**Public Deliberation about Gene Editing in the Wild: Cases**

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**Quick Reference Sheet**

**Genome editing** refers to a suite of technologies that allow scientists to alter an organism’s DNA by adding, removing, or altering genetic material at specific points. Although gene editing has been possible for over 40 years, new technologies, such as zinc finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs), have made accurate gene editing more feasible. CRISPR is the newest and, many believe, the most promising gene editing technology.

**CRISPR** stands for Clustered Regularly-Interspaced Short Palindromic Repeats. CRISPR is a combination of an RNA strand and a cleaving protein, such as Cas9 (CRISPR associated protein 9 derived from bacteria. Biologists have turned it into a tool that that can make precise genetic changes in a variety of cells. When introduced into a cell, the RNA strand attaches to a matching section of the organism’s DNA. The enzyme cuts the double helix at that location, and the cell’s DNA repair mechanisms close the break. Depending on the repair mechanism used, the gene may be inactivated or a new segment of DNA may be inserted. For molecular biologists, CRISPR is an easy, cheap, and comparatively precise way of inserting, deleting, or replacing genetic material. This is vital for gene drives, but the majority of current research applications use CRISPR outside of a gene drive context.

**Gene drive** causes a genetic alternation to an individual organism to spread through a population. In typical sexual reproduction, offspring have, on average, a 50% chance of inheriting a gene from one of their parents. Without selection pressures operating on that gene, its prevalence in a population will neither increase nor decrease. In contrast, gene drives are systems of biased inheritance that raise the rate of inheritance and thereby increase the spread of a gene in the population above chance. Various factors determine whether genetic modification of a population through gene drive can be effective.

**Daisy drives** are proposed gene drives whose spread through a population is designed to be self-limiting. They address concerns about the uncontrollability of gene drives by limiting the number of generations that carry the trait, which increases the likelihood that a release of GM organisms stays local.

**RIDL** stands for Release of Insects carrying Dominant-Lethals. It is a population control strategy for insect pests. In the RIDL approach, the progeny of a gene edited parent contain a genetic modification that kills them before reaching reproductive maturity. Because RIDL can have a significant impact on the target population but is not self-perpetuating, it can, in theory, be used to reduce populations without eliminating them or causing permanent genetic changes in them.

**The Coordinated Framework for the Regulation of Biotechnology** is the most likely regulatory structure for gene drive regulation in the United States. The CFRB is a collaboration among federal agencies that assigns the primary oversight responsibilities for biotechnologies to the EPA (pesticides), the FDA (animal drugs), and the USDA (plant pests). To assess potential impacts of biotechnology, the agencies under the Coordinated framework must abide by the National Environmental Policy Act (NEPA).

**NEPA**, the National Environmental Policy Act, is the overarching structure for environmental regulation in the United States. Under NEPA, the two established processes for assessing the impact of a proposed intervention are an environmental assessment (EA) and an environmental impact statement (EIS). An EA is a determination of whether a federal government decision to allow the introduction (field test of environmental release) of a specific biotechnology or related product has the potential to cause significant environmental effects. An EA is a detailed accounting of data sources, life history characteristics, and ecological information. It generally includes a wide range of scientific evidence. Although EAs contain a qualitative description of uncertainty in these datasets, they are not required to have quantitative probability estimates of potential effects or include a quantitative uncertainty analysis.

The NEPA process is triggered when a federally licensed action is proposed or a federal agency proposes an action. NEPA requires that federal agencies determine whether an environmental analysis is needed for a proposed action and assess the impacts of those actions that have the potential to harm the environment. Three levels of analysis are required: (1) An initial environmental evaluation is always performed. This can result in a categorical exclusion (CatEx), which means that a proposed action does not have a significant effect on the environment. If it is unclear if the environmental impacts are likely to be significant, then (2) an environmental assessment is performed, which includes public involvement. If there is a Finding of No Significant Impact (FONSI), the proposed action may be approved. But (3) if a proposed federal action has the potential to cause significant environmental effects, then an EIS is mandated, which involves a much more rigorous evaluation with multiple sites for public involvement and comment.

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**Blight-Resistant American Chestnut**

***The proposed release:*** The planting in eastern US forests of American chestnuts whose genomes contain two genes, derived from wheat, that impart tolerance to chestnut blight, a fungal disease that was accidentally imported to the United States in the early twentieth century and has rendered the tree functionally extinct. The long-term vision is that hundreds of thousands of trees would be planted and would spread on their own, returning the American chestnut to the place it occupied in eastern U.S. and Canadian forests prior to the near-eradication caused by the blight.

***Rationale:*** The American chestnut was once one of the most common trees in the eastern United States. It was considered an icon of eastern deciduous forests and is valued intrinsically, for its role in the environment (especially because of its nut production, which provided food for many animals), and for its aesthetic and economic contributions to human welfare. It grows well on disturbed soil, making it ideal for amending damaged land (such as former strip-mining locations), and, as a very fast-growing large tree, it would improve the ability of eastern forests to store carbon.

***Work to date:*** Modified trees were produced using an agrobacterium to alter cells that were grown into seedlings. The modification consists in the addition of genes that cause the tree to produce an enzyme (oxalate oxidase) which breaks down an acid (oxalate acid) that the fungus produces and that would otherwise kill the tree. The modification is heritable, and genetically diverse blight-tolerant trees can be produced by breeding the trees with wild-type trees. Several strains of the modified tree have been developed and planted in test plots, showing varying levels of blight tolerance.

The State University of New York College of Environmental Science and Forestry, where the research to develop the genetically modified chestnut was carried out, has applied to the United States Department of Agriculture for deregulation of the tree. In 2021, USDA announced that it will prepare an Environmental Impact Statement for the tree, and it sought public comment.

***Possible undesirable outcomes***: Questions should be asked about the effects on other organisms in the environment (other kinds of fungi and tadpoles, for example) and on human consumers of the nuts. Testing to date shows that the effects of the modified trees would not differ from those of unmodified trees.

***Alternative responses to the problem***:

* Accept the disappearance of the American chestnut. Other tree species now grow in the American chestnut’s stead, although they do not have the same characteristics.
* Cross-breed the American chestnut with the blight-resistant Asian chestnut. However, the product would probably have less blight tolerance than trees produced through genome editing and would likely retain other characteristics of the Asian chestnut.
* Develop a less damaging strain of the blight that could be released into the wild and would outcompete the extant strain.

