goals for use in environmental risk assessment. Operational protection goals can be case-dependent. For example, the level of tolerable harm may differ depending on the pest status of the modified species (e.g. whether it is known to be invasive/harmful or protected in a specific jurisdiction);
- The setting of protection goals involves normative considerations (e.g. about the tolerable level of harm). Given that risk assessors cannot define protection goals alone, an improved dialogue between risk managers and risk assessors, and stakeholder engagement for the definition of operational protection goals were advocated;
- Since the overarching goal of environmental risk assessments conducted for regulated stressors (such as pesticides, genetically modified organisms, invasive species and biocides) is to protect the same environment, protection goals should be similar for all regulated stressors;
- A list of protection goals, covering among others human and animal health, biodiversity, ecosystems, water quality, genomic purity, were briefly presented and discussed for the case studies used during the workshop. Some of the protection goals mentioned above are not explicitly addressed by EU legislation (i.e. genomic purity of wild-type/target organisms).

The following points on the elaboration of pathways to harm were raised:

- Various pathways could lead to a range of harms (e.g. removal of target population, loss of efficacy due to resistance evolution), and they can vary dependent on gene drive characteristics;
- Pathways to harm can be complex, as there may be more than one pathway to consider, while multiple pathways may share some of the same steps;
- Gene drive efficacy affects pathways to harm, so it was generally considered as a first step in any pathway to harm. Speed and success of suppression are inversely related to likelihood of harm;

- Pathways to harm would not differ between genetically modified mosquitoes and gene drive modified ones. The likelihood of already existing hazards would be increased, but no novel harms or new pathways would necessarily be associated with gene drive modified insects;
- The intended persistence of self-sustaining replacement gene drives will make a gene drive construct persist over generations. This can change pathways to harm owing to increased exposure and the potential for evolutionary responses.

The following points on the formulation of risk hypotheses about the likelihood and severity of possible harmful events were raised:

- The ability to appropriately consider rare or unlikely events in the problem formulation process was questioned. Such events may potentially have substantial environmental consequences, especially in the case of self-sustaining and low threshold gene drives;
- Rare or unlikely events would not necessarily translate into harm; only those that may be harmful should be considered further in environmental risk assessment. It is therefore important to link hazard to an exposure, and not to confuse hazard or exposure with risk.

The following points on the identification of possible information that would be useful to test these risk hypotheses were raised:

- Testing of all possible pathways to harm is the only way forward to avoid overlooking unintended effects and unknowns;
- Problem formulation is sufficiently robust to capture uncertainties by identifying issues that require further data for risk assessment purposes. Consequently, only plausible pathways should be taken into account, as it is unnecessary and unfeasible to test all possible pathways;
- It was suggested to prioritise pathways based on their level of validity and plausibility, and transparently report the rationale justifying why specific pathways are not considered plausible (e.g. based on evidence from the scientific literature);
- The comparative nature of risk assessments of genetically modified organisms was questioned, as absolute harms/risks should be quantified when conducting environmental risk assessments, instead of relative ones.

5.6. Potential harms

Several harms, covering among others the loss of gene drive efficacy due to resistance evolution, dispersal of gene drive modified insects beyond the target release area, loss of biodiversity due to hybridisation, disruption of the food web due to the removal of the target organism, loss of immunity, altered immune response following mosquito biting, were briefly presented for the two case studies used during the workshop and further discussed. Participants raised the following points:

- It was questioned whether CRISPR-Cas9-based gene drives would fully replace or suppress wild populations due to the potential for resistance to the gene drive to evolve. Resistance evolution should be carefully considered in environmental risk assessment. Modelling predictions and laboratory experiments suggest resistance to evolve to CRISPR-Cas9-based gene drives, which could slow or prevent the gene drive's ability to be preferentially inherited;
- There are no clear indications that all gene drives would spread in a similar and uncontrolled manner after their release. Self-sustaining gene drives are expected to be highly invasive provided that the evolution of resistance alleles can be minimised;
- Intermediate effects might take place if the goal of the gene drive is not achieved rapidly;
- A better understanding of the ecological and evolutionary impacts of gene drive modified insects for deliberate release into the environment is required due to the extended spatial scale and time scale at which gene drives may operate. This may allow for evolutionary processes to take place, a greater range of ecological interactions to occur and a higher potential for transboundary movement;
- Uncertainty may be higher for population replacement strategies than for population suppression strategies, as they require the modification to persist in the environment. However,

for both strategies gene drive modified insects will interact with wild-type populations that have heterogeneous genetic backgrounds;

