Briefing notes (last updated on 8 May 2019)

Problem formulation for the environmental risk assessment of gene drive modified insects | Brussels, 15 May 2019

Contents

Disclaimer

These briefing notes have been prepared by the European Food Safety Authority (EFSA) for the confirmed participants of EFSA's stakeholder workshop on the problem formulation for the environmental risk assessment of gene drive modified insects. The briefing notes are designed to provide participants with background information to ensure their preparedness for an interactive exchange of views and expertise during the event.

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Risk analysis of genetically modified organisms

In the European Union (EU), as in most jurisdictions, the use of genetically modified organisms (GMOs) is subject to a risk assessment and regulatory approval. In this process, the role of EFSA is to assess and provide scientific advice to risk managers on any plausible risk that the deployment of a GMO may pose to human health, animal health and the environment.

The decision on the level of acceptable risk and thus whether the use of a GMO ought to be permitted is taken by risk managers (the European Commission and EU Member States) who weigh policy options to accept, minimise, reduce or reject the characterised risks with other relevant information such as the economic, social or political implications of the proposed activity. Additional measures for prevention and control of specific risks may also be required. Any regulatory decisions should protect the health and well-being of citizens and the environment, whilst enabling innovation.

Risk communication involves dialogue between risk assessors, risk managers and other interested parties, and includes the explanation of risk assessment conclusions and the basis upon which regulatory decisions were made. Although interrelated, risk assessment, risk management and risk communication fulfil different roles in, and contribute differently to, decisions. In any case, the assessment, management and communication of risks are not to be carried out completely independently but must continually interact.

Mandate

The European Commission has mandated EFSA to deliver "*an opinion on genetically modified organisms engineered with gene drives (gene drive modified organisms) and their implications for risk assessment methodologies*".[1]

In particular:

1. "*EFSA is requested to identify potential risks in terms of impact on human and animal health and the environment that gene drive modified organisms could pose. In this respect EFSA is also asked to identify potential novel hazards of gene drive modified organisms, considering relevant comparators, where appropriate.*
2. *EFSA is requested to determine whether the existing guidelines for risk assessment are adequate and sufficient for gene drive modified organisms or whether there is a need for updated guidance.*
3. *In the latter case EFSA is requested to identify the specific areas where such updated guidance is needed*".

The European Commission has also requested the advice of the European Group on Ethics on gene drive modified organisms.[2]

[1] registerofquestions.efsa.europa.eu/roqFrontend/ListOfQuestionsNoLogin (EFSA-Q-2018-00619)
[2] https://ec.europa.eu/info/sites/info/files/research_and_innovation/ege/letter_chair_of_the_ege_group.pdf

The event at a glance

Background

Gene drives consist of genetic elements that can pass traits among sexually reproducing individuals with higher efficiency than expected under Mendelian inheritance. This emerging technology has sparked both enthusiasm and concerns. While 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 lead to undesired side effects and alter ecosystems in irreversible ways.

Objectives and expected outcome

Through this workshop EFSA aims to engage with stakeholders to discuss plausible environmental risks from gene drive modified insects. Participants will be invited to participate in an initial problem formulation (a process widely used in EFSA and other formal risk assessments) to:

1. Formally devise plausible pathways to harm that describe how the deployment of gene drive modified insects could be harmful;
2. Formulate risk hypotheses about the likelihood and severity of such events;
3. Identify the information that will be useful to test these risk hypotheses;
4. Identify how to acquire new data for hypothesis testing should tests with existing information be insufficient for decision-making.

The problem formulation exercise will be run for two case studies in two separate discussion groups:

1. Self-sustaining gene drives to control disease-spreading mosquitoes (e.g., *Aedes albopictus*);
2. Self-sustaining gene drives to control agricultural pests (e.g., *Drosophila suzukii*).

The outcome of the discussion groups will be presented and discussed in a final plenary session to formulate the conclusions of the workshop. These conclusions will address potential environmental risks associated with the release of gene drive modified insects, the plausible pathway(s) to such harm, and what information is genuinely needed to assess the likelihood of the harm to occur and its seriousness. EFSA acknowledges that the potential acceptance of this technology will vary depending on the perceived risks and benefits of specific applications and how the technology will be governed, but such considerations are beyond the focus of the workshop.

The input of workshop participants will support EFSA's expert Working Group on the environmental risk assessment of gene drive modified organisms to frame its work in the broader societal context, acknowledging the distinction between risk assessment and risk management considerations.

