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Research review paper

Risk management recommendations for environmental releases of gene drive modified insects

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ABSTRACT

The ability to engineer gene drives (genetic elements that bias their own inheritance) has sparked enthusiasm and concerns. Engineered gene drives could potentially be used to address long-standing challenges in the control of insect disease vectors, agricultural pests and invasive species, or help to rescue endangered species. However, risk concerns and uncertainty associated with potential environmental release of gene drive modified insects (GDMIs) have led some stakeholders to call for a global moratorium on such releases or the application of other strict precautionary measures to mitigate perceived risk assessment and risk management challenges. Instead, we provide recommendations that may help to improve the relevance of risk assessment and risk management frameworks for environmental releases of GDMIs. These recommendations include: (1) developing additional and more practical risk assessment guidance to ensure appropriate levels of safety; (2) making policy goals and regulatory decision-making criteria operational for use in risk assessment so that what constitutes harm is clearly defined; (3) ensuring a more dynamic interplay between risk assessment and risk management to manage uncertainty through closely interlinked pre-release modelling and post-release monitoring; (4) considering potential risks against potential benefits, and comparing them with those of alternative actions to account for a wider (management) context; and (5) implementing a modular, phased approach to authorisations for incremental acceptance and management of risks and uncertainty. Along with providing stakeholder engagement opportunities in the risk analysis process, the recommendations proposed may enable risk managers to make choices that are more proportionate and adaptive to potential risks, uncertainty and benefits of GDMI applications, and socially robust.

1. Engineered gene drives

Recent advances in molecular and synthetic biology enable engineering of gene drives that spread heritable genetic modifications of interest in interbreeding populations at a rate greater than the 50% expected by normal Mendelian inheritance (Burt and Crisanti, 2018). This preferential inheritance may allow engineered gene drives (including any genetically linked cargo/payload genes) to increase their prevalence in interbreeding populations, even if the introduced genetic modification imposes some fitness costs on their host (Alphey et al., 2020). The shorter the generation time of an organism, the faster is the potential of engineered gene drives to spread in interbreeding populations (Alphey et al., 2020). As is the case for any other currently applied insect genetic control approach (such as the sterile insect technique, *Wolbachia*-mediated incompatible insect technique, *Wolbachia*-mediated pathogen interference and genetically modified insects carrying a dominant [female] lethal gene), the use of engineered gene drives would involve the intended release into the environment of individuals (e.g. genetically modified insects with engineered gene drives, also termed gene drive modified insects [GDMIs]) that contain a genetic modification that is introduced into wild populations through mating (Alphey, 2014; Nolan, 2021).

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The ability to engineer gene drives has sparked both enthusiasm and concerns (Brossard et al., 2019; Deplazes-Zemp et al., 2020). Engineered gene drives could potentially be used to address long-standing challenges associated with the control of insect disease vectors (e.g. mosquitoes and ticks), agricultural pests (e.g. the Mediterranean fruit fly, screwworm) and invasive species (e.g. the Asian fruit fly, the common wasp), or help to rescue endangered species, and thus provide important public (health) benefits (NASEM, 2016; Burt and Crisanti, 2018; ESA, 2020; WHO, 2020; Nolan, 2021). This could be achieved by modifying, primarily for disease vector control, the genetic makeup of target populations to be less able to transmit disease (population modification), or by reducing (suppressing) the size/density of target populations (population suppression) (Alphey, 2014; James et al., 2018; WHO, 2021). For example, engineered gene drives can be tailored to suppress disease-transmitting mosquitoes (serving as vectors of malaria, dengue, Zika, chikungunya, yellow fever) via the inactivation of important genes involved in (sex-specific) survival or reproduction of the target population, or introduction of genes that reduce lifespan (Kyrou et al., 2018; Raban et al., 2020; Connolly et al., 2021; Hammond et al., 2021; Nolan, 2021). Engineered gene drives for population modification, on the other hand, intend to reduce/prevent disease transmission by killing the pathogen in the mosquito, blocking pathogen development, or by inactivating genes required for the target organism to transmit the pathogen (James et al., 2018; Pham et al., 2019; Adolfi et al., 2020; Carballar-Lejarazú et al., 2020; Nolan, 2021). Depending on the engineered gene drive system, theoretically, a genetic modification could spread spatially beyond target populations (non-localised) and persist for an indeterminate time, perhaps for many generations or until the target population is either eliminated or modified, or until resistance evolves (self-sustaining); or be restricted in spread (localised) or persistence (self-limiting) (Champer et al., 2016; Marshall and Akbari, 2018; Raban et al., 2020; Hay et al., 2021).

