The Case for a Global Moratorium on Genetically-engineered Gene Drives

A gene drive is a technique capable of intentionally altering or eliminating a species in the wild, without respect to a nation's borders. The CBD recognises through its Cartagena Protocol on Biosafety the principle of prior informed consent to the transboundary movement of a living modified organism that is released into the environment.

However, gene drives are deliberately designed to spread and persist, without respect to national borders, and as yet, there is no internationally agreed process for the effective governance of transboundary effects arising from the release of a gene drive.

Given this governance gap as well as the serious ecological and societal effects a release could introduce, a moratorium on the applied research, development and release of genetically engineered gene drives is the appropriate CBD response.

What are gene drives?

Gene drives are an experimental genetic engineering technology intended to aggressively spread a specific bioengineered trait among a species or population in nature. Normally, a genetically modified organism (GMO) released to the wild would pass on its bioengineered traits (e.g. herbicide resistance) to only about half of its offspring.[1] Gene drives are designed so that the bioengineered traits will be passed on to all or most offspring (even though they are unlikely to be one hundred percent effective).[2] If a gene drive were to be successful, the chosen genetically engineered traits would spread and become dominant in wild populations over a few generations of the species. A successful gene drive could intentionally or accidentally alter a species or crash it to extinction. So far, these artificial gene drives are developed using the new 'gene-editing' system known as CRISPR-Cas9.

What might gene drives be intended for?

Gene drives may be deliberately introduced into invasive species to eradicate them from the wild for conservation purposes, or into weed species to remove them from farmers' fields. They could be used to exterminate crop and livestock pests and destroy herbicide resistance in superweeds. Several groups have recently made news for proposing gene drive mosquitos to suppress or make extinct the species that transmit malaria.[3] Gene drives might also be pressed into use for military purposes as bioweapons, or to suppress food harvests.

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Civil Society Working Group on Gene Drives

1 National Academies of Sciences, Engineering, and Medicine. *Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values.* Washington, DC: The National Academies Press, 2016. doi:10.17226/23405.

2 Andrew Hammond et al. "A CRISPR-Cas9 gene drive system targeting female reproduction in the malaria mosquito vector Anopheles gambiae." *Nature biotechnology* 34, no. 1 (2016): 78-83.

3 Antonio Regalado, "The Extinction Invention" *Technology Review* April 13 2016. Accessed at www.technologyreview.com/s/601213/the-extinction-invention/

How quickly are gene drives being developed?

The first working CRISPR gene drive was reported in early 2014.[4] Since then, hundreds of millions of dollars of private, philanthropic and military funds have been directed into accelerating gene drive development.[5] While some developers estimate that they are at least a decade away from being ready for an environmental release of gene drives,[6] other proponents are proposing field trial releases of gene drive organisms as early as 2020.[7] So far gene drives have been put into mice, fruit flies, mosquitos, yeast and nematodes.

The temptations of gene drives

Some policymakers may be drawn to gene drives since they seem to propose a simple silver bullet solution to complex problems. Technicians and corporations may be thrilled by the apparent technical power gene drives offer and the potential for increasing profit.

While technical applications may be marketed with ambitious claims as ready-made 'solutions,' failed experiments with such technological 'solutions' in the past have demonstrated the need for precautionary approaches and deeper research into biological impacts.

4 Gantz VM, Bier E. The mutagenic chain reaction: a method for converting heterozygous to homozygous mutations. Science (New York, NY). 2015; 348(6233):442-444. doi:10.1126/science.aaa5945.

5 For example, The Bill and Melinda Gates foundation have pledged $75 million US dollars for Gene Drive research and development, The Tata foundation $70 million and US Defence Advanced Research Projects Agency is currently running at least two calls to find gene drive research: "Safe Genes" and "Insect Allies."

6 Personal Communication with Dr Kevin Esvelt, MIT "Sculpting Evolution" Group. Sept 2016.

7 GBIRd project (Genetic Biocontrol of Invasive Rodents) led by Island Conservation International – details at www.islandconservation.org/program-coordinator/.