Program

08:15-09:00	**Registration and welcome coffee**	
SESSION 1 (Room Thalys 4) | 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**	
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 (Room Thalys 3) | Case study: Gene drive modified mosquitoes Moderator: Fred Gould, North Carolina State University (US)	**SESSION 2B (Room Eurostar 1+2) | 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 (Room Thalys 4) | 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)

Abstracts

Gene drive modified insects – Hopes, fears, gene drive systems and problem formulation concepts

Fred Gould[1]

[1] Co-Director of Genetic Engineering and Society Center, Distinguished University Professor, North Carolina State University, US

Abstract

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".

Problem formulation consultations for gene drive modified mosquitoes designed to reduce malaria transmission in Africa

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[2] ILSI Research Foundation, US

[3] African Union Development Agency-New Partnership for Africa's Development, Industrialization (NEPAD), Science, Technology and Innovation Hub, SA

Abstract

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.

Problem formulation for the environmental risk assessment of gene drive modified *Drosophila suzukii*

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[1] Research Division Agroecology and Environment, Agroscope, CH

[2] Department of Gene Technology and Biological Safety, Centre for Safety of Substances and Products, National Institute of Health and the Environment (RIVM), NL

[3] Mathematical Ecology Research Group, Department of Zoology, University of Oxford, UK

Abstract

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 engineering, GE), biological control (caused by predators, parasitoids, or entomopathogens), and genetic control methods such as the sterile insect technique (SIT) or the incompatible insect technique (IIT) 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 (*Drosophila 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 GE insects (SIT) and IIT. 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.

Experiences with gene drives and risk assessment implications: Opinion of the Netherlands Commission on Genetic Modification (COGEM)

Marjan Bovers[1], Greet Smets[2], **Patrick Rüdelsheim**[2]

[1] The Netherlands Commission on Genetic Modification (COGEM), NL

[2] Perseus BVBA, BE

Abstract

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.

Briefing notes for the discussion groups

Problem formulation concepts

Problem formulation is a standard starting point in risk assessment, involving amongst other steps:

1. Formally devising plausible pathways to harm that describe how a proposed activity could be harmful (i.e., impact a protected value adversely);
2. Formulating risk hypotheses (i.e., hypotheses of no harm or of no unacceptable risk) about the likelihood and severity of such events;
3. Identifying the information that will be useful to test the risk hypotheses;
4. Developing a plan to acquire new data for hypothesis testing should tests with existing information be insufficient for decision-making.

A crucial step of problem formulation is to define what qualifies as harm under the relevant regulations. Policy protection goals are typically very broadly defined. Therefore, operational protection goals must delineate the environmental components that are valued and need to be protected (e.g., species, ecosystem services, habitats), where and over what time period, and the maximum tolerable impact. In this context, it is important to consider whether the proposed activity may lead to new harms, or only to different ways of causing harm that already result from current practice.

To frame an environmental risk assessment further, plausible pathways are constructed to describe how the proposed activity could lead to possible harm to operational protection goals. A pathway to harm is a causal chain of events that need to occur for a harm to be realised.

The steps in the pathway enable the formulation of risk hypotheses that can then be tested to characterise risk. A careful first scrutiny of the pathway, based on existing knowledge, can usually help to identify which of the step(s) may be the most decisive or easiest to test in attempting to disrupt the pathway with the highest degree of certainty.

Corroboration of risk hypotheses will build confidence that risk is negligible via the pathway in question; and corroboration following a rigorous test gives greater confidence than does a weak test. If a risk hypothesis is corroborated or falsified with sufficient certainty for decision-making, no further testing of that hypothesis ought to be necessary for the purposes of risk assessment.

Risk hypotheses may be tested with existing information and does not necessarily require experimentation. However, if these tests are inconclusive for decision-making, new studies may be undertaken to acquire the necessary data for hypothesis testing.

Gene drive strategies

Gene drives consist of genetic elements that can pass traits among sexually reproducing individuals with higher efficiency than expected under Mendelian inheritance. They positively bias their own inheritance and thus spread rapidly through populations, even if they incur a fitness cost.

First reported in the 1950s, natural gene drives have been well-characterised. However, the discovery of driving-endonuclease genes and recent molecular advances that allowed their introduction into insects gave new impetus. Most recently, the use of CRISPR/cas9 technology to create novel driving-endonuclease genes has further spurred interest,

suggesting that a practical application of gene drive mechanisms could be more readily achievable than previously believed.

Strategies to use gene drives in the context of GM insects can be classified mainly by:

- Desired outcome: Population suppression[3] vs. population replacement[4];
- Ability of the trait to establish or spread: Self-sustaining vs. self-limiting drives.

