This paper is part of the IRGC project "Ensuring the environmental sustainability of emerging technologies".
Suggested citation: Kuzma, J. (2022). Gene drives: Environmental impacts, sustainability, and governance. In M.-V. Florin (Ed.) (2023). *Ensuring the environmental sustainability of emerging technologies* (Edited volume). Lausanne: EPFL International Risk Governance Center. DOI: 10.5075/epfl-irgc-298445

Gene drives: Environmental impacts, sustainability, and governance

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Introduction

This paper, produced in the context of EPFL International Risk Governance Center's (IRGC) project on ensuring the environmental sustainability of emerging technology outcome, overviews gene drive organisms (GDOs), their potential impacts on sustainability and the environment, and special considerations for risk governance. GDOs are designed to spread their genes throughout a population in an ecosystem. Newer GDOs utilize gene editing technologies like CRISPR to bias inheritance of genes with each generation towards 100%. Gene drives can be designed to cause the population to decline (e.g., via female killing) or be beneficial to the population (e.g., via genes that immunize against a disease). Theoretically, the release of just a few organisms could change populations in ecosystems permanently. However, gene drive systems are also being developed and designed to be limited in geography or spread, or to be reversible. GDOs hold promise for controlling agricultural pests with fewer pesticides, protecting endangered and threatened species against pests and ecological hazards, and reducing the transmission of human and animal diseases. However, their open release presents characteristics of emerging risks that are accompanied by significant complexity, uncertainty and ambiguity. It is difficult to predict the risks of ecological release of GDOs prior to open release, and open release could cause widespread ecological impacts through complicated and sensitive ecosystems. This situation presents significant challenges for risk assessment, mitigation, management and international governance of GDOs. Given the near impossibility of amassing risk-relevant data prior to release, GDOs make the procedural validity of risk analysis and decision-making even more important in comparison to many other technologies and risks. More robust risk analysis methods and global governance systems are needed to ensure their safe, sustainable and equitable use.

1.

Gene drive technologies

Gene drives are "selfish genes" that bias their own inheritance greater than the typical 50% predicted by Mendelian inheritance. Naturally occurring gene drives, such as homing endonuclease genes (HEGs), have been proposed as ways to suppress or modify populations that carry disease for several decades (Burt, 2003; Curtis, 1968; Deredec et al., 2008; Sinkins & Gould, 2006). However, in recent years, with the advent of gene editing technologies biologists have been using the tools of molecular biology to engineer gene drive systems into animals, plants and microbes (reviewed in Bier, 2022). Most gene drive systems currently under development capitalize on CRISPR-Cas molecular tools (Esvelt et al., 2014). Cas proteins are nucleases that cleave

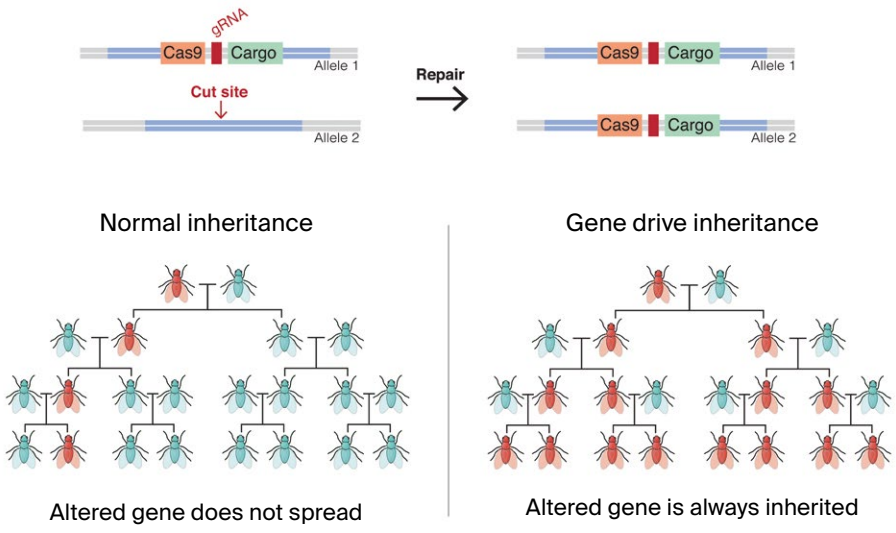

Figure 1 | How gene drives bias inheritance (reprinted from Mariuswalter, 2017)

DNA at "clustered regularly interspaced short palindromic repeats" (CRISPR) frequently present in genomes (Kuzma, 2020). CRISPR-Cas systems can be targeted toward any site in the DNA by "guide RNA" (gRNA) sequences. After the CRISPR-Cas system (with the gRNA) cuts the target DNA site, a double-strand break results, which can either be repaired by the cell or result in a mutation. However, if engineers provide an additional DNA template sequence with homology to either side of the break at its ends, it can be used for repair instead and copied into the break site. If the repair templates include DNA sequences coding for the CRISPR-Cas system and the gRNA, the gene drive system copies itself into cleavage sites via homology directed repair. When this gene drive system is introduced into germ-line cells, it biases inheritance away from 50% (predicted by Mendelian inheritance) towards 100% (depending on the efficiency) (Bier, 2022; Esvelt et al., 2014) (Figure 1).

The shorter the generation time of an organism, the faster the engineered gene drive will spread in populations that interbreed. "Cargo genes" confer any type of trait that can be genetically linked to an engineered gene drive system, and even with some fitness cost, these genes will spread through the population along with the gene drive (Bier, 2022). Cargo genes can be designed that confer desirable traits, like disease resistance, or harmful traits that cause the population to decline (e.g., female killing). In the latter case, theoretically, the release of just a few individuals with gene drives could cause the whole population to decline or collapse (given full population mixing and mating) (Esvelt & Gemmell, 2017). In theory, cargo genes can come from any species and be introduced into any host.

The efficacy of gene drives has been studied via mathematical modeling (see also Section 3.1). Efficacy is dependent on factors such as the fitness cost of the gene drive or gene drive/cargo system compared to wild-type genetics; the ratio of the number of organisms released to the total target population; the dominance of the genes targeted or introduced; and mating characteristics and spatial features of the population (Bier, 2022). Gene drives require sexual reproduction to work, as well as short generation times to fixate into the population within a reasonable time frame. With ideal assumptions like complete population mixing and mating, models have predicted it would take 10—20 generations to fix gene drives into wild populations when the initial frequency of GDO individuals released to the wild population was 0.001 (Unckless et al., 2015).