The Governance Gap and Need for a Moratorium

There is no internationally agreed process for the effective governance of transboundary effects arising from the release of a gene drive. This is an enormous governance gap.

The CBD has previously recognised the ecological, cultural and socio-economic risks posed by living organisms that are genetically modified (LMOs). Through the Cartagena Protocol on Biosafety, the principle of prior informed consent has been established with respect to the transboundary movement of LMOs that are released into the environment. This puts a duty on a party exporting such an LMO to seek prior consent from the destination country.

The procedures are designed to cover intended movement across the border of a single nation. They are clearly unsuited to the unrestricted flow of an LMO without respect for borders, which is intrinsic to the use of gene drives.As a gene drive deliberately aims to change or remove species, and species range across political borders, transboundary effects will tend to be inevitable across multiple countries.

So if a gene drive was proposed for release in one country, it follows that all potentially affected countries would need to be taken into a process of advance joint consideration under new procedures that do not yet exist. Due to this governance gap and the serious ecological and societal effects that a release could introduce, a moratorium on the release of genetically engineered gene drives is clearly the appropriate CBD response.

International Civil Society organisations are recommending that the UN Convention on Biological Diversity place an immediate moratorium on applied research, development and release of genetically engineered gene drives.

Inability to Adequately Assess Effects

Absence of an agreed procedure for considering a release is just the first roadblock to a functional governance arrangement. There is almost as large a gap in the key process that such an agreement would rely on. Currently, there is only a poor ability to predict the effects a gene drive would unleash – the information central to a meaningful release consideration.

Gene Drive Effects Difficult to Predict

The full ecological impacts of gene drives are unknown, but are likely to be complex and difficult to predict. Species may not respond as expected, instead developing mutations that in turn cause unexpected problems. Eradicating a single species or altering its behaviour can affect symbiotic and competitor species, community structure, food webs, pollination, predation, nutrient cycling and result in the loss of biodiversity and ecosystem functions. Pathogens and parasites may shift hosts and new ecological niches may be opened, which would invite new (or more) damaging and invasive species.[8] The assumption that gene drives will behave and function as planned in the laboratory ignores and denies the complexity and dynamism of natural systems and evolution. Gene drives in general pose a serious threat to the resilience of ecosystems.

Given the current state of ecological knowledge, it is not possible to adequately predict the cascade of ecological impacts resulting from gene drive release into wild systems (including non-linear and stochastic changes). Additionally, where gene drives are designed to aggressively spread in the wild, the changes they trigger will be not be contained locally.

> "There are considerable gaps in knowledge regarding a gene drive's effectiveness, both on the target organism and the environment, over time and across diverse genetic backgrounds. It is also essential to consider how gene drives will propagate throughout a population and affect not only the target species, but its entire ecological community.
>
> "Because gene-drive modified organisms are intended to spread in the environment, there is a widespread sense among researchers and commentators that they may have harmful effects for other species or ecosystems. For example, using a gene drive to suppress a non-native weed population may lead to unexpected consequences, such as the loss of habitat for native species or even the establishment of a second, more resilient invasive species."
>
> – US National Academy of Sciences, June 2016[9]

The biosafety risks and unpredictability of gene drives are greater than 'classic' GMOs

Previous biosafety practice has been to limit the uncontrolled release of GMOs to prevent environmental persistence. Gene drives by contrast are intended to not only persist in nature but to also spread and overwhelm wild species. If one spreads in the wild, the gene drive organism will be subject to mutation and evolutionary pressures, as will the wild species in attempts to 'resist' the 'invading' gene drive. One way or another, the gene drive may fail to work or the arising mutations may persist and spread through a population.

8 Bruce L Webber *et al,* "Opinion: is CRISPR-based gene drive a biocontrol silver bullet or global conservation threat?" PNAS, Aug 25th 2015 Vol 112, no 34, 10565-10567

9 National Academies of Sciences, Engineering, and Medicine. *Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values.* Washington, DC: The National Academies Press, 2016. doi:10.17226/23405.