Within each category, different technical approaches with differing characteristics are possible (e.g., homing-based drives using homing endonuclease genes; sex-linked meiotic drives; Medea, the maternal effect dominant embryonic arrest system; underdominance or heterozygote inferiority drives; heritable microorganisms as illustrated by Wolbachia) that evolve rapidly (e.g., conventional vs. integral gene drives; allelic gene drives).

Population suppression vs. population replacement

Population suppression strategies aim to reduce the size of a target population by imposing a fitness cost via the inactivation of important genes involved in the survival or reproduction of the target population (e.g., reducing fertility of progeny, bias of the sex ratio toward males). This causes population decline or even collapse.

Population replacement strategies for controlling vector populations are used to replace a current genotype with one less able to transmit disease (disease refractory). These strategies are based on inactivation of a gene or genes involved in pathogen survival in the vector (e.g., pathogen resistance) or that are required for the target organism to transmit the pathogen, such as a tendency to feed on humans in the case of mosquitoes. They can involve the introduction of a new gene or genes, such as those that produce molecules that will kill the pathogen in the vector.

Self-sustaining vs. self-limiting drives

Self-sustaining drives are gene drives that are designed to cause desirable genes to increase in frequency in a population (or populations) and ideally become fixed in the population (or populations). These drives will ideally sustain the high frequency of the desirable gene indefinitely unless actions are taken to reverse the impact and/or frequency of the drive through release of another transgenic strain. Natural resistance to a self-sustaining drive could evolve among wild individuals in a population and reverse its impact and/or frequency. A self-sustaining drive can be designed to be *spatially unrestricted* and move to any population that has gene flow with the population where the drive was released, or a self-sustaining drive can be designed to only spread within a single population or region. These are referred to as *spatially restricted* gene drives. Examples of spatially unrestricted drives are some CRISPR-based, simple homing drives and Medea drives when developed to have very low thresholds for release. Examples of spatially restricted drives are under dominance-based drives and Medea drives when developed to have high thresholds for release.

Self-limiting drives are gene drives that are designed to cause desirable genes to increase in frequency in a population for a limited period of time after which the genes decrease in frequency and are ideally lost from the population. The desirable genes could either be those that change the population's characteristics or suppress the population density. These type of gene drives are also referred to as *temporally limited* drives. Examples are daisy-chain gene drives and killer-rescue drives.

[3] Also termed: Population reduction

[4] Also termed: Population modification, population alteration, population transformation, or population conversion

Discussion groups

Discussion group 2A – Self-sustaining gene drives to control a disease-spreading mosquito species (e.g., *Ae. albopictus*)

Mosquito-borne pathogens cause some of the more deadly worldwide diseases, such as malaria and dengue. Tropical countries are more exposed to these diseases, but Europe is experiencing an increasing number of human cases of mosquito-borne diseases, both imported and indigenous.

Ae. albopictus, the Asian tiger mosquito, is an aggressive biting mosquito native to Asia that has colonised all continents, including Europe, 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.

Controlling disease transmission by mosquitoes is a long-standing public health goal, and the eradication of these human diseases would have tremendous economic and social benefits. However, current methods of vector control, including removal of standing water and use of insecticide-treated bed nets and insecticides, have not been entirely effective in combatting the spread of mosquito-vectored diseases worldwide. Moreover, there are geographic gaps in access to control measures. Consequently, novel vector control strategies, including genetic-based ones that utilise GM mosquitoes, have been developed and deployed.

The envisioned goal for applying gene drive technology in mosquitoes is to: (1) reduce the size of the vector population to such an extent that it will not be able to sustain disease transmission (population suppression), or (2) render them less competent to transmit pathogens (population replacement). Cage experiments and modelling have demonstrated the potential use of gene drives to control disease vectors in two species of malaria vector mosquitoes. However, challenges for gene drive use have been identified, including the development of target site resistance, their long-term efficacy in the field, their molecular complexity, and practical limitations for field testing.

Discussion group 2B – Self-sustaining gene drives to control agricultural pests (e.g., *D. suzukii*)

Agricultural productivity is significantly constrained by the attack of insect pests, which cause important yield losses. An effective control of pest populations is therefore key to guarantee crop production.

D. 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 industry. Females lay eggs inside ripening soft-skinned fruits, and larvae feed inside the fruit, which becomes soft and rots.

D. suzukii infestations are usually treated with broad-spectrum insecticides. However, these products do not always provide effective control and their intensive use can lead to resistance evolution and be harmful to the environment, non-target organisms and human health.