***Relevant existing regulatory and policy mechanisms for public input:***

* FDA, to assess nutritional quality; submission to FDA is technically voluntary.
* EPA, under the Federal Insecticide, Fungicide, and Rodenticide Act, to assess effect of a potential “pesticide”—that is, changes to tree to combat the blight. However, the modified tree withstands rather than kills the blight, and the biological mechanism employed by the tree is already widespread in the environment.
* USDA’s Animal and Plant Health Inspection Service, to assess safety for agriculture and the environment of a potential plant pest. The assessment of the American chestnut was triggered by the use of agrobacterium. Assessment includes an environmental impact statement (required under NEPA), which includes open comment periods for the public. Notifications may also be given to indigenous groups.
* Within the Department of the Interior, the Forest Service, National Park Service, and Fish and Wildlife Service: consulting but no direct regulatory roles.
* Canadian agencies will also be consulted.

***Public reaction:*** There does not appear to be a broad, strong response against the proposed release. The research is publicly supported by The American Chestnut Foundation. A 2019 report from the National Academies of Sciences, Engineering, and Medicine on forest management and biotechnology notes, “Needham et al. (2016) found that U.S. residents considered native tree breeding and other conventional forms of forest management to be most acceptable for addressing chestnut blight in American chestnut trees (68–88 percent), but a majority also supported using various types of biotechnologies for mitigating this issue (53–64 percent)” (p. 99). Among the biotechnological approaches, “changing genes in American chestnut trees (57–58 percent of U.S. residents supported this approach in general), such as adding genes from bread wheat (to produce oxalate oxidase, or OxO; 54–55 percent supported this approach in particular), was more acceptable for addressing chestnut blight than breeding with nonnative Asian chestnut species (43–46 percent supported).”

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**Daisy Drive to Control Invasive Vertebrates in New Zealand**

***The proposed release*:** Use a “daisy drive” system, which is a type of gene drive, to eliminate several invasive, non-native animal species such as rats, stoats, and possums that are decimating the country’s native flora and fauna. The government estimates that 4000 native species of fauna are at risk, with nearly a quarter in danger of extinction. The nation’s national bird, the flightless Kiwi, is said to be killed by invasive species at a rate of 20 a week.

***Rationale*:** Thegoal of the release would be preservation and restoration of Aotearoa New Zealand’s native species and ecosystems without a lower risk of collateral damage to species and ecosystems elsewhere. Because the default form of CRISPR-based gene drive system is self-propagating and predicted to be invasive, there is a risk that, intentionally or unintentionally, the genetically edited species could spread beyond the target geographical location and lastingly edit the genetics of the target species. Depending on its function, that may or may not negatively affect the ecosystem of the new location(s) it enters. Alternatively, an organism altered using a daisy drive system can be limited to the local environment in which it is released. A daisy drive system is self-exhausting because genetic elements are sequentially lost until the drive system stops spreading. The central goal of a daisy drive system is to contain the spread of species-specific genetic changes within a circumscribed area, in contrast to a gene drive system that will be invasive and is likely to spread well beyond the target geographic area.

***Work to date*:** With funding from the NIH and formerly from the “Safe Genes” program of the U.S. Defense Advanced Research Projects Agency (DARPA), genetic scientist Kevin Esvelt is leading a team at MIT to develop daisy drive platforms. The initial work is with nematodes and mice. Safe Genes is also funding a group at the Pirbright Institute to develop daisy drive in two key mosquito species that affect human and animal health. The lab’s preprints describing various methods of achieving daisy drives, namely daisy-chain, daisyfield, and daisy quorum, are currently available on *bioRxiv.*

***Possible undesirable outcomes*:** According to Esvelt, “The major risk is that a rare event will move DNA encoding a drive component from one element to another, thereby creating a 'daisy necklace' capable of global drive.” This possibility belies the underlying rationale for using daisy drives instead of a normal gene drive system, because the drive could spread beyond the target geographic area and perhaps become invasive. Furthermore, like any of the proposed methods for genetic modification, a daisy drive system might be used for biodefense or bioterror purposes. Esvelt has published a white paper describing how all forms of gene drive inherently favor defense because they are slow, obvious, and easily blocked.

***Alternative responses to the problem*:** Even if a daisy drive system is shown to be safe and effective, it’s possible there will still be opposition to genetically altering a species to make it locally extinct. Some critics of gene drives, as well as some who object to predator extermination as a means to protect biodiversity, might argue that non-genetic means of controlling invasive species (for these species, such means would primarily be hunting, poisoning, and trapping) should be used instead of any type of gene drive system or genetic modification. There is strong local political opposition to the primary method of rodent control, which involves aerial delivery of the rodenticide 1080, particularly by Māori, who view the use of poisons as contrary to their cultural values and responsibilities to the environment. Others view the poisonings of non-target animals by rodenticides, including those values by humans, as unacceptable.

***Relevant existing regulatory and policy mechanisms for public input*:** The regulatory framework is fragmented, with several legislative provisions addressing the use of genetically modified organisms (GMOs). If GMOs meet the definition of an “organism” and a “new organism,” gene drives will be regulated by New Zealand’s Hazardous Substances and New Organisms Act (HSNO Act). A “new organism” cannot be imported, developed, field-tested, or released without prior approval from the Environmental Protection Authority, which makes the formal determination if there is uncertainty about whether an entity is a genetically modified “organism” or “new organism.” Other legislative documents are the New Organisms and Other Matters Bill (2003) and the Hazardous Substances and New Organisms Act (1996). As a result of the broad definitions under these acts and the New Zealand High Court’s ruling in 2014 that a GMO comes fully within the HSNO and its implementing regulations, legislation was passed (New Organisms and Other Matters Amendment Act of 2015) to exempt organisms developed via standard mutagenesis (which does not involve gene editing) from regulatory requirements.

In another case, an environmental court ruled that under the Resource Management Act 1991 regional councils have the authority to control the use of genetically modified organisms through their regional policy statements and district plans. For pest control using gene editing technologies, there may be additional regulatory requirements pursuant to the Animal Welfare Act of 1999 and the Animal Welfare Amendment Act (No. 2) of 2015; the Agricultural Compounds and Veterinary Medicines Act 1997; the Biosecurity Act 1993; and the Conservation Act 1987.

The Environmental Protection Authority has a Public Consultations section on its web site that instructs the public on how it can comment on various proposed activities. There is no information on the web site about how the Authority uses the public comments regarding a proposed activity. In its 2017 report, “The use of gene editing to create gene drives for pest control in New Zealand,” the Royal Society Te Aparangi Gene Editing Panel noted that it was seeking to obtain Māori perspectives and broader cultural contexts regarding the genetic modification of organisms.