In addition, the underlying technology of CRISPR-Cas9 gene editing is still poorly understood. It appears to cause off-target effects (unintended breaks and insertions within the genome).[10]

These could cause unexpected phenotypes and other genetic expressions and behaviours in the targeted species. By building the molecular 'scissors' of CRISPR-Cas9 into the genome and letting them repeat their actions over several generations, the risk of off-target cuts and unpredictable effects may be magnified. At this point, it is counter to scientific evidence to present gene drives as a reliable working mechanism with a predictable outcome over time. They will be living, changing genetic elements replicating outside of human control or prediction.

"Because the CRISPR-Cas9 gene drive technology remains fully functional in the mutated strain after it is created, the chance of off-target mutations also remains and the likelihood increases with every generation pre- and post-release."
– Bruce L Webber *et al* (CSIRO Australia) in PNAS, August 2015[11]

Gene drive release may be irreversible and may jump species

The poor ability to predict effects cannot be overcome through an adaptive management approach, as there is currently no 'undo' function for recalling a gene drive from the wild.

Proposals to release 'reversal drives'[12] or to limit gene drive spread through theoretical 'local drive' systems[13] are highly speculative. Because they are subject to evolutionary pressures and ecological limitations, their reliability is questionable. In some cases, gene drives may spread beyond the target species (e.g. into closely related species).[14] Any assumption that gene drives will not jump species is intrinsically unreliable and not based in scientific evidence. Again, experience with GMOs has shown that horizontal gene transfer is far more prevalent than first understood.

"It is particularly imperative to use caution when considering the development of a "reversal drive" … as it may be impossible to effectively employ this strategy without off-target effects or to fully redress ecological and environmental effects from the original gene drive."
– US National Academy of Sciences, June 2016[15]

10 Bruce L Webber *et al,* "Opinion: is CRISPR-based gene drive a biocontrol silver bullet or global conservation threat?" PNAS, Aug 25th 2015 Vol 112, no 34, 10565-10567

11 *Ibid*.

12 K. A. Oye *et al*. "Regulating gene drives." *Science* Vol. 345, August 8, 2014, p.626. doi: 10.1126/science.1254287.

13 Kevin Esvelt, "'Daisy drives' will let communities alter wild organisms in local ecosystems." https://medium.com/mitmedia-lab/daisy-drives-will-let-communities-alter-wild-organisms-inlocal-ecosystems-cb626c5a9f38#.91i6eyhc0

14 Bruce L Webber *et al,* "Opinion: is CRISPR-based gene drive a biocontrol silver bullet or global conservation threat?" PNAS, Aug 25th 2015 Vol 112, no 34, 10565-10567

15 National Academies of Sciences, Engineering, and Medicine. Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values. Washington, DC: The National Academies Press, 2016. doi:10.17226/23405.

In light of the difficulty of predicting the effects that would result from a gene drive release, it would be premature to commence negotiations within the CBD on any procedure for considering a release proposal. Committing resources to finding a procedure for assessment in advance of a reliable ability to make such an assessment puts the cart before the horse. Further, it sets up incentives for negotiators to show progress by accepting systems for assessment that are substandard – and so dangerous in the gene drive context.

Lack of Agreed Standards

Besides fundamental uncertainties in gene drive biosafety there is also an absence of agreed standards for gene drive applied research and development.

No safe containment rules have been developed for gene drives

Existing rules for containment of GMOs presume that escapees will have a low persistence in the environment. Even so, rates of genetic contamination in agricultural crops and weed species by GMOs shows that even this assumption is not correct. While gene drive developers claim there may in future be technical and geographical means to effectively contain gene drive organisms, these hypothetical claims and assumptions need to be rigorously examined and tested. Strict laboratory handling and containment rules for all gene drive research should be internationally agreed upon and put into practice before further research can proceed even in the lab.

No monitoring procedures and practices

Critical to any release proposal would be development of internationally accepted procedures for monitoring impacts but also the spread of gene-drive constructs in the wild.