The envisioned goal for applying gene drive technology in *D. suzukii* is to suppress their populations by targeting genes essential for insect development or viability.

Potential discussion points

- What are policy objectives in terms of protection goals (protecting the environment and human and animal health) and social and economic goals?
- Based on these policy objectives, what are undesirable harms?
- How can the release of gene drive modified mosquitoes/agricultural pests lead to undesirable harms? What is the causal chain of events that need to occur for a harm to be realised (→ pathway to harm)? What are the key steps in the pathway to harm?
- How plausible is the proposed pathway to harm? What is the likelihood and severity of such events? Can existing information break the causal chain of events in the pathway to harm?
- What information will be useful to test risk hypotheses? What parameters should be assessed?
- Should tests with existing information be insufficient for decision-making, how should new data be gathered for hypothesis testing and under which conditions (e.g., unrealistically conservative conditions, more realistic conditions, or both following a tiered approach)?
- What can we learn from other vector/pest control methods, including the release of biological control agents, and disease mitigation strategies?
- Can other vector/pest control methods and disease mitigation strategies be used to put any potential harms identified for gene drive modified insects in context?
- Can mitigation measures be applied?
- …

Potential risks to consider on a case-by-case basis

Biodiversity and ecosystems

- Can proteins introduced as gene drive components and/or markers be toxic to non-target organisms consuming the gene drive modified insects and affect the ecosystem services they contribute to?
- In population suppression strategies, can the reduction of target insects serving as food source for non-target organisms adversely affect such organisms and the ecosystem services they contribute to (e.g., biological control)?
- Can gene drives spread to non-target organisms through hybridisation and adversely affect their progeny due to reduced fitness?
- Can gene drives alter the competition with/leave the niche to other species, resulting in adverse effects on biodiversity and ecosystems?
- Can pathogen resistance genes modify the "natural" fitness of mosquitoes and result in adverse effects?
- …

Human/animal health

- Can incidental exposure to gene drive modified insects through inhalation, ingestion, etc. result in any significant levels of exposure leading to harm to human/animal health?
- Can the elimination of a pathogen from a mosquito species leave the place to other pathogens?
- Can resistance alleles of the pathogen modify the "natural" fitness of the pathogen and result in adverse human/animal health effects?

- Can the genetic modification result in any increase in disease transmission (due to increased vectorial capacity?
- Can the genetic modification result in increased pathology (due to increased biting rate or behaviour, allergenicity, toxicology or parasite virulence) to humans and/or livestock animals?
- …

Plant health

- Can gene drives alter the competition with/leave the niche to other pest species, resulting in adverse effects on plant health, including the transmission of other plant pathogens?
- …

Water, soil and air quality, agriculture or natural resources

- Can larvae of gene drive modified mosquitoes impact water quality, considering that they spend part of their life cycle in aquatic habitats, which can be artificial or ephemeral?
- Can gene drive modified insects impact soil quality, air quality, agriculture or natural resources?
- …

Management practices

- Can the use of gene drive modified insects change the use of other vector/pest control methods and disease mitigation strategies, and can these changes adversely affect the environment?
- Can failure to sustain a successful vector or pest control strategy have harmful effects on disease or pest incidence?
- …