However, there are concerns that environmental releases of GDMIs, which undergo a prospective risk assessment as part of the regulatory decision-making process like any other genetically modified insect, may eradicate (in contrast to control) target organisms, lead to undesired effects and uncontrolled spread, affect non-target organisms and ecosystems in unwanted, unanticipated and irreversible ways, or adversely impact biodiversity and health with no current ability for recall (Simon et al., 2018; CSS–ENSSER–VDW, 2019; Rode et al., 2019, 2020; Courtier-Orgogozo et al., 2020; Dolezel et al., 2020; Then et al., 2020). Moreover, they may pose different or novel harms to animal and human health and the environment compared with many conventional methods (e.g. the use of biological or chemical insecticides, insect-resistant crops, biological control) or other genetic control systems, and raise novel risk assessment and risk management challenges (NASEM, 2016; Hayes et al., 2018; Simon et al., 2018; CSS–ENSSER–VDW, 2019; AHTEG, 2020; Devos et al., 2020, 2021; Dolezel et al., 2020; EFSA et al., 2020a; Then et al., 2020; Connolly et al., 2021). These risk concerns and associated uncertainty have led some scientists, scientific and non-governmental organisations and parliamentarians to call for either a global moratorium on environmental releases of GDMIs, or the application of other strict precautionary measures to mitigate perceived risk assessment and risk management challenges (Callaway, 2016, 2018). To address some of these concerns, recommendations have been made for: (1) testing GDMIs in a phased manner; (2) deploying them in a responsible and sustainable way; (3) engaging with relevant stakeholders; and (4) developing regional approaches for the international governance of GDMIs that may spread across jurisdictional boundaries (e.g. NASEM, 2016; Esvelt and Gemmell, 2017; Hayes et al., 2018; James et al., 2018, 2020; Hartley et al., 2019, 2021a, 2021b; Kuzma, 2019; Rabitz, 2019; Thizy et al., 2019; Kelsey et al., 2020; Long et al., 2020; Reynolds, 2020; WHO, 2020; Annas et al., 2021; Burgiel et al., 2021; de Graeff et al., 2021a, 2021b; Zoloth, 2021; WHO, 2021). Moreover, continued research to increase understanding of potential ecological and evolutionary impacts of environmental releases of GDMIs and their potential risks and benefits has been advocated (NASEM, 2016; ESA, 2020; WHO, 2021). Along with these developments, we provide supplementary recommendations targeting risk issues to enable risk managers to make more proportionate and adaptive risk management choices on environmental releases of GDMIs, which would account for potential risks, uncertainty, benefits and equity considerations (Fig. 1).

2. Recommendation #1 – develop additional and more practical risk assessment guidance

Currently, risk assessors, risk managers, developers, potential applicants and many other stakeholders are discussing whether there is a need to develop new or additional guidance for the risk assessment of environmental releases of GDMIs (Devos et al., 2020, 2021; Keiper and Atanassova, 2020). Some international/regional entities such as the National Academies of Sciences, Engineering and Medicine (NASEM, 2016), an *Ad Hoc* Technical Expert Group on risk assessment operating under the Cartagena Protocol on Biosafety to the Convention on Biological Diversity (AHTEG, 2020), the GMO Panel of the European Food Safety Authority (EFSA et al., 2020a), and the World Health Organization (WHO, 2021) concluded that: (1) the risk assessment of GDMIs can build on existing risk assessment frameworks for genetically modified insects without engineered gene drive; and (2) be informed by experience releasing insects for biological and genetic disease vector/pest control. However, it is recognised that there are specific areas where further guidance may be needed for the risk assessment of environmental releases of some GDMIs to ensure appropriate levels of safety (NASEM, 2016; AHTEG, 2020; Devos et al., 2020, 2021; EFSA et al., 2020a; WHO, 2021). Therefore, risk assessors and risk managers could take specific actions for the development of additional risk assessment guidance to ensure that safety for the environment and health is maintained, while not delaying potentially beneficial innovation. This may ensure preparedness for future challenges and help developers and potential applicants to ensure that engineered gene drive products can meet acceptable regulatory standards of safety, and receive public acceptance. However, the development of additional risk assessment guidance that is useful and practical is a challenge. Stakeholders, including risk assessors and risk managers, hold different, sometimes contrasting, opinions toward environmental releases of GDMIs (MacDonald et al., 2020; de Graeff et al., 2021a, 2021b). They may disagree about the perceived scale of risk assessment challenges, potential harms and the adequacy of current risk assessment frameworks (EFSA et al., 2020b), and how the uncertainty associated with GDMI environmental releases should be dealt with. Some stakeholders consider that uncertainty provides a rationale to refrain from releasing GDMIs into the environment, while others argue that GDMI environmental releases should be conducted in a phased and responsible manner to gain more knowledge about potential intended and unintended harms (de Graeff et al., 2021a, 2021b). Consequently, there may be contention about the definition of the scope of risk assessment guidance, topics to prioritise, and procedures to follow for guidance development (Devos et al., 2020, 2021), especially at an international level (Hokanson, 2019; Reynolds, 2020).