***Public reaction*:** In 2017, Esvelt co-authored a manuscript pointing out that self-propagating gene drives would be invasive and spread to other countries if used for invasive species control. Because his coauthor, Neil Gemmell of the University of Otago, was a New Zealander, they used Aotearoa New Zealand as an example. Esvelt failed to invite his Māori partners to offer suggestions on the manuscript during the revision stage. Along with nearly concurrent email revelations about other groups working on gene drive, including private discussions that those groups had had with New Zealand government officials, the manuscript sparked political turmoil in the New Zealand environmentalist community.

Esvelt’s failure to consult his Māori partners before publishing the manuscript was publicly strongly criticized by one of them. Melanie Mark-Shadbolt, now Chief Māori Advisor at the Ministry for the Environment, said “his naivety of the political situation Māori are in, and the publication of this paper without talking to the other partner (Māori) more than likely will have consequences for that partner (Māori) that the author (Esvelt) did not consider.”

In a public apology posted the same day, Esvelt agreed completely, noting, “This is precisely why Māori co-governance of daisy drive development is necessary if the method is ever to be used in Aotearoa: I know as little of the local ecosystem as I do of the local politics, meaning that I cannot possibly evaluate the likely consequences.”

He has since discussed the idea – opening with his failure – with Māori iwis and the New Zealand EPA on two separate visits, always opening with the story of his mistake as a cautionary tale for why local knowledge must guide research.

To date, his decision to focus outreach primarily on Māori rather than pakeha has not been controversial. Many New Zealand scientists who favored the use of invasive gene drive were angered by the perceived implication that they might have used an unsafe technology, while others remain skeptical that it would become invasive elsewhere.

Dearden et al. reported in 2017 that some Māori scientists support the use of genetic modification for the purpose of promoting health, but that Māori and other communities have raised concerns about the lack of meaningful public involvement in discussions about the use of genetic modification technologies in general and in decision-making processes.

Public survey results reported in late 2017 revealed that with respect to pest control technologies that included the use of gene drives, 32% said they were comfortable, 18% said it should never be used, and the remaining 50% said they were undecided or wanted some controls on the technology.

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**Coral Tolerant of Warm Water**

***The proposed release:*** Release of coral genetically modified for increased resilience to environmental threats, and especially to warmer ocean waters. The release could involve both seeding new coral colonies and reinforcing existing colonies and could potentially, but not necessarily, involve gene drives. Research into genetic modification of coral and its symbionts is still in its nascent stages, however, and no release of genetically modified or gene drive**–**modified coral has been formally proposed. Due to coral’s slow reproduction rate and the multiple genes implicated in coral’s temperature resilience, release into the wild is years, and potentially decades, away, assuming it is feasible at all. Alternatively, coral’s algal symbiont, zooxanthella, which is also implicated in the coral bleaching process, has been proposed as a target for genetic modification. Modification of zooxanthella presents greater initial technical obstacles, but the field release would probably be easier to scale up.

***Rationale:*** Coral reefs are considered a global marine treasure. The Great Barrier Reef, off the coast of Queensland, Australia, for example, is the largest single structure made by living organisms, a World Heritage Site, and one of the seven natural wonders of the world. However, increasing ocean temperatures are causing widespread coral death, known as bleaching, which has affected up to 50% of the world’s coral reefs (NASEM, 2018). Gene editing coral and its algal symbiont to be more resilient in the face of pollution, temperature rise, and other current and predicted trends is seen as part of a suite of strategies to preserve coral reefs, and, with them, large amounts of marine biodiversity that thrive in the environment.

***Work to date:*** A proof-of-concept study has been published showing the feasibility of gene editing coral using CRISPR/Cas9 (Cleves et al., 2018). Much more work is still needed to, for example, determine which genes are most relevant to resilience (NASEM, 2018). In algal symbionts, cellular features (for example, a thick cell wall and atypical chromosomal structure) have stymied attempts at genetic transformation.

***Possible undesirable outcomes:*** As this work is still nascent, possible undesirable outcomes have received little attention. Some frequent concerns about gene editing raised elsewhere apply to corals as well. These include spreading undesirable traits among natural populations, inadvertently impacting other beneficial traits of coral, and a developed drive resistance. It is worth noting, however, that it was recently discovered that coral reproduce within a surprisingly local area, generally of a few hundred kilometers. Thus, at first blush, it seems unlikely that a wild release in one coral reef site would rapidly have consequences for another some distance away.

Outside of the immediate impact of gene editing, it is possible that overconcentration of conservation efforts and funding on genetic solutions could hamper more traditional yet more promising conservation work, which would ultimately be detrimental to ocean and coral health generally.

***Alternative responses to the problem:*** The National Academies has organized a consensus study on interventions to increase the persistence and resilience of coral reefs, from which an interim report was released this November. They have proposed a suite of proposed interventions, among which genetic manipulation is only one. Other reproductive interventions include managed selection, managed breeding, gamete and larval capture and seeding, and coral cryopreservation. Physiological interventions include algal symbiont manipulation, microbiome manipulation, antibiotics, phage therapy, antioxidants, and nutritional supplementation. Coral population and community interventions include managing coral predators, competitors, and facilitators, and managed relocation. Environmental interventions include shading of coral reefs, mixing of cool water, abiotic ocean acidification interventions, and propagation of seagrasses meadows and macroalgal beds.

***Relevant existing regulatory and policy mechanisms for public input:*** Some reefs are within national waters; each country likely has environmental or reef-specific agencies that govern interaction and which would likely be part of any interventional process. The UN Convention on Biological Diversity would likely be relevant for coral reefs in international waters, including deep-water coral, which represents a majority of the earth’s coral.

***Public reaction:*** To date, there has been no clear reaction from the public and other stakeholders to the possibility of genetically modified coral. A 2021 study found moderate to high Great Barrier Reef. However, the clearest use of CRISPR at this time is lab work in basic coral biology to determine genes related to environmental resilience.

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**Glowing Thale Cress**

***The release:*** The glowing plant project was started in 2013 by a Kickstarter campaign that raised $484,013 to create bioluminescent plants. Kickstarter is a public-benefit corporation that maintains a global crowdfunding platform. The plan was to use gene-writing software and lab-made DNA to insert synthetic bioluminescence genes (identified in fireflies) into a thale cress (*Arabidopsis thaliana),* causing it to emit a faint green-blue light. The online campaign promised to send a glowing plant to anyone who donated $40. The founders hoped that, with additional funding, they could also produce a glowing rose.

***Rationale:*** The glowing plant project was designed as a demonstration of “do it yourself” (DIY) synthetic biology. According to the co-founder of the project, Antony Evans, the goal was to inspire more people to use this technology. They focused on an effort to make *A.* *thaliana* glow because they thought it would be a project that could be achieved in a garage lab. In addition, as discussed below, the glowing plant could be produced without triggering a Department of Agriculture regulatory review.