Background documents/references

- Brossard D, Belluck P, Gould F and Wirz CD, 2019. Promises and perils of gene drives: Navigating the communication of complex, post-normal science. Proceedings of the National Academy of Sciences, doi:10.1073/pnas.1805874115.
- Buchman AB, Ivy T, Marshall JM, Akbari O and Hay BA, 2018. Engineered reciprocal chromosome translocations drive high threshold, reversible population replacement in drosophila. ACS Synthetic Biology, 7, 1359–1370.
- Buchman A, Marshall JM, Ostrovski D, Yang T and Akbari OS, 2018. Synthetically engineered *Medea* gene drive system in the worldwide crop pest *Drosophila suzukii*. Proceedings of the National Academy of Sciences of the United States of America, 115, 4725–4730.
- Buchman A, Gamez S, Li M, Antoshechkin I, Lic H-H, Wang H-W, Chen C-H, Klein MJ, Duchemin J-B, Paradkar PN and Akbari OS, 2019. Engineered resistance to Zika virus in transgenic *Aedes aegypti* expressing a polycistronic cluster of synthetic small RNAs. Proceedings of the National Academy of Sciences of the United States of America, 116, 3656–3661.
- Burt A, Coulibaly M, Crisanti A, Diabate A and Kayondo JK, 2018. Gene drive to reduce malaria transmission in sub-Saharan Africa. Journal of Responsible Innovation, 5, S66–S80.
- Collins JP, 2018. Gene drives in our future: Challenges of and opportunities for using a self-sustaining technology in pest and vector management. BMC proceedings, 12(S8), 9.
- Collins CM, Bonds JA, Quinlan MM and Mumford JD, 2019. Effects of the removal or reduction in density of the malaria mosquito, *Anopheles gambiae s.l.*, on interacting predators and competitors in local ecosystems. Medical and Veterinary Entomology, 33, 1–15.
- Devos Y, Romeis J, Luttik R, Maggiore A, Perry JN, Schoonjans R, Streissl F, Tarazona JV and Brock TCM, 2015. Optimising environmental risk assessments – Accounting for biodiversity and ecosystem services helps to translate broad policy protection goals into specific operational ones for environmental risk assessments. EMBO Reports, 16, 1060–1063.
- Duvall LB, Ramos-Espiritu L, Barsoum KE, Glickman JF and Vosshall LB, 2019. Small-molecule agonists of *Ae. Aegypti* neuropeptide Y receptor block mosquito biting. Cell, 176, 687–701.
- Gantz VM, Jasinskiene N, Tatarenkova O, Fazekas A, Macias VM, Bier E and 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 of the United States of America, 112, E6736–E6743.
- Guichard A, Haque T, Bobik M, Xu X-RS, Klanseck C, Kushwah RBS, Berni M, Kaduskar B, Gantz VM and Bier E, 2019. Efficient allelic-drive in *Drosophila*. Nature Communications, 10, 1640.
- 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 and Nolan T, 2016. A CRISPR-Cas9 gene drive system targeting female reproduction in the malaria mosquito vector *Anopheles gambiae*. Nature Biotechnology, 34, 78–83.
- Kyrou K, Hammond AM, Galizi R, Kranjc N, Burt A, Beaghton AK, Nolan T and Crisanti A, 2018. A CRISPR–Cas9 gene drive targeting doublesex causes complete population suppression in caged *Anopheles gambiae* mosquitoes. Nature Biotechnology, 36, 1062–1066.

- Gould F, Huang Y, Legros M and Lloyd AL, 2008. A killer-rescue system for self-limiting gene drive of anti-pathogen constructs. Proceedings of the Royal Society: Biological Sciences, 275, 2823–2829.
- Gray AJ, 2012. Problem formulation in environmental risk assessment for genetically modified crops: A practitioner's approach. Collection of Biosafety Reviews, 6, 10–65.
- Hayes KR, Hosack GR, Dana GV, Foster SD, Ford JH, Thresher R, Ickowicz A, Peel D, Tizard M, De Barro P, Strive T and Dambacher JM, 2018. Identifying and detecting potentially adverse ecological outcomes associated with the release of gene-drive modified organisms. Journal of Responsible Innovation, 5, S139–S158.
- James S, Collins FH, Welkhoff PA, Emerson C, Godfray HCJ, Gottlieb M, Greenwood B, Lindsay SW, Mbogo CM, Okumu FO, Quemada H, Savadogo M, Singh JA, Tountas KH and Touré YT, 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. The American Journal of Tropical Medicine and Hygiene, 98(S6), 1–49.
- Kuzma J, 2019. Procedurally robust risk assessment framework for novel genetically engineered organisms and gene drives. Regulation & Governance, doi:10.1111/rego.12245.
- Murray JV, Jansen CC and De Barro P, 2016. Risk associated with the release of Wolbachia-infected *Aedes aegypti* mosquitoes into the environment in an effort to control dengue. Frontiers in Public Health, 4, 43.
- Nash A, Urdaneta GM, Beaghton AK, Hoermann A, Papathanos PA, Christophides GK and Windbichler N, 2019. Integral gene drives for population replacement. Biology Open, 8, bio037762.
- Noble C, Min J, Olejarz J, Buchthal J, Chavez A, Smidler AL, DeBenedictis EA, Church GM, Nowak MA and Esvelt KM, 2019. Daisy-chain gene drives for the alteration of local populations. Proceedings of the National Academy of Sciences of the United States of America, doi.org/10.1073/pnas.1716358116.
- North AR, Burt A and Godfray HCJ, 2019. Modelling the potential of genetic control of malaria mosquitoes at national scale. BMC Biology, 17, 26.
- Oberhofer G, Ivy T and Hay BA, 2019. Cleave and Rescue, a novel selfish genetic element and general strategy for gene drive. Proceedings of the National Academy of Sciences, 116, 6250–6259.
- Raybould A, 2006. Problem formulation and hypothesis testing for environmental risk assessments of genetically modified crops. Environmental Biosafety Research, 5, 119–125.
- Raybould A, 2007. Ecological versus ecotoxicological methods for assessing the environmental risks of transgenic crops. Plant Science, 173, 589–602.
- Raybould A, 2010. The bucket and the searchlight: Formulating and testing risk hypotheses about the weediness and invasiveness potential of transgenic crops. Environmental Biosafety Research, 9, 123–133.
- Raybould A and Macdonald P, 2018. Policy-led comparative environmental risk assessment of genetically modified crops: Testing for increased risk rather than profiling phenotypes leads to predictable and transparent decision-making. Frontiers in Bioengineering and Biotechnology, 6, 43.
- Roberts A, Paes de Andrade P, Okumu F, Quemada H, Savadogo M, Amir Singh J and James S, 2017. Results from the Workshop "Problem Formulation for the Use