Engineered gene drive technologies are evolving rapidly, and may deliver a range of gene drive products with different designs and modes of action (EFSA et al., 2020a; Raban et al., 2020; Hay et al., 2021). To address the rapid pace of scientific advances in the field of engineered gene drives and the diversity of potential engineered gene drive products, risk assessment guidance would need to offer an overarching framework, outlining general principles and methodology for risk assessment, that is adaptive to the specific properties of gene drive products under assessment. Problem formulation (the initial risk assessment step) may offer a fit-for-purpose and scientifically robust framework for case-specific risk assessment of GDMI environmental releases (Roberts et al., 2017; Teem et al., 2019; Devos et al., 2020, 2021; EFSA et al., 2020a; Romeis et al., 2020; Connolly et al., 2021).

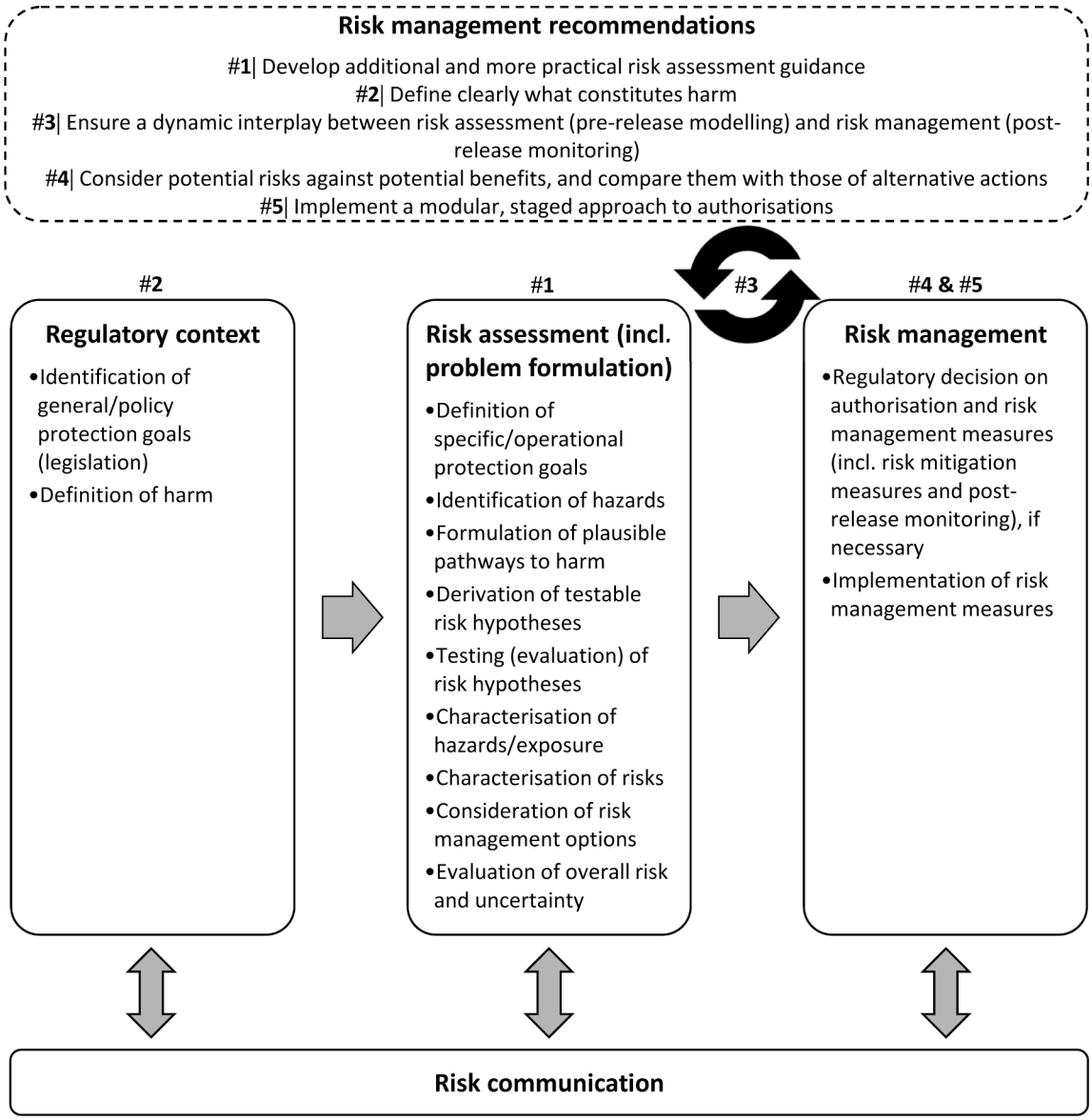

Fig. 1. Main components of the risk analysis process for genetically modified organisms, with risk management recommendations for environmental releases of gene drive modified insects.