***Work to date:*** To create the glowing plant, the team needed to insert six genes found in bioluminescent bacteria into the *A.* *thaliana* genome. The team was unable to insert all of the necessary genes at the same time, however, and the glow is fainter than had been hoped. As a result, they were unable to ship the promised plants to supporters and, in April 2017, they announced that the Glowing Plant Project had run out of money.

***Possible undesirable outcomes***: The main concern raised by opponents was uncertainty. The environmental group ETC argued that releasing genetically modified seeds could have unintended consequences if the genes that make the plants glow were passed from one generation of the plan to the next. In response, the leaders of the Glowing Plant Project indicated that they would engineer a variant of *A.* *thaliana* that would survive only if fed a nutritional supplement. This, they argued, would reduce the chance that the plant could spread. They also promised to conduct a public dialogue on the project’s ethical, legal, and environmental issues before shipping any seeds. Beyond the concerns about the impact of the glowing plant, opponents were concerned that allowing the unregulated release of modified plants into the environment would set a dangerous precedent. For example, Todd Kuiken, from the Woodrow Wilson International Center for Scholars, argued that the Glowing Plant Project did not seem risky, but that its regulatory precedent could be problematic if applied to riskier projects in the future.

***Relevant existing regulatory and policy mechanisms for public input:*** Animal and Plant Health Inspection Service (APHIS) at the US Department of Agriculture regulates genetically modified plants if plant pathogens are involved. To get around this regulation, the Glowing Plant team planned to use Agrobacterium only during preparatory work. When plants were produced for distribution, the team would shuttle the genes into cells using a ballistics-powered device called a gene gun. According to the Department of Agriculture, the use of this process took the Glowing Plant project outside the regulatory scope of APHIS.

***Public reaction:*** The reaction to the Kickstarter campaign generated contributions from about 8000 people, along with significant media attention. The project generated a significant negative response from the environmental community.

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**Gene Drive to Reduce Populations of Non-native Island Mice**

***The proposed release:*** Release of gene drive-modified mice (the common house mouse, *Mus musculus*) on a small island in the Pacific Ocean to force a reduction in the population of house mice that have been introduced to the island through human activities and are threatening native populations of seabirds or other animals. (For the purposes of this case, the island is presumed to be U.S. territory.) The drive would work by creating an imbalance in the sex ratio. The likeliest mechanism, as reported by the 2016 report on gene drives from the National Academies of Sciences, Engineering, and Medicine, “takes advantage of an endogenous region of high meiotic drive (meaning it is more likely to be inherited) in the mouse genome found on chromosome 17 (an autosome) called the t-complex. In this scenario, male mice are genetically engineered to possess the Sry gene, which promotes male characteristics…, on chromosome 17 instead of its usual location on the Y chromosome. An XY Sry male is fertile, and upon mating to a wild-type XX female, both the XY and XX offspring… possess Sry and physically develop into male mice, with XX male mice being sterile” (p. 55). Fewer female mice means fewer pups. The expectation is that the drive would tend eventually to disappear, due to natural and perhaps sexual selection, requiring large or multiple releases of the GD-modified mice.

***Rationale:*** The benefit is that of halting human-caused species extinction. For most island species, that benefit may just be the intrinsic value of the species or of the ecosystem, place, and history of which it is thought to be an integral part. Economic and even aesthetic value will probably be minimal. Species extinction is particularly common on islands—nearly half of all species considered threatened with extinction live on islands, and most extinctions of mammals, reptiles, and birds occur on islands—and the house mouse, through predation and environmental effects, is a major factor in these extinctions.

***Work to date:*** Research into the release is under way through the Genetic Biocontrol of Invasive Rodents (GBIRd) program, a partnership of nonprofit organizations and research universities. GBIRd describes a decision to proceed with release as at least a decade away, and it declares that the decision forefronts values and requires “engagement with stakeholders and communities.”

***Possible undesirable outcomes***: The primary concern is that the genetic modification might jump the natural boundary provided by the ocean, surmount the challenges of natural and sexual selection, and lead to population crashes of the house mouse elsewhere in the world. An additional concern is that a large release might temporarily lead to an uptick in the island’s house mouse population, causing environmental harm, and/or that the ecosystem would have become dependent on the house mouse, so that an eventual crash would be harmful. A more remote concern is that the genetic modification might jump to another species.

***Alternative responses to the problem***: Rodents have been eradicated from hundreds of islands through the use of traps and rodenticides. These methods can be labor-intensive, can cause some environmental harms, can harm other animals (and humans), and raise concerns about animal welfare, as the methods are painful (death is through massive internal hemorrhaging).

***Relevant existing regulatory and policy mechanisms for public input:*** Mice that have been modified so as to cause a population crash over a series of generations might be subject to three U.S. federal regulatory structures, or may not be subject to any of them:

* the FDA, which regulates “new animal drugs,” which refers to “an article (other than food) intended to affect the structure of function of the body of … animals”)
* the EPA, under the Federal Insecticide, Fungicide, and Rodenticide Act, which regulates “pesticides” (that is, chemicals that defend against pests or microbes that have been modified to defend against pests)
* the USDA’s Animal and Plant Health Inspection Service, which regulates “plant pests”

***Public reaction:*** Some environmental NGOs have called for a moratorium on all use of gene drives, but a moratorium was rejected on November 29, 2018, by the signatories to the Convention on Biological Diversity. The nonprofits Island Conservation (U.S) and Landcare Research (New Zealand) support the research. The goal of environmental conservation and the fact that the work would avoid some of the problems of alternative methods might be attractive. Also, the fact that the Sry modification would be cisgenic rather than transgenic (that is, a modification of the species’ own genome rather than an insertion of genetic material from another species) may mean that the alteration will be more acceptable to the public.

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**Phytoplankton or Other Plants Modified to Pull CO2 from the Atmosphere**

***The proposed release:*** The proposal involves using gene editing technology, such as CRISPR/Cas9, to alter plants so that they take up carbon dioxide from the air more efficiently. The hope is that this would lead to a self-replicating system: changes would propagate through living organisms to improve carbon dioxide uptake. For example, some scientists have suggested modifying the genes of phytoplankton to enable them to sequester carbon in areas of the global ocean that lack the nutrients needed for photosynthesis. In 2017, the U.S. Global Change Research Program, which coordinates federal funding for climate change research, released a report in which it endorsed the use of federal funds to support research designed to explore these technologies.

***Rationale:*** If genetically modified plants could pull additional carbon dioxide from the air and store it long term, they would contribute to efforts to address climate change.