- In situations where there is both insufficient sterility and subsequent control by continuing sterile insect technique releases, the persistence and invasiveness of the factory genome in the wild-type population may impact native/wild-type genetic diversity. However, this would not be exclusive to gene drive modified insects, as it could also happen with non-genetically modified insect comparators such as the classic sterile insect technique approaches;
- Potential interactions between different gene drive modified insects intended to be deliberately released simultaneously into the environment should be considered, in order to address possible combinatorial effects;
- It was questioned whether risk assessment should consider if a proposed activity may lead to new harms/risks, or only to different ways of causing harm that already result from current practice, as this helps to put potential impacts in the context of those caused by existing practices.

5.7. Comparators

The following points on the selection and suitability of comparators were raised:

- For malaria-transmitting mosquitoes, comparators should be the unmodified mosquitoes in the presence of commonly used control measures (such as insecticides). No comparison should be made in the absence of existing control measures;
- Alternative control methods should be considered (i.e. organic farming);
- In some cases, no other control measures may be available (e.g. for *D. suzukii* no native biological control agents have been found in Europe and insecticides may not always provide effective control);
- Removing an invasive species from a receiving environment using gene drives would not necessarily lead to the situation that existed before, given that other measures that have been taken (netting, insecticides) and which can impact biodiversity could be kept in place even after the invasive species has been removed.

5.8. Receiving environments

The following points on receiving environments were raised:

- Genotype × environment interactions: It was questioned whether knowledge of organisms in a given receiving environment can be extrapolated to another receiving environment;
- Possible interactions of the gene drive with other vector/pest control methods might become more relevant in the context of climate change.

5.9. Risk management

The following points on risk management were raised:

- Only self-limiting gene drives (which are restricted either spatially, temporally, or both) and reversal gene drives should be proposed for deployment. However, it was noted that reversal gene drives, which are designed to mitigate potential unintended consequences of another drive, may induce further changes that may undo a phenotypic alteration caused by the initial drive, so they may not restore the original modification to the wild-type or redress fully ecological effects from the original drive;
- The most plausible approach to the deliberate release into the environment of gene drive modified organisms is on islands due to the lower genetic drift, which would result in lower sequence variability of the targeted gene drive;

- There is deep concern that gene drive technology would be used as a biological weapon for military purposes;
- Both risks and benefits should be considered by risk managers. This requires the risk assessment to be completed with a benefit assessment;
- For homing endonuclease gene-based gene drives the inserted sequence would be the only traceable element for traceability purposes when the gene drive moves through the target population;
- Possible delays encountered in the regulatory process should be avoided, as by the time one gets clearance to deliberately release a gene drive modified insect into the environment, the receiving environment considered during the environmental risk assessment may have changed. For example, an invasive species might have been outcompeted or got established. However, it was noted that this should not be a concern, as applicants are typically asked to keep their environmental risk assessment up to date;
- Dialogue with risk managers from the very early stages of gene drive development would be useful to explore if potential adverse effects associated with their use (in comparison with existing insect pest control strategies) are acceptable or not;
- The business model to deliberately release into the environment of gene drive systems for commercial purposes would be driven by the potential for resistance to evolve and thus allow applicants to market gene drives every few years. Yet, it was noted that the business model would be more similar to that of vaccines, given their potential to protect whole nations, but that the approach followed would be case-specific;
- The amount and nature of risk assessment information/data required for systems designed to suppress pest populations with insecticides, crop resistance, mechanical or habitat modification are not the same as for gene drive modified insects, though such control systems may have similar long-term population suppression effects on target organisms, achieved through different mechanisms;
- The precautionary principle does not provide sufficiently definite guidance on how to balance potential risks of gene drive modified insects for deliberate release into the environment with the protection of the environment;
- Since gene drive modified insects designed for self-sustaining vector/pest control can have effects that may be unlimited in space and time, without an obvious way of containing or reversing environmental impacts, the application of the precautionary principle would preclude the deliberate release of gene drive modified insects;
- The deployment of gene drive strategies in insects can be compatible with the precautionary principle, as it states that "*where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation*";
- Self-sustaining gene drives may eventually spread over entire continents and establish across national borders, raising issues of transboundary movements and international governance to address under the Convention on Biological Diversity and its Cartagena Protocol on Biosafety.