Problem formulation involves the following successive main steps (Fig. 2): (1) identify protection goals (e.g. human and animal health, biodiversity, ecosystems, ecosystem services, soil health, water quality) and make them operational in risk assessment (i.e. operational/specific protection goal) by specifying the ecological entity and attribute to protect, the maximum tolerable impact and the spatial and temporal scale of protection; (2) devise plausible pathways to harm that describe how a proposed environmental release of a GDMI could be harmful to the identified operational/specific protection goal, through a causal chain of events; (3) formulate risk hypotheses about likelihood and severity of such events for each individual step in the pathway; (4) identify information needed to test risk hypotheses and thus reduce identified areas of uncertainty surrounding each pathway to harm; and (5) develop analysis plans to acquire information for hypothesis testing (evaluation) (Raybould, 2006, 2020; Devos et al., 2015, 2019a, 2019b; Connolly et al., 2021). Problem formulation informs the next steps of the risk assessment, which involve exposure, hazard and risk characterisation, based largely on the outputs of the analysis plans identified (Fig. 1).

Risk hypotheses can be tested in a number of ways that include, but are not limited to, using existing information, modelling, new empirical investigations, previous experiences, or any combination thereof (Connolly et al., 2021). In practice, some hypotheses may be difficult to test or testing using available information may not produce definitive conclusions regarding the likelihood of a particular step in a pathway to harm. As part of the risk assessment, such uncertainty may be addressed and reduced through an iterative and tiered-based testing approach, by consideration of multiple lines of evidence in a weight of evidence approach, and/or by new studies being undertaken (NASEM, 2016; Hayes et al., 2018; James et al., 2018; EFSA et al., 2020a; Romeis et al., 2020; WHO, 2021). However, in some cases, uncertainty may remain that must be addressed by risk managers and decision makers.

The stepwise approach followed in the problem formulation facilitates the systematic identification of potential harms and associated uncertainty, as well as their routes of exposure, while being transparent about the assumptions made during the process. Recently, Connolly et al. (2021) reported 46 plausible pathways to harm, which were systematically and comprehensively mapped through a problem formulation approach, for a hypothetical environmental release of an investigational gene drive product to suppress malaria-transmitting mosquitoes and thus reduce malaria transmission in West Africa. Eight