Scientists are working on a variety of types of gene drives (Bier, 2022). Technological choices associated with gene drives include (1) whether the gene drive is designed to suppress the target population or to replace it with a genetically modified population; (2) the rate of its spread; (3) whether it is locally confined or not; (4) whether it has a fitness cost; (5) the rate of DNA sequences resistant to the gene drive with each generation; (6) whether it is reversible; and (7) whether it can be reversed to the original wild-type sequence (Champer et al., 2017). Some gene drives are designed to act globally with no limitations on spread. These are termed "global drives", and theoretically, the release of one individual can drive the genes through the target population to achieve fixation. Other gene drives can be engineered to be "limited" in theory (e.g., reduce only 20% of the population as "self-limited" gene drives, or target only certain genetic variants of the organism in a particular geographic region as "local" gene drives). Others can require a certain proportion of individuals to be released to drive the gene into the population (e.g., 1,000 individuals per 10,000 wild population need to be released to achieve full spread—a "threshold drive"). However, getting gene drives to work in the field as they are predicted to behave mathematically or as they behave in the laboratory may be challenging (see Section 3.1).

2. Use of gene drives

Gene drive systems enable the genetic modification of entire populations in situ (within the ecosystem) through the release of just a few individuals of that species. Given their potential power to control or protect species, gene drive research and projects have grown extensively in the past 5 to 10 years, and GDOs are being developed for multiple purposes and societal goals. No gene drives have been released yet into the ecosystem; however, several laboratory cage trials have occurred. To date, synthetic gene drives have been developed in yeast (*Saccharomyces cervisiae, Candida albicans*), fruit flies (*Drosophila melanogaster*), the plant *Arabidopsis thaliana*, diamondback moths (*Plutella xylostella*), mosquitoes (*Anopheles gambaie*, *Aedes aegypti*, *Anopheles stephensi*) and mice (*Mus musculus*) (Verkuijl et al., 2022).

Technology developers are contemplating GDO releases for disease control (e.g., malaria, Dengue, Zika, Lyme's), pest control (e.g., mice on islands,

diamondback moths or fruit flies in agriculture), and conservation (e.g., prevent bird malaria in Hawaii, control mice on islands to protect endangered birds, protect black-footed ferret from plague) (Anthony et al., 2017; Baltzegar et al., 2018; Bier, 2022; Buchman et al., 2018; Davies & Esvelt, 2018; Fidelman et al., 2019; Medina, 2017; Reynolds, 2021). Other places where gene drives are being considered include coral reefs so that they can withstand rising sea temperatures and invasive species programmes of countries like predator-free New Zealand (Dearden et al., 2018; Rode & Estoup, 2019).

Each GDO purpose will have multiple types of ways that gene drives could be designed to accomplish the protection goal. For example, strategies for reducing the disease impacts of insect-transmitted pathogens could involve reducing the population of the insect (i.e., population suppression) or immunizing the insect from carrying the disease (i.e., population modification) (Bier, 2022). Many population suppression approaches rely on using gene drives to cause most or all genetic offspring to be male or members of one sex to be infertile (Bier, 2022). This allows for gene drive spread via one sex (e.g., males) that can mate with the wild-type organism in ecosystems, while also reducing the population (e.g., by killing females before emergence). Gene drives are being developed not only for eradicating agricultural pests (population suppression) (Devos et al., 2021; National Academies of Sciences, Engineering, and Medicine (NASEM), 2016; Romeis et al., 2020), but also to add beneficial genes (e.g., immunizing genes) to protect desired populations (population modification) (Devos et al., 2021; National Academies of Sciences, Engineering, and Medicine (NASEM), 2016).

General applications for gene drives introduced into populations in the environment fall into general categories of eradicating vector-borne human disease, enhancing agricultural safety and sustainability, protecting threatened species, and controlling invasive species (Esvelt et al., 2014; Kuzma & Rawls, 2016). Categories of modes of action include populations suppression (e.g., GDOs with global, self-sustaining gene drives that prevent reproduction), enhancement (e.g., with cargo genes that confer an advantage to the GDO), immunization (e.g., with cargo genes that protect GDOs from disease), or sensitization (e.g., with cargo genes that make an invasive species susceptible to pesticides) (Kuzma & Rawls, 2016). Risk, ethical, societal, regulatory, and ecological issues depend at least in part on the purpose and mode of action of gene drives (Sections 3 & 4).

Human health applications have been the focus of much research on gene drives, especially gene drives to control human disease vectors like mosquitoes transmitting Zika, dengue and malaria. A CRISPR gene drive has been developed that achieved a total population collapse of *Anopheles gambiae* mosquitoes, the carrier of the malaria parasite, in laboratory cage trials (Kyrou et al., 2018). This was achieved by designing the gene drive to insert itself into (and thus disrupt) a sex determination gene (*doublesex*). The females were less fit and not able to reproduce, leading to an eventual crash of the population within 7 to 11 generations in the trials. How these lab trials translate to the field remains to be seen. A separate theoretical modeling study found that the impacts of GDO mosquitos on malaria control in West Africa are likely to vary — from population suppression to complete elimination — depending on sub-regional environmental and physical characteristics (North et al., 2019).

To harness and promote gene drives for controlling mosquito-borne diseases, research consortia have arisen. Target Malaria is a group of scientists and stakeholders joining together in a non-profit consortium to develop *Anopheles* malaria-reducing GDOs for use in sub-Saharan Africa (Target Malaria, n.d.). GDOs are also being developed for other insect-borne diseases like Chagas, sleeping sickness, Leishmaniasis, West Nile virus, and other encephalitic viruses (Bier, 2022).

Gene drive systems in vertebrates, plants, and bacteria are also under research and development (Bier 2022). Gene drives have been successfully developed in mice. Grunwald et al. (2019) reported on the use of a split CRISPR-Cas9 system with female mice carrying the gene Cas9 and males carrying the gene for the gRNA and a gene that modifies the mouse's coat color (Grunwald et al., 2019). They were able to increase inheritance for coat color from the predicted 50% for Mendelian inheritance to 72%.

A research consortium is tackling the conservation application of gene drives for controlling mice on islands. The Genetic Biocontrol of Invasive Rodents (GBIRd) project aims to reduce rodent populations on islands where endangered birds and other species

are being destroyed by invasive mice[2]. Currently, rodenticides like Brodifacoum are dispensed through bait stations or aerial methods, and they not only cause a painful death of internal bleeding in the mice but also harm nontarget species that may be endangered. The GBIRd group is harnessing a natural gene drive that works during meiosis, called the t-haplotype, and inserting into it a male-determining gene called Sry to reduce mouse fertility and cause population suppression (Leitschuh et al., 2018). Gene drives with an immunization mode of action have also been proposed in mice to control Lyme's disease in the U.S. on Nantucket Island. Gene drives would be used to spread antibodies toward the parasite causing Lyme's disease in the reservoir species, white-footed mice (Davies & Esvelt, 2018).