***Work to date:*** Scientists at the Max Plank Institute have developed a molecular transformation chain that is 25 percent more efficient than the enzyme chain used in photosynthesis. In theory, a genetically modified plant using this pathway could metabolize carbon dioxide two or three times as fast as it otherwise would, but this has not yet been attempted. Through photosynthesis, plants already pull in more than 860 gigatons of carbon dioxide each year from the atmosphere, storing it in their leaves, shoots, and roots. Unfortunately, much of the carbon dioxide is re-released back into the atmosphere when the plants, including annual crops such as rice, wheat, and maize, are harvested or degraded by bacteria, fungi, or animals. Joanne Chory of the Salk Institute for Biological Sciences is attempting to engineer legumes that produce extra-deep roots with lots of suberin, a waxy, water-repellent, carbon-rich compound, for long-term carbon storage. She is employing cross-breeding rather than a gene editing tool like CRISPR, to avoid political opposition, but gene editing could prove more effective.

***Possible undesirable outcomes***: The concern is that the release of plants engineered to be more efficient at photosynthesis would lead to unintended and unpredictable consequences that may negatively impact ecosystems and communities. Because these plants would be more efficient at metabolizing carbon dioxide, they would likely displace non-modified plants and crops.

***Alternative responses to the problem***: One alternative to genetically modifying plants to address climate change is to reduce carbon emissions. A second strategy is to capture carbon dioxide from industrial emissions and either convert it into something useful or store it deep underground. For example, direct air capture sucks carbon dioxide out of the air by using fans to move air over substances that bind to carbon dioxide. When the substances are exposed to heat and chemical reactions, they release the CO2, which can be compressed and stored underground. Most studies suggest that none of these strategies on their own are sufficient to address climate change and that a portfolio of strategies are needed.

***Relevant existing regulatory and policy mechanisms for public input:*** The U.S. “Coordinated Framework” assigns different roles and responsibilities to different agencies to regulate genetically modified plants. The Department of Agriculture evaluates whether a plant is safe to grow, the Food and Drug Administrations evaluates whether the food derived from GM plants are safe to eat, and the Environmental Protection Agency evaluates certain GM plants that are resistant to pests for environmental safety. Outside the United States, more than 75 countries certify genetically modified products for cultivation, importation, and/or field trials and testing.

***Public reaction:*** Generally, there is a strong negative reaction to genetically modified plants, particularly genetically modified foods. To date, however, there has been no clear reaction from the public about the possibility of creating a genetically engineered super plant designed to pull and store more carbon dioxide.

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**Oxitec Mosquito**

***The proposed release:*** Release of genetically modified (GM) male *Aedes aegypti* mosquitoes in Harris County, Texas, and the Florida Keys. Oxitec’s approach to mosquito control is called Release of Insects carrying a Dominant Lethal Gene (RIDL). “Dominant lethal” genes, also known as “self-limiting” genes, cause premature death in host organisms. The mosquitoes carry two additional genes, tTAV and DsRed2, which they pass on to their offspring when they mate with wild-type females. Their offspring produce tTAV protein at levels that interfere with regular cellular functions, causing the insects to die before reaching adulthood. The lab-raised male mosquitos survive only because they were reared in the presence of tetracycline, an antibiotic that strongly reduces the production of the tTAV protein. The DsRed2 protein emits light under certain conditions and is used as a marker for reproductive success.

***Rationale:*** Proponents of the experiments cite human health as the justification for the research. Mosquito-borne illnesses cause untold morbidity and mortality around the globe. *Ae. aegypti* is a known vector of the viruses that transmit yellow fever, dengue, chikungunya, and Zika. Successive releases of male mosquitoes with dominant lethal genes will, over time, reduce the local insect population, preventing the transmission of disease.

***Work to date:*** In 2021, Oxitec conducted trial releases of roughly 200,000 GM mosquitoes in the Florida Keys, and it reported in April 2022 that the genetic modification performed as expected. Continuation of that work was planned for 2022, and Oxitec also announced plans in 2022 to conduct a trial release in California. Data from field releases of the GM mosquito in the Cayman Islands, Brazil, Malaysia, and Panama show that repeated releases have suppressed wild populations by more than 80% relative to an untreated area.

Oxitec approached the Florida Keys Mosquito Control District in 2010 to explore the possibility of doing a field release in the area. There had been over 60 cases of dengue in the Florida Keys during a 2010 outbreak. After finding a suitable site for the experiment—Key Haven, FL—based on the site’s topography, Oxitec began the process to test and license its product.

At the time, the GM mosquito was deemed an “animal drug,” and Oxitec submitted an application to license its product to the Center for Veterinary Medicine at the FDA. After a long process, which involved a federally mandated public comment period, voters in Key Haven rejected the experiment in its proposed location. A referendum on the experiment was included on the November 2016 ballot both in Key Haven and the wider Monroe County. Voters in Monroe County voted for the experiment, but voters in Key Haven voted against it. Ultimately, the Florida Keys Mosquito Control Board, the county’s local governing body, decided that Oxitec could not move forward with the experiment in Key Haven but could consider other sites within its jurisdiction.

The EPA and FDA determined that the GM mosquito would be regulated as a pesticide, and jurisdiction of the product was moved to the EPA. In March 2018, the EPA notified the public that it had received an application from Oxitec to license its GM mosquito as a pesticide, and sought an Experimental Use Permit to release its GM mosquito in field trials in another location in Monroe County and in Harris County, Texas, outside Houston. The EPA approved the project in April 2020, and in August of that year, the Florida Keys Mosquito Control Board voted to proceed with a trial.

***Possible undesirable outcomes***: Some scientists and mosquito control experts are skeptical of the approach and have raised safety concerns:

1. Some question whether the technology will actually be able to deliver the promised public health benefits. Experiments have shown up to 90% suppression with repeated releases, but is that enough to stop the spread of dengue or Zika?
2. Others question whether the approach is scalable. Field tests in other countries have occurred in moderately populated and geographically bounded areas. But what about more densely populated areas, or the hundreds of miles of cities and towns along the Gulf Coast? It would require release of billions of mosquitoes to eliminate mosquitoes in some places. How much will this cost? Will towns, cities, or states be able to afford the intervention?
3. Another objection is that releasing GM mosquitoes is the wrong fix for social problems related to overcrowded cities, slums, and lack of water and waste management infrastructure.