of Gene Drive in Mosquitoes". The American Journal of Tropical Medicine and Hygiene, 96, 530–533.
- Ryan SJ, Carlson CJ, Mordecai EA and Johnson LR, 2019. Global expansion and redistribution of *Aedes*-borne virus transmission risk with climate change. PLoS Neglected Tropical Diseases, 13(3), e0007213.
- Schetelig MF, Lee K-Z, Otto S, Talmann L, Stökl J, Degenkolb T, Vilcinskas A and Halitschke R, 2018. Environmentally sustainable pest control options for *Drosophila suzukii*. Journal of Applied Entomology, 142, 3–17.
- Schmidt TL, Barton NH, Rašić G, Turley AP, Montgomery BL, Iturbe-Ormaetxe I, Cook PE, Ryan PA, Ritchie SA, Hoffmann AA, O'Neill SL and Turelli M, 2017. Local introduction and heterogeneous spatial spread of dengue-suppressing *Wolbachia* through an urban population of *Aedes aegypti*. PLoS Biology, 15(5): e2001894.
- Scott MJ, Gould F, Lorenzen M, Grubbs N, Edwards O and O'Brochta D, 2018. Agricultural production: Assessment of the potential use of Cas9-mediated gene drive systems for agricultural pest control. Journal of Responsible Innovation, 5, S98–S120.
- Tepfer M, Racovita M and Craig W, 2013. Putting problem formulation at the forefront of GMO risk analysis. GM Crops and Food: Biotechnology in Agriculture and the Food Chain, 4, 1–6.
- US EPA (US Environmental Protection Agency), 1998. Guidelines for ecological risk assessment. Washington (DC), USA: USEPA Risk Assessment Forum. EPA/630/R-95/002F. Available from: http://rais.ornl.gov/documents/ECOTXTBX.PDF.
- Wolt JD, Keese P, Raybould A, Fitzpatrick JW, Burachik M, Gray A, Olin SS, Schiemann J, Sears M and Wu F, 2010. Problem formulation in the environmental risk assessment for genetically modified plants. Transgenic Research, 19, 425–436.

Program contributors and their role in order of appearance

Chairs

Name	Affiliation and country	Comment
Barbara Gallani	European Food Safety Authority, IT	
Leslie Firbank	University of Leeds, UK	Also discussion group moderator

Speakers

Name	Affiliation and country	Comment
Fred Gould	North Carolina State University, US	Keynote speaker and also discussion group moderator
Stephanie James	Foundation for the National Institutes of Health (US)	
Jörg Romeis	Agroscope, CH	
Patrick Rüdelsheim	Perseus, BE	
Marjan Bovers	The Netherlands Commission on Genetic Modification (COGEM), NL	

Rapporteurs

Name	Affiliation and country	Comment
John Mumford	Imperial College London, UK	-
Michael Bonsall	University of Oxford, UK	-

Biographies in order of appearance

Barbara Gallani

Affiliation	European Food Safety Authority (EFSA)
Country	IT
Biography	Barbara Gallani is Head of EFSA's Communication, Engagement and Cooperation Department. She was listed as one of the UK Top 100 Scientists by the Science Council in January 2014 for her work on the application of science and evidence to ensure proportionate regulation. Barbara has extensive experience of communicating complex issues in the areas of food safety, authenticity and research to lay audiences; managing incidents and food scares; and developing and delivering specialist training courses on risk communication for UK and global audiences. Barbara is a Chartered Scientist and Fellow of the Institute of Food Science and Technology (IFST) and has 16 years of professional experience, both in the public and private sector. Before joining EFSA, she worked in the UK at the Food and Drink Federation, at the British Retail Consortium and at the UK Food Standards Agency, including a secondment to the European Commission (DG SANCO) and a BA Media Fellowship on science communication at the Daily Telegraph. She also worked at the European Consumers' Organisation (BEUC) in Brussels. Barbara holds a Bachelor's Degree in Physics, a Post Graduate Certificate in Education PGCE (Physics and Sciences) and a Master's Degree in Advanced Instrumentation Systems