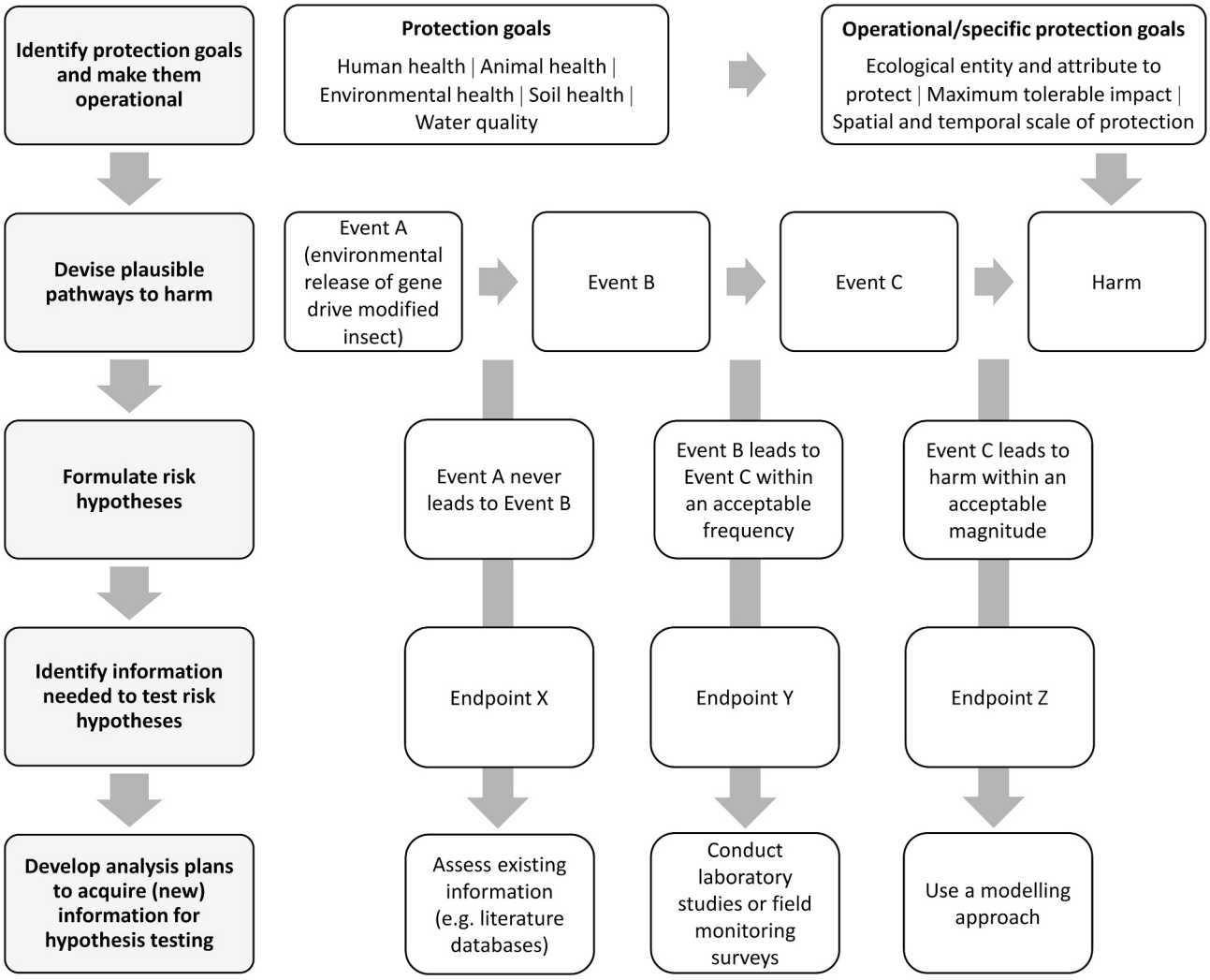

Fig. 2. Main steps of the problem formulation, including a generic pathway to harm with examples of types of hypothesis that may be tested to characterise risk and what types of information can be used to test such hypotheses (adapted from Devos et al., 2019a; Raybould, 2020; Connolly et al., 2021).

potentially harmful effects to protection goals (e.g. human and animal health and the wider environment) were identified such as reduced density of valued species or ecosystem services, or increased disease transmission in humans (Connolly et al., 2021). To allow for risk concerns to be fully explored and defined, stakeholder engagement (through the active participation of interested and affected actors) has been advocated before and during the problem formulation (NASEM, 2016; Hartley and Kokotovich, 2018; Hayes et al., 2018; Devos et al., 2020, 2021; EFSA et al., 2020a; Connolly et al., 2021; WHO, 2021).

There is currently no direct experience conducting risk assessment for environmental releases of GDMIs. Therefore, the development process of additional risk assessment guidance must involve a range of expert input including relevant stakeholders, be iterative, and build on a review of actual case studies by risk assessment experts (Devos et al., 2020, 2021). Once in place, regular review must be continued to ensure overall utility of risk assessment guidance and its applicability, and to assess where any refinements are necessary. This may help to ensure that risk assessment guidance is realistic and proportionate, and remains consistent with the weight of scientific evidence and familiarity gained with environmental releases of GDMIs and genetically modified insects without engineered gene drive (EFSA et al., 2020a).

3. Recommendation #2 – define what constitutes harm

While problem formulation is conceptually straightforward, its implementation is often hindered by an absence of clear policy goals and regulatory decision-making criteria on what constitutes harm (e.g. setting of specific/operational protection goals, limits or thresholds of concern, trigger values for action or acceptance of risk, judgments on sufficiency of scientific knowledge and agreement on the extent uncertainty should be reduced for regulatory decision-making) that are needed to guide interpretation of scientific information in risk assessment (Raybould and Macdonald, 2018; Devos et al., 2019a, 2019b; Connolly et al., 2021). Even in jurisdictions with well-developed regulatory systems, such criteria are often general, requiring refinement for operational use (Sanvido et al., 2012; Garcia-Alonso and Raybould, 2014). If what constitutes harm is not clearly defined, risk assessors have no effective way to decide whether particular potential effects of a GDMI environmental release are relevant to risk assessment (Devos et al., 2015). While causal pathways to harm have a scientific rationale, the definition of harm is subjective and rooted in societal values (Sarewitz, 2004; Devos et al., 2014, 2015, 2019a, 2019b; Raybould and Macdonald, 2018; Elliott, 2019). Consequently, risk managers must interpret objectives of policy and regulations, so that they can be translated into specific/operational protection goals for risk assessment purposes. This provides a context and boundaries to frame risk assessments, and guides

risk managers in making regulatory decisions that align with societal goals. Actively engaging society through stakeholders about social and cultural acceptability of the risk analysis process for GDMIs would be essential, and could contribute to improving quality, legitimacy and sustainability of regulatory decision-making processes (NASEM, 2016; James et al., 2018, 2020; Hartley et al. 2019, 2021a; Thizy et al., 2019; Kelsey et al., 2020; Long et al., 2020; Annas et al., 2021; Burgiel et al., 2021; WHO, 2020, 2021; Zoloth, 2021). WHO (2021) noted that stakeholder engagement may enable those with interests or risk concerns (including non-technical actors) to bring valuable knowledge that could improve risk decisions, and to make informed decisions about the acceptability of GDMI environmental releases.

Existing insect disease vector/pest control strategies are known to cause some incidental harm, so when defining harm risk managers could consider whether a proposed environmental release of a GDMI may lead to less, more or new harms, compared with current practices (see recommendation #4 for more details). Since some risks anticipated from environmental releases of GDMIs may have been encountered before, from use of genetically modified insects without engineered gene drive, and from other current insect disease vector/pest control strategies, they are not necessarily novel (Roberts et al., 2017; James et al., 2018, 2020; EFSA et al., 2020a; Romeis et al., 2020; Annas et al., 2021; Devos et al., 2021; Zoloth, 2021).