Population suppression drives are being considered and developed for agricultural pests. CRISPR-Cas9 gene drives have been proposed for New World screwworm (a pest of livestock still a problem in tropical South America and on some Caribbean islands), the fruit fly *Drosophila suzukii*, the diamondback moth, and the red flour beetle (Scott et al., 2018). Companies are starting to commercialize gene drives for such purposes. For example, one company is pursuing a gene drive for population suppression of the fruit pest, Spotted Winged Drosophila (SWD) (*D. suzukii*). The gene drive system uses a synthetic *Medea* drive with a maternal toxin and an antidote in the zygote (fertilized egg) to kill females with each generation (Buchman et al., 2018). This drive system can bias inheritance up to 100% in the laboratory, but modeling studies suggest that in the field, a relatively high number of GDOs may need to be released.

Other groups have proposed gene drives for the control of agricultural weeds. Genes that confer susceptibility to herbicides could be introduced into weeds that are resistant to the herbicides (National Academies of Sciences, Engineering, and Medicine (NASEM), 2016). However, a challenge with plant-based GDOs is that gene drives rely on sexual reproduction and many plants self-cross, reproduce asexually, have perennial life cycles, or produce seed banks that are dormant (Neve, 2018).

3.
Risk pathways and endpoints of concern

Gene drives seem to present characteristics of all three types of emerging risks (IRGC, 2015): "(1) high uncertainty and a lack of knowledge about potential impacts and interactions with risk-absorbing systems; (2) increasing complexity, emerging interactions and systemic dependencies that can lead to non-linear impacts and surprises; and (3) changes in context (for example social and behavioral trends, organizational settings, regulations, natural environments) that may alter the nature, probability and magnitude of expected impacts". Gene drives involve the complicated context into which they are deployed (socio-ecological systems); uncertainty, as field-level effects cannot be well characterized until ecosystem release; and ecological disturbances that may lead to ecological surprises or non-linear impacts.

One of the first steps of risk analysis is problem formulation. Problem formulation in the context of gene drives involves identifying endpoints to be protected that are of societal value (e.g., health, biodiversity, social or cultural systems, certain species, ecological services, etc.); considering pathways by which events can lead to harm; developing hypotheses about the likelihood and severity of the harm to the endpoints from those pathways; identifying information and data needs for testing those risk hypotheses; and developing a risk assessment plan bringing together data, information, and public engagement in the process (Devos et al., 2021; Roberts et al., 2017). As problem formulation presents value judgements, engaged models for risk analysis of gene drives and other emerging technologies have been recommended so that diverse experts, stakeholders, communities, and marginalized or indigenous groups are consulted (Devos et al., 2021; IRGC, 2015; Kofler et al., 2018; Kuzma, 2019; Kuzma et al., 2018).

Subsequent steps in risk analysis involve exposure assessment, hazard and risk characterization, risk mitigation and management, and risk communication. However, the state of the field of risk analysis for gene drives is still very much in the problem formulation stage, as data and information are lacking, especially on the impacts of field releases of

[2] See geneticbiocontrol.org.

gene drives. A detailed problem formulation for gene drive risk assessment was recently published that focused on a population suppression GDO designed to combat malaria-transmitting mosquitoes in West Africa. It reported 46 plausible pathways of harm, most of which involved increased human or animal disease transmission as the risk endpoints (Connolly et al., 2021).

Although the ultimate adverse outcomes associated with GDOs may be the same kind as those associated with related technologies like biocontrol or first-generation genetically engineered organisms (e.g., species loss, increased disease), the causal pathways that lead to those outcomes —and their likelihood and magnitude— are likely unique (Hayes et al. 2018). Two approaches to hazard identification for gene drives have been suggested: (1) evaluate hazards identified for more or less similar situations like biocontrol or genetically engineered organisms (GEO) in a "checklist-like approach", and (2) structured hazard identification to anticipate what might go wrong, such as fault-tree analysis (Hayes et al. 2018). With respect to the first approach, a study by Hayes et al. (2018) outlines hazardous occurrences or pathways that could arise at three different levels —the molecular, population or ecosystem level (summarized in Table 1). In the following sections, this paper considers some of these pathways from molecular to population and ecosystem levels.

3.1 Molecular risk pathways

Unintended consequences to the environment or human health may arise from a lack of stability and efficacy of the gene drive molecular system.

Table 1 | Hazardous events that could lead to adverse outcomes (adapted from Hayes et al., 2018; also appearing in Kuzma 2020)

Scale	Hazardous events	Examples of potentially adverse ecological outcomes
Molecular	Cas9 cleaves loci with similar, but not identical, homology to the target loci	New phenotype with a different (possibly increased) capacity to spread diseases or pathogens
	Mutated gRNA causes Cas9 cleavage of nontarget sequence	New phenotype with a different (possibly increased) capacity to spread diseases or pathogens
	Cas9 fails to edit or target all alleles	Changes the target organism's ability to survive, reproduce or spread
	Mutations occur during repair of multiple cleavage sites	Changes the target organism's ability to survive, reproduce or spread
Population	Assortative or non-random mating between new phenotypes	Drive is reduced and/or competitive advantage accrues to a more virulent phenotype leading to an increase in the incidence of the disease or pathogen of concern
	Intraspecific (admixture) and interspecific hybridization	Gene drive is acquired by, and spreads within, nontarget population or nontarget species leading to the suppression or modification of this population or species
	Unpredicted phenotypes from gene by environment interactions	Gene drive fails to produce refractory organisms in the wild but increases target organism's capacity to spread diseases or pathogens
Community ecosystem	Population/species suppression changes competitive relationships	Release from competition allows a detrimental population or species to increase in abundance
	Population/species suppression causes extinction of (prey) species	Cascading effects on food web caused by decrease in abundance of predators leading to possible loss of ecosystem services
	Horizontal (lateral) transfer of gene drive to distant species	Gene drive is acquired by, and spreads within, nontarget species, leading to suppression or modification of the nontarget species

Molecular failure pathways can lead to adverse consequences or undesired outcomes related to risk endpoints. For example, with introduced genes for population suppression designed for pest eradication (like female-killing systems), resistance to the gene drive may develop over time depending on the mutation rate of the target site for the gene drive nuclease, fitness costs of the introduced genes like the CRISPR-Casx system or cargo genes, and the likelihood of non-homologous end joining (NHEJ) occurring prior to copying the gene drive into the homologous chromosome (Bier, 2022). The design of gene drives to include target sites that have lower genetic variation in the population (low polymorphisms) can both increase the probability that the drive will be propagated through the intended population and decrease the chance that it will disrupt nontarget species in the ecosystem (a population or ecosystem risk).