Leslie Firbank

Affiliation	University of Leeds
Country	UK
Biography	Les Firbank is Professor in Sustainable Agriculture at the University of Leeds, a member of EFSA's GMO Panel and Chair of the EFSA Working Group on the environmental risk assessment of gene drive modified insects. He was brought up on a small farm in northern England, took a degree in zoology before researching into interactions between farming and the environment. His early work focussed on weeds and crops, before moving to the Centre for Ecology and Hydrology where he led large scale studies on the environmental effects of set-aside, organic farming and GM crops. He moved to North Wyke Research where he developed the concept of an intensive, farm-scale research platform to look at the mechanisms underpinning more sustainable farming in the face of increasing climate, market and policy uncertainty. He was a member of ACRE (the UK Advisory Committee on Releases to the Environment) from 2009-15 before joining EFSA in 2018. At Leeds, he is researching methods of more sustainable arable production, especially by manipulating rotations, and is involved in the promotion of sustainable urban food systems through the Leeds Food Partnership. He is a Fellow of the Royal Society of Biology, Speciality Editor of Frontiers in Sustainable Food Systems and former Independent Director of the Red Tractor UK food assurance scheme

Fred Gould

Affiliation	North Carolina State University
Country	US
Biography	Dr Gould is Co-Director of the Genetic Engineering and Society Center of North Carolina State University and Director of the NSF-sponsored, interdisciplinary, graduate training program on Agricultural Biotechnology. He conducts research on the application of evolutionary biology and population genetics to enable

	sustainable use of insect resistant crops and genetically engineered agricultural pests. He also does research on strategies for development and use of engineered mosquitoes to decrease human disease. In this regard, Dr Gould and his colleague have studied the field ecology of the mosquito, *Aedes aegypti*, that vectors dengue virus. They have also developed a range of mathematical models to assess current gene drive systems and to conceptualise novel gene drive mechanisms. In 2011, Dr Gould was elected to the US National Academy of Sciences (NAS). He has served on several National Academy of Sciences Engineering and Medicine (NASEM) committees studying the environmental and health effects of the commercialisation of genetically engineered crops. He chaired the 2014-2016 NASEM committee on "Genetically Engineered Crops: Experiences and Prospects" and was a reviewer of the NASEM 2016 report on Gene Drives. He serves on the NASEM's Board on Agriculture and Natural Resources. Dr Gould received his BS in biology from Queens College and a PhD in ecology and evolutionary biology from the State University of New York at Stony Brook

Stephanie James

Affiliation	Foundation for the National Institutes of Health (FNIH)
Country	US
Biography	Dr James is the Senior Vice President for Science at the Foundation for the National Institutes of Health (FNIH) in Bethesda, MD, where she leads several research partnerships with an emphasis on global health research. Prior to joining FNIH in 2004, Dr James served as Chief of the Parasitology and International Programs Branch in the Division of Microbiology and Infectious Diseases, NIAID, NIH, and subsequently as Deputy Director and director of the Global Infectious Disease program at The Ellison Medical Foundation. While at NIH, Dr James was responsible for programmatic development of the Tropical Medicine Research Centers and the International Centers for Excellence in Research, and she was instrumental in the formation of the International Centers for Tropical Disease Research and the Multilateral Initiative on Malaria. At the Ellison Medical Foundation, she started a new funding program to foster discovery research on global health. At FNIH, she was part of the team that developed the original Grand Challenges in Global Health initiative and oversees a team responsible for managing a portfolio of research projects that have included innovative methods for controlling mosquito vectors of human disease, influence of enteric infections on child growth and development, discovery of new drugs and treatment or prevention regimens for tuberculosis, discovery and evaluation of HIV/AIDS vaccines, and identification of biomarkers for onchocerciasis infection

Jörg Romeis

Affiliation	Agroscope
Country	CH
Biography	Dr Jörg Romeis heads the Biosafety Research Group at Agroscope in Zurich, Switzerland. Agroscope is the Swiss center of excellence for agricultural research and is affiliated with the Federal Office for Agriculture. In addition, he is lecturer at the University of Bern and adjunct professor at the Institute of Plant Protection of the Chinese Academy of Agricultural Sciences in Beijing. Jörg holds an MSc and PhD in biology and was trained as an applied entomologist with a focus on biological pest control and multi-trophic interactions. He has more than 19 years of experience in the risk assessment of genetically modified (GM) crops and in particular in the design and execution of non-target laboratory studies. His research has focused on the effects of insect-resistant GM plants, such as Bt maize and cotton, on arthropod herbivores and their predators and parasitoids.