A general safety worry is that release of the mosquito could cause damage to humans, animals, and the environment. And in certain scenarios, it would be very difficult to undo. Specific concerns include:

1. Removal of one species of mosquito from a region could also allow new mosquito species to move into the area, and they could transmit different viruses, more virulent viruses, or the same viruses at a higher rate.
2. Horizontal gene transfer to non-target species.
3. Fear that the GM mosquito could mutate into something more dangerous.
4. Fear that some biting female mosquitoes with a dominant lethal gene will inevitably be released, and that Oxitec has not provided sufficient evidence that being bitten by, or swallowing, these mosquitoes will be safe for humans or other animals.
5. The use of tetracycline—an antibiotic—in the rearing of the GM mosquitoes raises concerns about the safety of waste from rearing facilities, since tetracycline use is being phased out or is already banned in many countries.
6. Concern that the RIDL strategy will not work reliably. Tetracycline “de-activates” the dominant lethal gene, meaning that GM mosquitoes that have access to tetracycline in their natural environment will not die. Although rare, some GM mosquitoes might encounter tetracycline and persist in the environment, with unknown effect.

In 2018, the Cayman Islands government reneged on an $8M deal with Oxitec to scale up release of the GM mosquito to the whole country, amid budget cuts and concerns that the technology has yet to fully prove itself. The Cayman Islands is carrying a 10-month evaluation program that began in May 2018, as part of a larger comparative study of various mosquito control methods on the islands.

***Alternative responses to the problem***: (1) Insecticide spraying, (2) massive door-to-door campaigns to eliminate standing water in backyards and public spaces, (3) developing vaccines for infectious diseases, (4) release of Wolbachia-infected mosquitoes, (5) irradiated “sterile” mosquitos, and (5) alternative genetic strategies, including gene drives.

***Relevant existing regulatory and policy mechanisms for public input:*** The FDA previously oversaw the Oxitec mosquito when it was regulated as an “animal drug. In 2017, the FDA finalized a “Guidance for Industry” statement clarifying that transgenic mosquitoes such as Oxitec’s mosquito will be regulated as “pesticides” per FIFRA, transferring jurisdiction to the EPA.

***Public reaction:*** The public comment period in 2016 provided an opportunity to gauge public reaction. According to an analysis of the comments, most were opposed (74.8%), almost none were neutral (3.6%), and fewer than a quarter (21.6%) were supportive. Objections included ecological safety (51.2%), human health implications (67.3%), genetically modified organisms generally (65.1%), and mistrust of government or industry (23.6%). Supportive comments focused on human health (86.8% among supporting comments, as opposed to 61.4% among opposing comments). Opposition was significantly higher (as determined by zip codes associated with some comments) in metropolitan areas, higher elevations, lower average house values, and lower household incomes.

In a 2015 survey of 88 people living in Key Ha­ven Island, the most commonly cited reason for opposing GM mosquito use was the general response “over­all concerns”—and people chose this response over specific human health and animal health concerns. Even if GM insects and animals did not harm human or ecosystemic health, other concerns are in play, such as suspicion of biotech companies’ motives.

Researchers reporting on social media coverage of the 2016 Zika outbreak said, “All over social media sites, flagrant conspiracy theories are usurping the information on the benefits of genetically modified mosquitoes.... Twitter, Reddit, and Facebook enthusiasts are screaming that Oxitec is solely responsible for spreading the Zika virus.” They attribute some of the reaction to general anxiety and lack of understanding about the Zika virus specifically; however, it also reflects a deeper mistrust of corporate biotech companies. The *New York Times* has reported that Russia’s disinformation campaign may be responsible for propagating lies about the relationship between GM mosquitoes and Zika.

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**Oxitec Diamondback Moth**

***The proposed release:*** Releasing genetically modified (GM) diamondback moths Plutella xylostella within Cornell University’s Agriculture Experiment Station. Oxitec’s approach to moth control is called Release of Insects carrying a Dominant Lethal Gene (RIDL). “Dominant lethal” genes, also known as “self-limiting” genes, cause premature death in host organisms. The GM male moths carry two additional genes, tTAV and DsRed2, which they will pass on to the next generation when they mate with wild-type females. Their offspring then produces levels of tTAV protein that interfere with regular cellular functions, causing the insects to die before reaching adulthood. Lab-raised male Oxitec moths survive only because they are reared in the presence of tetracycline, which strongly reduces the production of tTAV. The DsRed2 protein emits light under certain conditions and is used as a marker for reproductive success.

***Rationale:*** The diamondback moth is one of the most destructive crop pests in the world. It feeds on brassica crops including cabbage, broccoli, cauliflower and canola. The moth is found around the world and costs growers US$4-5 billion each year. The caterpillars chew on leaves and can kill young plants or make older plant parts unmarketable. The moth now shows resistance to almost every insecticide used to try and control it, including both synthetic and organic pesticides.

***Work to date:*** Oxitec completed laboratory and greenhouse studies prior to consideration of outdoor studies. Oxitec has been working with the Shelton Lab in Cornell University’s Department of Entomology for field trials. Work at Cornell University in the summer of 2015 assessed the performance of the self-limiting male moths in large field cages. These trials found that the moths performed well with respect to longevity and mating ability. Open field trials were conducted in the summer of 2017 at Cornell’s Agriculture Experiment Station in Geneva, NY. These trials examined the ability of the diamondback moth to survive and disperse in the field. Mathematical modelling has indicated that regular releases of the moths would be effective at suppressing a pest population.

***Possible undesirable outcomes***: None are anticipated, though the impact of these on pesticide use has been questioned. The Washington, D.C.-based Center for Food Safety, a consumer advocacy organization, is concerned that the use of the GM moths will not reduce pesticide use. Other pests also pose a problem, and farmers will have to spray pesticides anyway.

A coalition of organic farmers in New York State has raised a concern about organic farming: If GM moths fly on their property, do they lose their status as organic farmers?

***Alternative responses to the problem***: (1) Insecticide spraying, (2) Release of moths sterilized by radiation, and (3) Alternative genetic strategies, including gene drives. The second alternative is a precursor to the GM RIDL approach. One drawback to the release of irradiated sterilized moths is that large quantities of both males and females are released. The large releases can themselves cause crop damage, and the possibility that sterilized males will mate with sterilized females reduces the usefulness of the release.

***Relevant existing regulatory and policy mechanisms for public input:*** The moths are regulated as a “plant pest” and fall under the jurisdiction of the Animal and Plant Health Inspection Service of the U.S. Department of Agriculture, which issued a Finding of No Significant Impact before the caged and open field trials began.

***Public reaction to date:*** Various groups, on behalf of organic farmers in upstate New York, registered complaints with the USDA, Cornell University, and the governor of New York for “quietly” approving the GM moth trial in 2014, ahead of caged releases, even though APHIS responded to comments that raised substantive issues when it approved the permit for release in November 2014. They were also worried that there had been inadequate risk assessment and that the presence of GM moths might threaten their organic farming certifications. APHIS later rescinded their FONSI, citing “administrative error,” as they had failed to properly inform the public of the public comment period. Cornell subsequently successfully applied for a second permit to release, and it was granted, ahead of the 2017 open releases.