In experimental studies, one of the main reasons that gene drives fail, or disappear from the population, is due to emergence of mutations causing resistance to cutting at the DNA recognition or target site (Unckless et al., 2017). The rapid evolution of resistance could present an important risk for disease eradication and suppression drives, as the released GDOs would not lead to a population decrease but instead would increase the population size (from released GDOs adding to the wild population) and thus potentially increase the chance of disease transmission. Mutations can make the wild-type chromosomes resistant to further cleavage by the Cas9 endonuclease and cease the spread of the gene drive. To combat resistance, it has been proposed to use several gRNAs that target multiple sites (Bier, 2022; Noble et al., 2017), much like using multiple antibiotics to combat bacteria resistant to disease treatment. Experimental studies have found that targeting multiple sites does indeed decrease resistance (Champer et al., 2018). However, multi-site targeting might also lead to greater unintended effects by increasing the potential for the gene drive to cut and mutate off-target sites (discussed below).

Another molecular risk pathway stems from off-target binding, cutting, and edits or deletions in DNA regions with some homology to the target site for the gene drive system. Furthermore, the gRNA used to target sites with CRISPR-Casx gene drives could also mutate, causing additional off-target effects (Scharenberg et al., 2016). These off-target edits could have a variety of impacts, including fitness costs, which would be undesirable for immunization or protection drives designed to increase species survival. CRISPR-Cas gene drives are designed to be active over many generations, and with every one, the chance of mutation at off-target sites increases. With each generation in the gene drive heritance chain, mutations could therefore accumulate, increasing the likelihood of detrimental effects.

Cutting at off-target sites could disrupt genes that are important for survival. If the gene drive is meant to immunize a valuable or endangered species for example against a disease, an off-target mutation that is detrimental to the organism could spread and lead to a substantial risk to the health and survival of the species instead of achieving the intended benefit of increased survival. Furthermore, the gene drive could be transferred to another species or subspecies that is important to the ecosystem either through mating (if sexually compatible with the GDO) or horizontal gene transfer, albeit there is a low probability for the latter. Off-target mutations in the recipient species could then accumulate and cause a reduction in fitness. On the flip side, with gene drives intended to suppress or eradicate a population, off-target mutations could instead counteract this goal and make the organisms more fit or a bigger threat to the ecosystem. The unexpected survival of the population, despite the suppression drive, could lead to increased pestilence, disease transmission, or predation of other important species.

Some studies have shown no off-target mutations after careful selection of unique target sequences and optimization of both the gRNA and Cas nuclease (Cho et al., 2014). However, a meta-analysis of mouse studies using CRISPR-Cas9 for gene editing found off-target edits in 23% of the experiments (Anderson et al., 2018).

3.2 Population and ecosystem risk pathways

Changes to populations of important species in an ecosystem may have wide-ranging effects on biodiversity, food webs and ecosystem services (Connolly et al., 2022; Devos et al., 2021; Esvelt & Gemmell, 2017; Greenbaum et al., 2019; Hayes et al., 2018; Webber et al., 2015). For population suppression or eradication gene drives, where the goal is species decline, the demise of that target population could lead to decreases in their predators or increases in species on which they prey. If the GDO with the suppression drive is a predator that keeps another pest population in check, increases in pestilence or disease may result from the

overabundance of the prey. In the case of disease-carrying organisms being suppressed or eradicated with gene drives, this might lead to the filling of the ecological niche with organisms that carry even worse diseases (Bier, 2022).

Furthermore, if the GDO is an invasive species to an ecosystem and is eradicated through a population suppression drive, another more harmful alien invader could take its place, potentially causing more damage to the ecosystem. For example, the eradication of feral goats and pigs on the Sarigan islands in the Western Pacific led to the proliferation of a new invasive vine in the region (Kessler, 2002). In summary, removing a species (whether native or invasive) with gene drive technology "could produce unintended cascades that may represent a greater net threat than that of the target species" (Webber et al., 2015).

Unanticipated ecological impacts may arise from a gene drive itself spreading into a nontarget population of the same or a different species, which is referred to as a "spillover" (Greenbaum et al., 2019). Spillover effects can be beneficial, neutral, or detrimental to the ecological health of the recipient species, predators or symbionts that depend on the species, or ecosystem services to which the species contributes. Risk has two components: the likelihood of exposure to a hazard and the severity of adverse effects stemming from that exposure. The ecological risk from gene drive spillover depends on both. In other words, the mere presence of gene drives in nontarget species does not necessarily lead to harm. Rather, it is the effects of those events that matter. Three risk pathways leading to unanticipated gene drive movement and exposure to non-target populations are migration, hybridization, and horizontal gene transfer.

A species that is invasive or considered a pest in one geographic region may be native or desired in another region. If a GDO containing an eradication or suppression drive migrates outside the target area, it could cause beneficial populations in those areas to crash. Migration patterns and other ecological or weather-related variables are difficult to model and predict (Greenbaum et al., 2019). In addition, human travel patterns and commodity trading in a global market could lead to the movement of a GDO far beyond the expected range.

Hybridization of GDOs with sexually compatible species could also be problematic. There is precedent for transgenes from genetically engineered plants in field trials to contaminate native populations. For example, glyphosate-resistance genes originally present in contained field trials of genetically engineered bentgrass have been found in native grass populations on National Parklands and in intergeneric crosses with other grass species (Zapiola & Mallory-Smith, 2012). Likewise, population suppression drives introduced into an invasive species may be transferred to a beneficial native species in that area through sexual hybridization. If the target DNA site for the gene drive is conserved between the two species, the gene drive would be active in the native population, and if it is a suppression drive the desired population could also decline. Even if the target site for the gene drive is carefully selected to be unique to the invader, the transfer of the gene drive may lead to off-target mutations in the native species and potentially cause harm if essential genes are inactivated.

In addition to migration and hybridization, gene drives could be transferred from one species to another through horizontal gene transfer. Horizontal gene transfer can occur via symbiotic or parasitic viruses, bacteria, fungi, and insects which can act as vehicles to transfer DNA between species. However, transfer from prokaryotes to eukaryotes seems to be more common than the reverse (Keeling & Palmer, 2008). The horizontal gene transfer of the gene drive system would be a low-probability event but potentially has high consequences. These "fault tree" events are largely unpredictable in risk analysis, although better understanding of genomic regions with propensity for horizontal gene transfer may assist with prediction in the future (e.g., Clasen et al., 2018).