	In addition to primary research, Jörg has been actively involved in defining operational environmental protection goals, and in developing guidelines for risk assessment and non-target testing. His activities cover the assessment of RNAi-based pest control products (GM plants and spray products), macroorganisms used for biological control of arthropods, and GM insects with gene drives

Patrick Rüdelsheim

Affiliation	Perseus
Country	BE
Biography	Patrick Rüdelsheim obtained his PhD in biology/botany at the University of Antwerp, Belgium. He started his career in D.J. Vanderhave BV, a Dutch Seed company where he was involved in the application of plant cell biology in classical breeding. In 1990, he joined Plant Genetic Systems NV, Ghent, Belgium as Field Trial Supervisor. After overseeing Product Development and Registration, he was appointed Director Regulatory Affairs and Member of the PGS Board. In 1996, following the acquisition of PGS by AgrEvo, he became Global Head of Biotechnology Regulatory Affairs for the AgrEvo group. In this function, he ensured the scientific argumentation for Product Safety and Quality as well as the compliance with all regulatory acquirements related to genetic engineering. After the creation of Aventis S.A. due to the merger of Hoechst and Rhône-Poulenc, Dr Rüdelsheim became Global Head Regulatory Affairs BioScience of Aventis CropScience and following the acquisition of Aventis CropScience by Bayer in 2002, he was confirmed in that position for Bayer CropScience. In 2003, he founded and became General Partner of Perseus BVBA, a service company focused on bio-safety and related regulatory requirements. Since mid-2015, he is Senior Regulatory Advisor for ABS-int, a multi-disciplinary initiative dedicated to Access and Benefit Sharing requirements

Marjan Bovers

Affiliation	The Netherlands Commission on Genetic Modification (COGEM)
Country	NL
Biography	Marjan Bovers is Scientific Secretary of the Subcommittee Agricultural Aspects of the Netherlands Commission on Genetic Modification (COGEM). In close collaboration with COGEMs experts, she advises the Dutch government on environmental risks of genetically modified organisms (plants, insects, micro-organisms etc.) and on measures to contain them. In addition, she prepares opinions to inform policy makers on new developments that are related to genetic modification. She has been a member of the steering committee of several research projects commissioned by COGEM (for instance on previous experiences with gene drive systems, and on options to contain genetically modified arthropods). Before joining COGEM, she finished her PhD at the Westerdijk Fungal Biodiversity Institute & University of Utrecht, and studied Plant Breeding and Crop Protection at Wageningen University

John Mumford

Affiliation	Imperial College London
Country	UK
Biography	John Mumford is an entomologist and agricultural economist with experience in the design, operation and evaluation of area-wide insect control programs with national governments, FAO and IAEA. He has an interest in plant health pest risk analysis and has worked with national governments, EFSA, IPPC and WTO on

	issues of commodity pathway analysis. He chairs the Non-native Species Risk Analysis Panel for Great Britain, which oversees national risk assessments for alien invasive species. He has been a member of working groups related to risk assessment and management of genetically modified insects with WHO and EFSA

Michael Bonsall

Affiliation	University of Oxford
Country	UK
Biography	Mike Bonsall completed his undergraduate and doctoral training at Imperial College London. After two postdoctoral positions (also at Imperial) he was awarded a Royal Society University Research Fellowship. He is now Professor of Mathematical Biology at the University of Oxford, and Fellow at St. Peter's College, Oxford. He leads a research group on mathematical biology (http:\\merg.zoo.ox.ac.uk) that focuses on integrating theoretical and empirical problems in the life sciences. Particular themes of research in the group range from problems in mammalian developmental biology and stem cell dynamics, through to evolutionary and ecological biology, the application of mathematics to understanding gene editing and the dynamics of psychiatric disorders such as bipolar disorder. Mike has interests in science policy particularly at the interface of genetic modification, its regulation and implementation. Mike has worked with the FNIH, WHO, House of Lords, DEFRA (UK) and EFSA on GM policy and guidance statements