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**Gene Drive to Control Palmer Amaranth (Pigweed)**

***The proposed release:*** There are two possible targets for gene editing of Palmer amaranth (*Amaranthus palmeri)*. One is Palmer amaranth’s recently evolved overexpression of an enzyme that renders the plant resistant to glyphosate (also known as Roundup), the world’s most common herbicide. Genetic manipulation of the Palmer amaranth genome in this way would return the plant to its original level of susceptibility to glyphosate. The other target is suppression of Palmer amaranth by causing the plant to produce only male offspring. Gene drive Palmer amaranth would be released in North America, especially in the American South.

***Rationale:*** Palmer amaranth is the weed with the greatest impact on agricultural productivity across North America, especially in the American South, where it thrives. The plant can grow up to an inch a day, taking mineral and water resources from crops and blocking sunlight. Additionally, it stores nitrate, which can be toxic to livestock when consumed (for example, in corn intermixed with Palmer amaranth).

***Work to date:*** Background work has been done to identify traits that make Palmer amaranth especially suitable for gene drive alteration. Example traits that make it a good candidate include an annual reproductive cycle, separate sexes on separate plants (that is, it is dioecious), no in-ground seed repository likely, and wind versus animal fertilization. Additionally, Palmer amaranth has already been genetically modified in the lab, suggesting that gene drive modification is feasible. Finally, research has identified the genetic mutations that make the plant resistant to glyphosate.

***Possible undesirable outcomes:*** Although Palmer amaranth is a weed in the United States, in other countries similar species of amaranth are grown as crops. It is possible that gene drive Palmer amaranth could hybridize with these plants and disrupt agriculture in more vulnerable areas of the world. Even within the United States, the extent to which gene drive-modified Palmer amaranth might mate with wild species of amaranth, and what the downstream effects might be, are unclear.

Other possible undesirable outcomes relate to socioeconomic considerations within agriculture. As has happened with GM crops, if a gene drive-modified Palmer amaranth were patented and deployed, its appearance on farms could make farmers financially responsible for benefitting from its appearance. Similarly, proliferation of gene drive Palmer amaranth could reduce farmer autonomy and increase reliance on the technology for sustained competitiveness in the market. This is especially likely if commercial versions of the modified Palmer amaranth use self-limiting versions of gene drives known as “daisy drives.”

The spread of gene drive Palmer amaranth also poses problems for land sovereignty. It would be highly possible for gene drive Palmer amaranth to spread to land owned by people who oppose the species appearing on their land. This would be especially problematic for spread to indigenously owned land, which is legally sovereign and where a history of not respecting land sovereignty looms large.

***Alternative responses to the problem***: Outside of gene drive modification, management strategies fall into four major categories. Mechanical and physical methods involve hand weeding and tilling the soil to uproot Palmer amaranth seedlings, which increases soil erosion. Agricultural practices include crop rotation using plants that outcompete Palmer amaranth, and using drip irrigation to limit water to planting rows, which works well only in dry regions where farms rely on irrigation. Biological control methods include animal grazing and the release of animals that target Palmer amaranth, such as microbes, insects, and other animals such as nematodes, fish, and birds; these strategies are used primarily in low-intensity management of rangelands, forests, preserved natural areas, and waterways.

***Relevant existing regulatory and policy mechanisms for public input:*** In the United States, regulation would fall under the auspices of the Coordinated Framework for the Regulation of Biotechnology. Because gene drive-modified Palmer amaranth would, at least in its primary application, be most analogous to a pesticide, oversight would likely be primarily by the Environmental Protection Agency.

The National Environmental Policy Act regulates biotechnological products that that have potential environmental effects. NEPA requires an Environmental Assessment to determine the potential risk to the environment, and a more substantial Environmental Impact Statement if there is a finding of significant impact. There are established processes for public engagement at both stages.

Internationally, UN Convention on Biological Diversity deliberates on the potential risks and benefits of gene drives. Signatories are obliged to pass national laws implementing CBP provisions.

***Public reaction:*** Environmental and civil society groups seem strongly opposed. Large agricultural companies are among those that stand to profit most from widespread use of gene drive technology, and many foresee deleterious effects for smaller farmers and the environment at large.

***Source***

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**“De-extinction” of the Passenger Pigeon**

***The proposed release:*** Use of a combination of genome editing and reproductive interventions to produce a self-sustaining, 10,000-member breeding population of a bird that functionally replaces the passenger pigeon in the eastern United States. Passenger pigeons were nomadic, nesting in extremely large flocks throughout eastern U.S. forests, and the eventual goal would be to produce free-roaming flocks. An intermediate goal would be creation of contained flocks.

***Rationale:*** The benefit would be that the newly created population would be close enough genetically and in appearance and behavior to the passenger pigeon that it might be described as a de facto recreation of the species, effectively reversing its extinction. As in the case of eradicating non-native island mice, the benefit may just be the intrinsic value of the species or of an ecosystem, place, or history that the newly created population could help preserve. Some ecological benefits are possible; the forest disturbances created by very large migrating flocks of passenger pigeons may have helped create varied forest habitats. (In the early 1800s, flocks of passenger pigeons are thought to have held hundreds of millions of birds, making it probably the most populous bird in the world at the time, an icon of Eastern U.S. forests, and a significant ecological force. It went extinct due to overhunting and habitat destruction.)

***Work to date:*** Some preliminary steps have been taken. These include sequencing of passenger pigeon and band-tailed pigeon genomes, steps toward the genome editing of a band-tailed pigeon genome into a functional recreation of a passenger pigeon genome, and preliminary planning of further steps to achieve live births (using rock pigeons), create a breeding population, and introduce animals to the wild. The research has been funded and is publicly supported by the Long Now Foundation. The work has been carried out by the nonprofit Revive & Restore and the UC Santa Cruz Paleogenomics Lab. Revive & Restore’s stated goal is to begin release of “test flocks” between 2030 and 2040.

***Possible undesirable outcomes***: The newly created birds might turn out to be significantly different from passenger pigeons, and the environment may also have changed since passenger pigeons last flourished. Bad outcomes could include environmental harms and economic damage from reintroduction of flocks of birds that do not behave in the wild as expected, and perhaps also from birds that behave just as expected: very large flocks of passenger pigeons would likely be highly destructive and might be considered serious pests.

***Alternative responses to the problem***: The alternative is to halt the work and attempt to honor the values at stake through other kinds of environmental preservation efforts.