4. Recommendation #3 – ensure a dynamic interplay between risk assessment (pre-release modelling) and risk management (post-release monitoring)

Risk assessment for environmental releases of some GDMIs is expected to require greater reliance on pre-release modelling and post-release monitoring to address uncertainty, compared with genetically modified insects without engineered gene drive or other self-limiting genetic control approaches (NASEM, 2016; James et al., 2018, 2020; North et al., 2019, 2020; Devos et al., 2020, 2021; Dhole et al., 2020; EFSA et al., 2020a; Sánchez et al., 2020a; Golnar et al., 2021).

- *Pre-release modelling*: Modelling approaches are typically followed to predict outcomes from data and understand how complex systems work (Golnar et al., 2021). Modelling may enable extrapolating data gathered from confined experimental systems (e.g. laboratories, indoor cages, small-scale physically and/or ecologically confined field trials) to field conditions. Moreover, modelling addresses the wide spatial and long temporal scales of effects of specific GDMIs that may be empirically unrealistic to study in all relevant receiving environments prior to release (Golnar et al., 2021). While fundamental challenges with models remain because extrapolation beyond the range of practical datasets involves considerable uncertainty, some modelling processes allow uncertainty to be more thoroughly understood (e.g. formal sensitivity analyses of predictions to parameter variation, consideration of outcomes at the bounds of acceptability related to specific/operational protection goals), or reduced (e.g. iterative process of model-driven data collection and data-driven model prediction). Therefore, models can provide a valuable contribution to a weight of scientific evidence approach followed in risk assessment (EFSA et al., 2020a; Golnar et al., 2021; WHO, 2021);
- *Post-release monitoring*: Monitoring may allow one to cross-validate risk assessment assumptions against outcomes, and assess the relevance of model predictions, which can then support the effectiveness of specific risk mitigation measures. Thereby, monitoring would serve as an early warning check of outcomes that diverge from expected results, to rapidly implement or modify risk mitigation measures from within a pre-planned range of management options, or implement remedial measures that have already proven to be effective, such as insecticides or sterile insects. Monitoring may also help to address risk assessment issues that are subject to a degree of uncertainty, for example, possible effects that may appear only where environmental releases are on a large-scale. Thus, it may complement risk assessment as a tool to manage and reduce remaining uncertainty further (EFSA et al., 2020a).

Improving the integration of pre-release modelling and post-release monitoring through a more dynamic, iterative interplay between risk assessment and risk management would reduce risk uncertainty associated with the environmental release of some GDMIs. While monitoring would provide new data for (response) models, such data would also support model validation and calibration for future regulatory purposes. However, for this approach to be more or fully effective, both modelling and monitoring capabilities would need to be enhanced further (NASEM, 2016; AHTEG, 2020; Dhole et al., 2020; Champer et al., 2021; Golnar et al., 2021; Wu et al., 2021). Moreover, risk management plans, which propose measures to mitigate risks and remedy potential observed specific outcomes of monitoring, should be established prior to a proposed environmental release of a GDMI, undergo systematic evaluation in a manner consistent with risk assessment, and ensure that the effectiveness of the proposed measures has been determined (Devos et al., 2020). Research efforts are ongoing to develop reversal engineered gene drives as genetic remediation or neutralising systems that could disable or reverse the effects of a previously released GDMI in the event of unintended consequences (Gantz and Bier, 2016; Vella et al., 2017; Friedman et al., 2020). The development of such gene drives is proceeding in insects such as mosquitoes and fruit flies (e.g. Oberhofer et al., 2020; Xu et al., 2020; Taxiarchi et al., 2021), while their potential use is explored with population genetic models (e.g. Girardin et al., 2019; Rode et al., 2020). For example, using cleave and rescue gene drive systems, Oberhofer et al. (2020) showed that engineered gene drive-mediated population modification in *Drosophila* can be overwritten with new content, and old elements of an initial gene drive that has lost efficacy be eliminated. Systems have also been designed to either turn on or turn off gene drive activity in the presence or absence of small organic molecules that can easily enter cells (Heffel and Finnigan, 2019; López Del Amo et al., 2020). While reversal and inducible engineered gene drive systems hold promise for risk management, developers themselves caution against unforeseen consequences (Xu et al., 2020), and indicate that reversal engineered gene drives may not necessarily be the first choice for remediation efforts due to the associated uncertainty of introducing another gene drive approach (Marshall and Vasquez, 2021).