Another potential risk pathway is the gene drive system itself causing toxicity to nontarget organisms from contact or consumption. For humans, the likelihood of consuming or coming in contact with a gene drive is low, and the adverse effects of such small exposures are likely to be close to zero. However, for predators or prey that feed on large numbers of species with a gene drive, this could be a significant pathway.

3.3 Social, cultural, and economic risk pathways

Societal impacts associated with GDOs will vary based on the type of GDO, geographical setting, governance system, social and cultural setting, and ownership and power structures. Furthermore,

societal impacts of GDOs are intertwined with each other and the socio-ecological systems into which they are deployed (Kuzma et al., 2018). As discussed above, a population targeted by a population suppression gene drive in one geographic area could be a culturally or economically desirable species in an adjacent area. Political and social discord could then ensue over the deployment of a gene drive (Reynolds, 2021). Eradication of an important species could cause direct or indirect economic damage. Direct economic damage could result if the target species for the GDO has economic value itself (e.g., for food, fiber, timber, or fuel). Indirect economic damage may arise from broader ecological consequences. For example, if the target species plays an important role in maintaining ecosystem services or keeping human diseases under control, its decline could result in economic costs such as lost revenues from natural products or increased expenses in health care. It is important to take not only the health and ecological risks into consideration, but also the broader socio-economic impacts, in making decisions about whether to release a GDO organism. Integration of social, cultural, and economic values has been previously recommended for decision modeling of biocontrol of invasive species (Maguire 2004), and these should be considered for GDOs as well.

Non-use values of species are also important to consider in deploying GDOs. For example, if GDOs become pervasive and persist in the environment, as would be the case with population replacement or immunization to protect endangered species, people may view the natural world as tainted. Public rejection of current GMOs often relates to a lack of "naturalness" (Lull & Scheufele, 2017). Even if the species is preserved and can provide ecosystem services through the use of GDOs, current and subsequent generations may obtain less enjoyment from their natural-world surroundings knowing that they are genetically engineered (Kuzma & Rawls, 2016). On the other hand, if no other options exist for saving an endangered species, these impacts may be tolerable to the communities surrounding GDO deployment. Arguments can be made that there is an ethical obligation to deploy GDOs in cases where no alternatives exist for saving human lives or endangered species (e.g., Kuzma & Rawls, 2016).

Animal welfare is another important consideration for GDOs. In some cases, a gene drive approach may be harmful to an animal (Reynolds, 2021). Alternatively, for population control, a GDO could be superior to chemical or other eradication measures that cause greater suffering (Leitschuh et al., 2018). For example, the anticoagulant Brodifacoum has been used to eradicate invasive rodents on islands to protect endangered birds. This chemical kills the animals over a period of days and can cause great suffering to them. Gene drive options that affect rodent fertility may be a superior approach with regard to animal welfare (Leitschuh et al., 2018).

Negative public perception is sometimes seen as a societal risk to be mitigated. Scientists developing GMOs in the past have expressed the need to educate the public so they do not fear genetic engineering. These views are in line with the "deficit model" thinking of risk communication, which espouses that with more education, laypeople will be convinced of the lower risk of the technology in comparison to alternatives (e.g., Ahteensuu, 2012). Public backlash and pressure could stall or even stop GDO development and deployment, however, most of the gene drive community recognizes the failures of deficit model thinking and unidirectional risk communication (Kuzma et al., 2018). Instead, they are turning toward public engagement and bidirectional communication to allow the public to learn more about the risks and benefits of GDOs so they can make their own informed decisions about any future releases in their communities (Gusmano et al., 2021; Harmon, 2016; Kaebnick et al., 2016; National Academies of Sciences, Engineering, and Medicine (NASEM), 2016; Target Malaria, n.d.).

It will be important for the impacts of gene drives to be fairly and equitably distributed. Environmental justice includes making sure that marginalized or under-represented communities do not bear the risks of GDOs disproportionately (distributive justice) and have a voice in decision-making affecting them (procedural justice). Another issue is economic justice. For example, if GDOs are deployed in agriculture for pest control, organic farmers may suffer lost sales and revenue due to contamination by GMOs. Target genes and CRISPR-based gene drives are under consideration for controlling the fruit fly Drosophila suzukii on soft fruits such as cherries, blueberries and raspberries (Scott et al., 2018). It is currently not clear if the presence of GDO insect parts in organic berries would impact organic certification and associated product premiums (Baltzegar et al., 2018).

4.

Risk governance

GDOs raise new and magnified challenges for risk governance in comparison to the deployment of other genetic engineering technologies. Current governance systems for first-generation GEOs have been designed to limit their spread in natural ecosystems through bioconfinement strategies or limited use in managed agricultural settings (Kuzma et al., 2018). In contrast, gene drives are meant to spread through populations, leading some to call for precautionary approaches to the release of GDOs (Kaebnick et al., 2016). The goal of GDO spread also presents challenges to field monitoring and testing, requiring wide boundaries and more resources for data collection. The escape of even one GDO from a laboratory or limited field trial could in some cases (depending on gene drive design) spread a gene throughout an entire population (Min et al., 2018). How we mitigate the chance of escapees from the lab, make decisions about the first open releases, conduct risk assessments under uncertainty, manage potential risks, and include diverse experts and communities in decision-making, are considered below under the umbrella of risk governance.

4.1 Molecular confinement strategies

Methods based on molecular biology have been proposed for stopping, recalling, or reversing gene drives once GDOs are released (Vella et al., 2017). Development of these risk mitigation technologies is important given that GDOs are designed to spread and impact entire populations in ecosystems, yet their adverse impacts are difficult to assess prior to release. One strategy for reversibility after a GDO is released is to subsequently release drive-resistant individuals that carry a synthetic yet functional copy of the targeted gene without the Cas9 (or other GD nuclease) recognition sequence. These are called synthetic resistant (SR) drives (Vella et al., 2017). This approach is likely effective for eradication drives that impose significant fitness costs, but not for gene drives that have mild, neutral, or advantageous fitness costs.

A second strategy is to release a GDO with a different guide RNA to alter the recognition site of the original gene drive so that it is no longer recognized by the original nuclease. This is called a reversal drive (RD) (Esvelt et al., 2014). This strategy could be used to immunize a species in a certain geographic area against the spread of the GDO from another area (Esvelt et al., 2014). However, theoretical modeling studies have shown that SRs and RDs are not guaranteed to eliminate an unwanted gene drive from a population and could instead result in a mixture of organisms containing the unwanted gene drive, wild type, and RD or SR allele in the species (Vella et al., 2017).