5.10. Post-market environmental monitoring

The following points on post-market environmental monitoring were raised:

- For homing endonuclease gene-based gene drives it was indicated that the inserted sequence would be the only traceable element for monitoring purposes when the drive moves through the target population. Molecular markers such as fluorescent markers could be used for monitoring purposes;
- In the context of monitoring, baselines should be established to enable checking whether an ecosystem has shifted or not.

6. Workshop participants

Name	Country
Aarhus University	Denmark
Agroscope	Switzerland
BASF Agricultural Solutions NV	Belgium
BeeLife	Belgium
Crop Research Institute	Czech Republic
EcoNexus	United Kingdom
Emerging Ag Gene Drive Research Outreach Network	Spain
Environment Agency Austria	Austria
EPBA	Germany
European Commission	-
European Parliament	-
Federal Agency for Nature Conservation (BfN)	Germany
Federal Office of Consumer Protection and Food Safety (BVL)	Germany
Ghent University/Free University of Brussels	Belgium
Greens/EFA in the European Parliament	-
Haut Conseil des biotechnologies	France
Imperial College London	United Kingdom
Institute for the Environmental Protection and Research (ISPRA)	Italy
Justus-Liebig-University Gießen	Germany
Liverpool School of Tropical Medicine	United Kingdom
Logos Environmental	United Kingdom
Ministry of Agriculture	Hungary
Ministry of Environment of the Slovak Republic	Slovakia
Ministry of Social Affairs and Health	Finland
Ministry of the Environment and Spatial planning	Slovenia
Moredun Research Institute	United Kingdom
National Biosafety Commission, Ministry for Ecological Transition	Spain
Netherlands Food and Consumer Product Safety Authority (NVWA)	Netherlands
Norwegian Institute for Nature Research	Norway
Dutch National Institute for Public Health and the Environment (RIVM)	Netherlands
Ruth Müller's lab	Italy
Save our Seeds / Zukunftsstiftung Landwirtschaft	Germany
Sciensano	Belgium
Testbiotech eV	Germany
Third World Network	United Kingdom
Università di Torino	Italy
US Department of Agriculture	United States
Flanders Interuniversity Institute for Biotechnology (VIB)	Belgium

7. Conclusion

Points raised by the workshop participants reveal different often contrasting opinions/perspectives toward gene drive and their risk assessment. Overall, there was agreement that the problem formulation process is fit-for-purpose for the environmental risk assessment of gene drive modified insects, but it was acknowledged that practical challenges may be encountered.

Points raised by the workshop participants, on defining protection goals, formulating specific pathways to harm and on structuring risks, have been considered by EFSA's Panel on genetically modified organisms during its deliberations, and they informed its draft scientific opinion on the "*evaluation of existing EFSA guidelines for their adequacy for the molecular characterisation and environmental risk assessment of genetically modified insects with synthetically engineered gene drives*".

References

EFSA (European Food Safety Authority), 2012. Scientific Opinion on the Guidance on the risk assessment of food and feed from genetically modified animals and animal health and welfare aspects. EFSA Journal, 10(1):2501. [43 pp.] doi:10.2903/j.efsa.2012.2501

EFSA (European Food Safety Authority), 2013. Guidance on the environmental risk assessment of genetically modified animals. EFSA Journal, 11(5):3200, 190 pp. doi:10.2903/j.efsa.2013.3200