5. Recommendation #4 – consider potential risks against potential benefits and compare them with those of alternative actions

Risk debates about genetically modified organisms, including GDMIs, often expand to considering whether emerging biotechnologies contribute to sustainable development goals (which were adopted by the United Nations in 2015 as a universal call to action to end poverty, protect the planet, and ensure that by 2030 all people enjoy peace and prosperity), and how potential risks and benefits associated with the deployment of such biotechnologies are distributed (EFSA et al., 2020b; de Graeff et al., 2021a, 2021b). In most jurisdictions, however, regulatory systems for genetically modified organisms are designed to consider primarily potential risks and their likelihoods, but not potential benefits and costs. Consequently, whether a proposed GDMI environmental release is likely to meet wider socioeconomic and ecological aspirations and other policy targets is not explicitly addressed in the risk analysis process. Moreover, potential risks and their likelihoods are not necessarily being compared with those of commonly applied management interventions (such as the use of insecticides, bed nets, sterile insect technique, *Wolbachia*-mediated incompatible insect technique, *Wolbachia*-mediated pathogen interference, potential vaccines) or alternative management interventions (such as genetically modified insects without engineered gene drive). Both types of intervention have their own

potential risks and costs in terms of ongoing adverse impacts and/or management resources (Burgiel et al., 2021; de Graeff et al., 2021a, 2021b), and thus are not free of potential risks. Hence, decisions about the acceptability of emerging biotechnologies must be made in the context of other risks as well as the costs of not using such technologies (e.g. non-intervention), as it may enable an interpretation of the precautionary principle through a proper evaluation of the options available for decision-making and estimation of the costs and benefits associated with possible decisions as well as the costs of non-intervention (Tait, 2001; Tait and Barker, 2011). According to Zoloth (2021), maintaining the *status quo* through non-intervention, especially for disease vector control, would be morally unacceptable, as the current situation may not be sufficiently safe, and lead to continuing disease burden (see also WHO, 2020, 2021; de Graeff et al., 2021a, 2021b).

To be more robust, meaningful and legitimate, decisions about whether to authorise a proposed environmental release of a GDMI, in particular those targeting human/animal disease vectors, may need to consider the assessment of both potential risks and benefits (including the necessity to take action to minimise potential harms and/or maximise potential benefits) (EFSA et al., 2020a). These potential risks and benefits must be established by the social, political, ecological and technical contexts of the proposed intervention (Hartley et al., 2021a; Zoloth, 2021). This will require comprehensive understanding of how to assess and weigh potential risks and benefits, and to consider input of relevant (potentially impacted) stakeholders (Hartley et al., 2021b).

6. Recommendation #5 – implement a modular, phased approach to authorisations

Authorisations of GDMI environmental releases may benefit from being modular (in design) to ensure an incremental approach to such releases. Based on the familiarity gained with a GDMI environmental release and data gathered through post-release monitoring (ESA, 2020), the scale of environmental releases could be increased gradually and possible risk mitigation measures to limit engineered gene drive spread and/or persistence could be relaxed. Thereby, environmental releases of GDMIs would proceed iteratively through successive stages (from small-scale environmental release with risk mitigation, to large-scale environmental release with low/no risk mitigation, to full-scale environmental release with low/no risk mitigation), with each phase involving a larger spatial scale and higher degree of exposure. This approach would enable separating environmental releases of GDMIs spatio-temporally, to make risk mitigation achievable and commensurate with levels of stakeholder acceptance of stated uncertainty. However, it will require regular review (based on new empirical and post-release monitoring data) to assess whether to move forward to a larger and/or longer release scale to be conducted at a single site or multiple sites. Such an approach would be consistent with and complement the stepwise approach followed internationally for the environmental risk assessment of genetically modified organisms (OECD, 1993) and the revised guidance framework for testing genetically modified mosquitoes for use against disease vectors developed by the WHO (2021). According to the WHO (2021) framework, testing must proceed iteratively through multiple phases (contained laboratories, indoor cages and insectaries; physically and/or ecologically confined/isolated field trials [e.g. large cages, physical islands]; small-scale open release trials; large-scale open release trials; and environmental releases), with each phase involving a larger spatial and temporal scale and a higher degree of human or environmental exposure and realism (see also NASEM, 2016; James et al., 2018, 2020). Relevant data gathered under controlled, contained conditions would provide confidence that the GDMI can safely progress to the next testing and release phase (NASEM, 2016; Hayes et al., 2018; James et al., 2018; WHO, 2021). The WHO recently updated its guidance framework to incorporate specific considerations for engineered gene drives, as some of them are predicted to have potential impacts during several of the multiple phases of the testing framework. For example, in the case of non-localised and self-sustaining engineered gene drives intended for widespread and long-standing use, WHO (2021) indicated that field testing may better be conceived as a continuum of expanding releases.