Another scheme for limiting the spread of gene drives involves the use of CRISPR-based “daisy-chain drive” that contains genetic drive elements that are not linked (e.g., on different chromosomes) and are serially dependent or arranged to work in a chain (Esvelt & Gemmell, 2017; Min et al., 2017). Each element drives the next, but their ability to spread is limited due to the successive loss of the elements from the end of the chain via natural selection (Noble et al., 2019). Daisy-chain drives could theoretically drive a useful genetic element to local fixation in a population, while making the changes temporary and limited in geography. However, like SRs and RDs, modeling studies have suggested that daisy-chain drives would only work under a limited set of conditions (Dhole et al., 2018). Other split gene drive systems and “gene drive neutralizing” molecular systems strategies have been proposed with suggestions that they may require less stringent laboratory confinement conditions if employed (Bier, 2022).

Regardless, there is significant worry that molecular approaches to counteract gene drives based on gene drive technology would not only fail in the field given the ecological complexities, but also potentially lead to additional, unintended adverse effects. The public may also be uncomfortable with using a technological fix to prevent future technological failures. For example, with reversal and immunizing drives, the “wild” population would continue to carry engineered genes for Cas nucleases and guide RNA. This could perpetuate off-target mutations in the species, leading to potential ecological, health, or societal impacts (Section 3). Robust physical confinement and good risk assessment methods are still of utmost importance for preventing premature release.

4.2 Biosafety and biosecurity

Specific protocols for physical, reproductive, ecological and molecular barriers for biosafety in laboratory studies using GDOs have been proposed (Akbari et al., 2015). Ecological barriers include performing experiments outside the habitable range

of the GDO, or in areas without potential wild mates, so that in the event the GDO escapes from the laboratory, the spread would be unlikely. Reproductive strategies involve using strains in the lab that cannot reproduce with wild relatives in the surrounding area. Molecular containment methods include using strains with specific target sequences for the gene drive that do not exist in the wild population. It has been recommended that physical barriers occur at multiple levels, along with reproductive and molecular barriers. Redundant containment is important so that if one level fails, another barrier could stop an escapee from spreading the gene drive (Akbari et al., 2015; Esvelt et al., 2014).

Stepwise guidelines for testing gene drives have been proposed to allow for time for anticipating risks before full-scale release (Bier, 2022; James et al., 2018; National Academies of Sciences, Engineering, and Medicine (NASEM), 2016). Phase 1 involves laboratory development and cage trial testing. Phase 2 consists of confined outdoor tests (either in large cages in the area of proposed release or in isolated environments such as islands). In Phase 3, there is limited open-field testing in areas of release. Finally, in Phase 4, there is full release and implementation with monitoring. However, the guidelines remain unclear on the exact criteria, types of risk studies, nontarget endpoints to be assessed, or tolerable risk levels that would be used in decision models to move from lab or cage trials to the first open-release field trials (particularly from Phase 1 to 2 or Phase 2 to 3). The uncertainties associated with GDOs are immense, and more specific decision protocols are needed to help determine when the first open release does not present an unreasonable potential risk.

Attributes of social and economic systems will also influence the spread of gene drives. Human patterns of movement may carry GDOs into unwanted areas via passive transport across national borders through trade or travel (Esvelt & Gemmell, 2017; Gloria-Soria et al., 2014). Unfortunately, the unintended movement of species via humans or goods can be sporadic, causing great uncertainty in the probability of occurrence. To minimize risk from these stochastic events, it has been suggested that the first open releases of GDOs should be on isolated islands with no-to-low human traffic, good border control, and large physical distances from the shore (Webber et al., 2015). Others have recommended that self-sustaining and global gene drives should only be used on target species for which global eradication of the species would not be seen as a problem (Esvelt & Gemmell, 2017; Noble et al., 2018).

Deliberate unapproved releases of GDOs by humans could occur and may be incentivized by potential economic or personal gain. For example, even if GDO rats are intended for release only on isolated islands, there would be little to prevent a rogue actor from smuggling a few GDOs to mainland areas for disseminating cheap and effective pest control (Esvelt & Gemmell, 2017). GDOs might also be released by rogue actors for more maleficent purposes to wreak havoc on ecosystems, agriculture, socioeconomic systems and human health.

Biosecurity to prevent intentional misuse of GDOs will be difficult in the future. Currently, the technical challenges with successfully engineering a gene drive that is effective in an ecosystem provide a significant barrier to misuse. However, once working GDOs are more readily available, they could be used to harm or eradicate desirable species. Some have called for the scientific research community to prevent the disclosure of instructions for making gene drives in scientific manuscripts or patent applications, citing the historical case in which nuclear weapons technology remained classified for 70 years after the Manhattan Project (Gurwitz, 2014). Others disagree, arguing that if GDO developments were kept secret, it would prevent the progress of science not only in addressing important health and ecological problems in the future, but also in defending against the misuse of gene drives (Oye & Esvelt, 2014).

The Defense Advanced Research Projects Agency (DARPA) in the U.S. has invested significant resources in the "Safe Genes" programme, upwards of $100 million, to develop tools and methodologies to "control, counter, and even reverse the effects of genome editing — including gene drives"[3]. However, DARPA's leadership in this area could be met with the suspicion that the underlying purpose is really for future weaponization (Callaway, 2017). In parallel, a unit of the Office of the Director of U.S. National Intelligence, the Intelligence Advanced Research Projects Agency (IARPA), is working on capabilities to detect harmful GMOs and GDOs (Callaway, 2017).

[3] See www.darpa.mil/program/safe-genes.

4.3 Risk analysis

Even with strict biosafety, biosecurity and countermeasures, 100% containment or prevention of risk is not likely. Risk analysis methods, such as fault-tree analysis, can be used to estimate low-probability and potentially high-consequence adverse events associated with GDOs and seem well-suited for thinking about the risks of GDOs from laboratory or confinement breakdowns. However, our current ability to quantify such failures is severely limited by the significant uncertainties associated with GDOs in part stemming from a lack of relevant ecosystem and biological studies (Section 1).

Risk analysis is laden with assumptions and interpretations based on values. For example, the endpoints we choose to evaluate in a risk assessment are based on what we care about (e.g., certain species, certain natural resources, certain human illnesses, etc.). Also, uncertainty in risk analysis leads to various interpretations of the data to which we bring our own experiences, cultures, and worldviews. Even if we have good information, the level at which something is presumed "safe" is debatable as safety is a socially defined concept. Science gives us a guide, but what risks are acceptable are based on values, taking into consideration our experiences, culture, perceptions of the benefits, control over the situation, and trust in those managing the risks (Kuzma, 2017).