***Relevant existing regulatory and policy mechanisms for public input:*** The International Union for the Conservation of Nature has adopted guidelines for the release of newly created proxies for extinct species. The guidelines call, among other things, for analysis of costs and benefits and environmental risk assessments.

Relevant U.S. regulatory structures include the USDA’s Animal and Plant Health Inspection Service (APHIS), on grounds that the pigeon’s health is in question, and the FDA, if the genome modifications proposed to create a passenger pigeon are held to constitute an “animal drug” (because they affect the bird’s “structure and function”). The Animal Welfare Act, enforced by the USDA, appears not to apply, as it excludes birds. An unresolved question is the applicability of the Endangered Species Act, enforced by the USDA’s Fish and Wildlife Service.

***Public reaction:*** “De-extinction” (of various forms, some of which involve genome editing and cloning) is the subject of considerable public commentary, and reaction has been mixed. The prospect has sparked examination of what a species is, what is valuable about a species and what values are lost when a species goes lost, whether de-extinction of a species is possible either practically or in principle, and how the values at stake would be affected by a de-extinction effort. De-extinction projects may be “a source of inspiration and wonder” to some people (as the International Union for the Conservation of Nature observes in its guidelines for “de-extinction”), while others see them as wasting resources, misunderstanding the nature of species, and deepening the human domination of nature.

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**Gene Drive to Reduce Populations of Malaria-Carrying Mosquitos**

***The proposed release:*** Target Malaria, a non-for-profit research consortium with funding from the Gates Foundation, the Open Philanthropy Project, and others, is working on a project to use a “gene drive” to modify three species of mosquitoes (out of 3500 found around the world) that are most responsible for transmitting the parasite that causes malaria among humans—*Anopheles gambiae*, *Anopheles coluzzii*, and *Anopheles arabiensis*. A gene drive is a system of biased inheritance in which the ability of a genetic element to pass from a parent to its offspring through sexual reproduction is enhanced. The result of a gene drive is the preferential increase of a specific genotype, the genetic makeup of an organism that determines a specific phenotype (trait), from one generation to the next, and potentially throughout the population. The goal of Target Malaria is to release mosquitoes modified by a gene drive that cause offspring to be male. This would dramatically reduce, if not eliminate, the species’ populations, leading to the extinction of the microbe that causes malaria (*Plasmodium*).

***Rationale:*** Malaria is one of the leading causes of preventable death in low-income countries. In 2017, malaria deaths reached 435,000, but some estimates suggest that as many as 720,000 people died from malaria. In 2017, about 92% of the malaria cases and 93% of the malaria deaths took place in Africa. Globally, malaria is the leading cause of death among children ages 5-14, resulting in 66,901 deaths in this age group in 2016. If the Target Malaria project is successful at reducing the population of mosquitos that transmit malaria, it could reduce premature death dramatically, especially in the world’s lowest income countries.

***Work to date:*** Target Malaria has released sterile male (nonbiting) *A. coluzzii* mosquitos that are genetically modified but do not have gene drives in Burkina Faso as a first step toward eventually releasing mosquitos with gene drives. The release was monitored, and the results were published in 2021. Laboratory studies of similarly modified sterile male mosquitoes were conducted in Mali, and studies of gene drive-modified mosquitoes in large cages in Italy and the United Kingdom demonstrated successful population reduction. The project is also undertaking risk assessment and is conducting its own stakeholder engagement. Teams working with communities in Mali, Burkina Faso, and Uganda have developed glossaries in local languages of key technical concepts. The organization hopes that it will be prepared to release mosquitos modified with gene drives by 2029.

***Possible undesirable outcomes***: Along with a general concern about unintended consequences and possible adverse effects on human or animal health or the environment, opponents have raised concerns about possible weaponization of gene drives and they note that the U.S. Department of Defense is a leading funder of gene drive technology. Opponents worry that the same technology that would be used to reduce the population of mosquitos or make it impossible for them to transmit the parasite that causes malaria could also be used insert a gene drive into a biting insect population to deliver toxins. Some biosecurity experts express skepticism that weaponization is a likely scenario.

***Alternative responses to the problem***: One alternative response is to use gene drives to make mosquitoes immune to malaria, rather than a drive that would make it difficult for them to reproduce. A second response would be to focus on existing vector control approaches. These include chemical spraying, environmental management strategies that can reduce or eliminate vector breeding grounds (e.g., improved design or operation of water resources development projects), and the use of biological controls (e.g., bacterial larvicides) that target and kill vector larvae without generating the ecological impacts of chemical use. A third alternative is to focus on improved personal protection/prevention strategies, including the use of insecticide-treated bed nets. A fourth approach is to strengthen health systems in lower-income countries and expand access to diagnosis and antimalarial treatment. In 2021, a moderately effective but difficult-to-use malaria vaccine was approved for use by the World Health Organization.

***Relevant existing regulatory and policy mechanisms for public input:*** The United Nations Convention on Biological Diversity (CBD) reached an agreement at its biannual meeting in 2018, which rejected calls for a moratorium on gene drive technology and instead called for an assessment of the risks of gene drive releases on a case-by-case basis. The CBD treaty, which was not signed by the United States, also called on groups proposing to release organisms modified with gene drives to consult with local communities and indigenous groups potentially affected by the release. Target Malaria holds that community consultation is a priority, and it has established stakeholder engagement teams. Critics dispute the adequacy of these efforts and claim that local authorities are inadequately informed. Along with the CBD agreement, the Target Malaria project is regulated, locally, by the National Biosafety Agency (NBA) of Burkina Faso. In 2017, they, in collaboration with the Institut de Recherche en Sciences de la Santé/Centre Muraz (IRSS), received authorization from NBA to conduct the small-scale release of genetically modified sterile male *A. Coluzzii* mosquitoes in Burkina Faso. This was the first approval for field release of genetically modified mosquitoes in Africa.

***Public reaction to date:*** Response to the Target Malaria effort has been mixed. In November 2018,a group of scientists, including a large number of African scientists from countries with high rates of malaria, wrote an open letter to CBD asking it not to pass a moratorium on the release of gene drives. Several advocacy groups have expressed opposition to the use of gene drives and have argued that Target Malaria should do more to consult with and receive consent from effected communities. Mariann Bassey-Orovwuje, of Friends of the Earth Africa, and chair of the Alliance for Food Sovereignty in Africa, issued a statement in response to the 2018 CBD decision saying that: “In Africa we are all potentially affected, and we do not want to be lab rats for this exterminator technology…. Farmers have already marched in the streets of Burkina Faso to protest genetically engineered mosquitoes and we will march again if they ignore this UN decision. We are giving notice now that potentially affected West African communities have not given their consent or approval to this risky technology.”

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