Implementing a modular, phased approach to authorisations for non-localised and self-sustaining engineered gene drives remains conceptual at present, in part due to their current inability for recall. Therefore, developers and potential applicants may wish to consider the utility of prior field testing of a closely related self-limiting and/or localised strain as an intermediate step to gather evidence for model development and refinement, and reduce uncertainty in risk assessment (James et al., 2018; EFSA et al., 2020a; Marshall and Vasquez, 2021; WHO, 2021). Self-limiting and/or localisation approaches could be used as biological or molecular risk mitigation strategies to limit the spread and/or persistence of engineered gene drives. In effect, they would constitute biological or molecular confinement that may supplement physical and ecological confinement through geographical, spatial and/or climatic isolation (James et al., 2018; Hammond et al., 2021; Lanzaro et al., 2021; WHO, 2021). This would be in tune with the safe-by-design concept (i.e. through built-in safety/risk reduction mechanisms implemented at the genetic level, during the design of a GDMI) (Asin-Garcia et al., 2020). Current research efforts focus on the development of engineered gene drives that would be confinable (i.e. limited in spread and/or persistence) and reversible (i.e. recallable from the environment) (e.g. Backus and Delborne, 2019; Li et al., 2020; Maselko et al., 2020; Sánchez et al., 2020b; Webster et al., 2020; Buchman et al., 2021; Hay et al., 2021; Kandul et al., 2021; Oberhofer et al., 2021; Terradas et al., 2021; Willis and Burt, 2021). Several theoretical approaches – some of which have already been tested experimentally under laboratory settings – have been proposed to restrict spread of engineered gene drives within a specified target population or geographic region, or their persistence (Raban et al., 2020). Examples include: high threshold engineered gene drive systems (such as underdominance [heterozygote inferiority] gene drives; tethered homing-based gene drives; and split rescue gene drives) that require the release of gene drive modified individuals above a certain threshold density to be able to spread to fixation (EFSA et al., 2020a; Hay et al., 2021). Release of fewer individuals would inhibit spread and persistence, as the threshold density needed to drive would not be reached. Other localisation approaches under development and/or investigation are: engineered gene drive systems that target alleles that are only present in a genetically isolated (local) subpopulation of the target species or fixed in such isolated subpopulations (Sudweeks et al., 2019; Willis and Burt, 2021); and split homing-based engineered gene drives, in which the Cas9 nuclease is separated from the guide RNA at different loci on chromosomes or lines of insects and would need to be crossed (Li et al., 2020; Kandul et al., 2021; Terradas et al., 2021). Recently, Nash et al. (2019) evaluated theoretically the concept of integral gene drives that are based on multiple interacting components, each one of which could be tested separately or in combination. The modularity and interdependence of integral gene drive components may enable testing from self-limited to self-sustaining components in the field by modulating the propensity to spread in target populations (Nash et al., 2019).

Theoretically, the design of engineered gene drives could be phased, fitting the modular, phased approach to authorisations. This approach would also allow the iterative testing of pre-release models, by validating model predictions through data obtained under contained or confined conditions (WHO, 2021). However, it will take many years before a modular, phased approach for engineered gene drive systems can be applied to practical disease vector/pest management (EFSA et al., 2020a).

7. Conclusion

Instead of a global moratorium on GDMI environmental releases or the application of other strict precautionary measures to mitigate

perceived risk assessment and risk management challenges, we recommend: (1) developing additional and more practical risk assessment guidance to ensure appropriate levels of safety; (2) making policy goals and regulatory decision-making criteria operational for use in risk assessment so that what constitutes harm is clearly defined; (3) ensuring a more dynamic interplay between risk assessment and risk management to manage and reduce uncertainty through closely interlinked pre-release modelling and post-release monitoring; (4) considering potential risks against potential benefits, and comparing them with those of alternative actions (including non-intervention) to account for a wider (management) context; and (5) implementing a modular, phased approach to authorisations for incremental acceptance and management of risks and uncertainty. In addition, providing stakeholders with opportunities for active engagement in the risk analysis process may help to clarify policy goals and regulatory decision-making criteria, explore and define broad interests and risk concerns, demonstrate how to navigate regulatory processes, clarify data requirements, examine risk management options, build trust and legitimacy, and increase public safety. Such stakeholder engagement can be incorporated into all relevant risk analysis (including risk assessment) steps, but who to involve and how to structure engagement may vary across steps (Hartley and Kokotovich, 2018; Hartley et al., 2021b). While potentially challenging to implement in practice, the recommendations offered above may enable risk managers to: (1) make choices that are more proportionate and adaptive to the potential risks, uncertainty and benefits of GDMI environmental releases; (2) better balance openness and engagement with scientific robustness; and (3) improve the relevance of risk analysis frameworks for engineered gene drives.

Disclaimer statement

The views expressed in this publication are those of the authors and should not be interpreted as representing the official position of the European Food Safety Authority (EFSA). EFSA assumes no responsibility or liability for any errors or inaccuracies that may appear. Part of this publication builds on EFSA et al., 2020a to which the authors contributed actively.

Author contribution

YD wrote the manuscript and conceived it. All authors read, reviewed, edited and approved the manuscript.

Declaration of Competing Interest

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