Furthermore, uncertainty due to natural-world variables stems from several dimensions discussed in Section 3. Ecological sources include, but are not limited to: (1) the low, but nonnegligible, probability of horizontal gene transfer of a population suppression drive to a desirable or beneficial species resulting in its demise; (2) the ramifications of population reductions of the target species on other species like predators; (3) the possibility that another, more harmful species could fill the ecological niche of the eradicated population; and (4) potential impacts on ecosystem services from reductions in the target population. As previously discussed, a significant challenge with GDOs, is that field trials are the best way to study such interactions and gather data. Yet, we want to do risk assessment prior to field trials as GDOs are meant to spread and field trials are likely to result in GDO spread via open release.

Not only do population, ecological, mating, and genetic characteristics matter for the impacts of gene drives, but so do biophysical attributes of weather and climate and geographic features of habitats such as barriers (Kuzma et al., 2018). Sporadic and severe weather and climate events make the prediction of risk difficult. These events will affect the spread of GDOs and their distribution for mating with other subpopulations. Even if a field trial can be confined, it is unlikely to capture the range of physical conditions under which gene drives will be deployed. These conditions will impact interactions with and potential risks to other species, such as predators and prey. There is a need for better ecosystem and population models of GDOs that account for variability in biophysical parameters across temporal and geographic scales.

GDOs have features of "emerging risks" that are "characterized mainly by uncertainty regarding their potential consequences and/or probabilities of occurrence" which "can be due to a lack of knowledge about causal or functional relationships between new risk sources and their environment or to the insufficient application of available knowledge to the case in question" (IRGC, 2015). For these situations, evaluating the "substantive validity" of risk assessments — where outcomes of the risk assessment are compared to what happens in reality — is not feasible, especially prior to any environmental release. Therefore, "procedural validity" of the risk assessment, that is how the risk assessment is conducted, becomes even more important than attempting to ascertain the substantive validity of particular risk evaluations prior to GDO release and field data collection.

Methods for making the process of risk assessment for GDOs more legitimate and robust have been suggested. These approaches make use of ideas from post-normal science (PNS) (Brossard et al., 2019; Funtowicz & Ravetz, 1994). PNS suggests that when the "decision stakes are high and the system uncertainties great, extended peer and stakeholder communities (beyond scientific researchers) should be consulted to interpret what is known and what it means for the policy decision at hand" (Funtowicz & Ravetz, 1994, as cited in Kuzma 2021). Diverse values become an explicit part of risk assessment as the "facts" are uncertain and require interpretation for their meaning (Funtowicz & Ravetz, 1994). People with "on-the-ground" knowledge, who are "interested and affected" (National Research Council [NRC]), 1996), are invited into the deliberations about risk and safety measures, along with a broader range of scholars such as ethicists and social scientists. Scientific experts and government managers still provide important technical analysis, but democratic engagement opens up the policy process for

characterizing risk to communities in areas of potential GDO deployment, giving them not only a voice but also a choice in deciding what levels of risk are acceptable to them (National Research Council [NRC], 1996). Bayesian approaches to estimating the risk, drawing on the mental models of a diverse group of experts and stakeholders, can provide important information on parameters for which little is known and thus signal areas where more research is crucial (Hayes et al., 2018). Another framework for conducting risk analysis on GDOs to increase the procedural validity in support of decision-making has been proposed. The Procedurally Robust Risk Analysis Framework draws upon principles of responsible research and innovation, such as humility, procedural validity, inclusion, anticipation, and reflexivity (Kuzma, 2019).

The following recommendations for GDOs risk assessment have recently been made by Devos et al. (2021): "(1) developing 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 modeling 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."

4.4 Risk management considerations

The use of gene drives could present a "moral hazard" in precluding other approaches to protecting ecosystems and combating disease (e.g., Lin, 2013). For example, if we know that a GDO can help to mitigate human diseases or ecological risks in the future, we could be less likely to invest in prevention or control methods today, as future generations will bear the risk. Without comprehensive cost-benefit analyses of GDOs deployment that account for a range of health and environmental externalities into the future (Kuzma & Rawls, 2016), we might naively forgo investing in safer, better known, and more effective control methods for disease prevention like bed nets or vaccine development (Kuzma & Rawls, 2016). In the context of GDOs designed to conserve species, the moral hazard may come from undermining efforts to conserve biodiversity through non-technological approaches like habitat protection, reducing greenhouse gases, or ecosystem services protections (Reynolds, 2021).

Gene drive governance has parallels to the governance of other common pool resources (Brown, 2017; Kuzma et al., 2018; Ostrom, 2011). They also share features with public goods, in that their impacts, both positive and negative, are likely to be nonexcludable. Parties without direct control over deployment are likely to experience benefits or harm from GDOs as they spread across landscapes. Likewise, because the deployers of gene drives might not bear all the adverse impacts, they might make riskier decisions than would be socially desirable to release a gene drive (Mitchell et al., 2018). Given the shared features of GDOs with common pool resources and public goods, behavioral and value systems of communities will be important for managing risk through shared governance and collective action (Kofler et al., 2018; Ostrom, 2009).

Gene drive release will require ongoing cooperation between different sectors and geographic regions to plan for, execute, and monitor gene drive releases and their impacts. Shared goals are important for collective-action settings, and in limited geographic areas, goals are more likely shared. As self-sustaining gene drives are designed for greater geographic areas and even for crossing national borders, the potential for shared values and norms is lower (Kuzma et al., 2018). Risk management and governance for gene drives will be a greater challenge across national or cultural boundaries, than for local, self-limited gene drives unlikely to travel outside of a defined area within a nation.

Policies and regulations may limit the types of impacts considered in risk management and governance. In current U.S. regulatory decision-making about GEOs, direct harms, such as toxicity to humans or nontarget organisms, are a primary (and often sole) focus of decision-making (Meghani & Kuzma, 2018; Thompson, 2007). For certain GDOs, the types of risks considered in regulatory decision-making may be further limited depending on the assigned federal agency, the rule evoked, and the GDO species (e.g., Kuzma, 2019; Meghani & Kuzma, 2018). However, non-governmental actors, such as the non-profits and academics developing gene drives, are broadening the scope of governance

questions beyond formal regulatory authority (e.g., James et al., 2018; Target Malaria, n.d.).

At the organizational level, capacities among regulators, risk managers, and technology developers to assess and manage risks associated with GDOs need to be bolstered. As discussed, gene drives present the features of emerging risks (IRGC, 2015). IRGC guidelines for emerging risks (2015) suggest that governance institutions should implement four distinct key capabilities: "(1) Enhancing proactive thinking to identify future threats and opportunities; (2) Evaluating the organisation's willingness to bear or to avoid risk (risk appetite) for the definition of future strategies; (3) Prioritising investments in certain key emerging issues according to their potential impact; and (4) Fostering internal communication and building a forward-looking culture to benefit the whole organisation".

4.5 Global governance

There are currently no approved field releases of GDOs, and several national and international bodies have been developing reports and guidelines to make recommendations about their governance in order to prepare for proposals for release. The most relevant international agreement to govern GDOs is likely to be the Convention on Biological Diversity (CBD) and its Cartagena Protocol on Biosafety (Biosafety Protocol, BSP) (Reynolds, 2021). The CBD BSP governs the transboundary movement of living modified organisms (LMOs) as well as providing risk assessment guidance for LMOs and their movement. Also under the CBD is the Nagoya - Kuala Lumpur Supplementary Protocol on Liability and Redress, which requires signatories to create mechanisms for responses and civil liability in the case of significant damage to biological diversity that resulted from the transboundary movement of LMOs.

Since 2018, the CBD has been dealing with risk assessment and other issues surrounding GDOs. The CBD's Ad Hoc Technical Expert Group (AHTEG) on Synthetic Biology has been tasked with undertaking "a review of the current state of knowledge by analyzing information, including but not limited to peer-reviewed published literature, on the potential positive and negative environmental impacts, taking into account human health, cultural and socioeconomic impacts, especially with regard to the value of biodiversity to indigenous peoples and local communities, of current and near-future applications of synthetic biology, including those applications that involve organisms containing engineered gene drives" (Convention on Biological Diversity [CBD], 2018). In the interim, the Conference of the Parties to the CBD calls on governments to apply a precautionary approach to introducing GDOs and to obtain the prior informed consent of indigenous and local communities where appropriate (Convention on Biological Diversity [CBD], 2018). Although GDOs will likely come under the UN CBD-BSP framework for LMOs, this framework is not focused on GDOs; not all countries are party to the CBD-BSP (including major actors in GDOs such as the U.S.); and it mainly provides for advance notice of GMO importation and risk assessment guidance.

Safe, sustainable and equitable deployment of GDOs will require governance across national borders (international) to respect diverse values (especially those of indigenous and marginalized groups), world views, and perspectives on species, ecosystems, and technology. Political conflicts between groups or nations might ensue from GDO deployment. For example, pigs were brought to Hawaii by the Polynesians, and later the Europeans when settling the Hawaiian Islands. The pigs soon established themselves in the wild. In doing so, they disrupted native ecosystems and allowed for other invasive species to move into the area, which ultimately impacted the health of native birds and forests (Maguire, 2004). The eradication of wild pigs in Hawaii using population suppression by conventional techniques (traps, shooting, etc.) is seen as desirable from an ecosystem damage perspective, but Native Hawaiian communities, relying on the feral pigs for cultural events and food, value the pigs for cultural preservation (Maguire, 2004). Wild pig eradication remains a contentious issue. GDOs may face similar situations where cultural and ecological values conflict.

Identifying possible risks through global governance is important, but ethical principles also need to be integrated into processes for determining whether a field trial or release should take place. Many believe that scientists have a social responsibility for informing and engaging publics that will be affected by a gene drive (e.g., Thompson, 2007). However, recommendations have been made that engagement should not be hosted by those who have a conflict of interest in seeing the technology progress, but rather should be led by local communities in areas that are candidates for deployment, while supported by global governance structures to provide the resources and expertise for deliberative engagement

(Kofler et al., 2018). To date, such global governance systems for supporting engagement, conducting procedurally robust risk analysis, and comparing gene drives to other technological and non-technological alternatives are lacking.

5.

Lessons for other emerging technologies

Given that GDOs present a leap in our capabilities to engineer wild populations and come with great uncertainties about their potential impacts, it seems crucial that we provide as much attention and resources to the development of robust and deliberative mechanisms for risk analysis and governance as we do to the development of gene drive technologies. In the face of high uncertainty and ambiguity, stakeholder and public communities should be consulted to identify risk endpoints of concern (which may differ based on geography or culture), define concepts of "safety", and determine acceptable levels of uncertainty or risk-benefit distributions. Equal funding for risk studies and assessment methods (compared to the funding for gene drive development and efficacy studies) also seems warranted, as well as efforts to conduct ecological studies in field cages in the area of release (confined, mesoscale field trials). Stakeholders and publics should also be involved in developing and examining future risk-based scenarios for GDO deployment to inform risk assessments and governance options.

Further guidance is needed for risk assessment of GDOs, along with specific risk-based decision criteria for moving from confined laboratory or caged field trials to open releases. Regardless, the staged model for GDOs release proposed by their developers may provide a good example for risk governance of other emerging technologies. Technology communities for artificial intelligence, nanomaterials, and alternative energy might find the staged release guidelines useful for developing their own approaches for stepwise, responsible technological deployment. Another positive lesson from the GDOs case study is the value of a concomitant investment in technology to reverse or limit gene drives should the need arise based on risk-based monitoring (e.g., the DARPA "Safe Genes" programme). Other technological areas should consider this model for ensuring the reversibility of their technologies should adverse impacts arise.

Although global mechanisms for governance are currently not sufficient for GDOs, there are efforts to address GDOs at international levels, for example, through the UN CBD and BSP, as described above. Other emerging technological areas that are even less far along with international governance could learn from these emerging experiences with GDOs. The UN CBD also provides a mechanism for liability and redress under the Nagoya Protocol for LMOs, which likely applies to GDOs and can provide an example for the governance of other emerging technologies.

Currently, there is disagreement among gene drive developers and stakeholders about whether to impose a moratorium on gene drive releases. Some suggest a moratorium on any GDO release, while others propose a moratorium only on global or self-sustaining gene drives (but not self-limited gene drives). Other developers are more cavalier about open release of gene drives, maintaining faith in the low probability of harm, as well as in reversal drives or other molecular confinement strategies to mitigate risk. There is even more disagreement among global conservation groups, NGOs and civil society actors. GDOs bring to surface the many diverse values associated with ecological protection and restoration, human health protection, technological optimism versus pessimism, and the inherent or non-use value of ecosystems and species. Most agree, however, that gene drives illustrate the need for precautionary approaches, postnormal science, and responsible innovation paradigms, given their ability to widely and permanently alter ecosystems (much like geoengineering).

Acknowledgements

IRGC would like to thank Kenneth Oye for offering comments on a first draft of this paper. The views presented in this article are those of the author and are not a consensus judgement by IRGC.

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