This would involve developing practical means to detect gene drive constructs in wild populations, obtaining agreement on the scope of effects that should be monitored and importantly, the methodologies to be employed. Without detailed research into these topics, it is not practical to begin to frame agreements. Research is also required into how responsibility for the costs of monitoring should be distributed, and how liability rules would be framed.

Fundamental Social, Economic and Security Concerns

The potential impacts of gene drives can run so deep that depending on how they are directed, they could have far reaching social, economic and security effects.

Gene Drive releases pose threats to food security and farmers rights

A gene drive release could impact the food supply by intentionally or accidentally suppressing pollination, by changing food webs, by jumping from wild to farmed species, and by creating or opening the way for new invasive species.
Gene drives could be used deliberately for hostile purposes against agriculture or by corporate entities to gain market advantages at the expense of smallholders.

Gene drives may have dual use (military) purposes including bioweapons.

The US military's Defence Advanced Research Project Agency (DARPA) is currently one of the largest funders of gene drive research and development. Its 'Safe-Genes' project explicitly acknowledges that gene drives pose 'bio-threats' from "irresponsible actors who might intentionally or accidentally release modified organisms."[16]

16 DARPA website, "Setting a Safe Course for Gene Editing Research" 9/7/2016 accessed at www.darpa.mil/news-events/2016-09-07

Hostile uses of gene drives include supercharging the spread of harmful engineered parasites or insects, or releasing gene drives to suppress open pollinated crop harvests by reducing fruiting or seed production. The development of 'local' gene drives offers potential for more targeted weaponisation in particular. Because of their ability to re-shape ecosystems, gene drives appear to be relevant to the 1977 ENMOD (Environmental Modification) treaty.[17]

> "Environmental modification techniques" refers to any technique for changing – through the deliberate manipulation of natural processes – the dynamics, composition or structure of the Earth, including its biota."
>
> – 1977 ENMOD convention against hostile uses of environmental modification techniques.

Gene drives could be deployed to increase monopolies, posing economic and livelihood threats.

Patent applications on CRISPR gene drives include proposals to render on-farm weed species susceptible to proprietary agrochemicals (e.g. Monsanto's Roundup weed killer).[18]

The purpose of deploying such a gene drive would be to bolster agrochemical sales by existing agri-monopolies. Gene drives associated with strong intellectual property protection might be leveraged to exercise control over other aspects of biodiversity that deliver important ecosystem functions to farming (e.g. pollinators or other beneficial species). An aggressive spread of gene drive organisms could adversely impact the integrity of organic and agroecological farming systems.

Gene drives advance techno-fix 'silver bullet' responses that distract and divert resources from systemic solutions (e.g. conservation, disease.)

While gene drives are likely to make their biggest impact in agriculture and military, there is already a vigorous attempt to brand gene drives as simple 'solutions' to conservation challenges and as silver bullets for diseases such as Malaria and Zika. There is a long history of previous failed attempts to address both vector-borne disease and invasive species through 'saviour' technological innovations – including large scale deployment of chemicals such as DDT[19] or intentional release of biological predators.[20] Currently, successful malaria control depends heavily on context, social factors and healthcare provision – not quick technology 'fixes.'[21]

17 United Nations Convention on the Prohibition of Military or Any Other Hostile Use of Environmental Modification Techniques, 1977 – accessed at www.un-documents.net/enmod.htm

18 WIPO Patent no WO 2015105928 A1, "RNA Guided Gene Drives"

19 Pesticide Action Network, "The DDT Story" – accessed at www.panna.org/resources/ddt-story

20 Carol Kaesuk Yoon, "When Biological Control Gets Out of Control" *New York Times,* March 6th 2001. Accessed at www.nytimes.com/2001/03/06/science/when-biological-control-gets-out-of-control.html

21 Anne Platt McGinn. "Malaria, Mosquitoes, and DDT" *Worldwatch Magazine* May/June 2002, Volume 15, No. 3. Accessed online at www.worldwatch.org/node/517

The Moral Dimension

Changing and eradicating entire species creates significant ethical, spiritual and moral concerns

While gene drive developers assume authority to 'sculpt evolution,'[22] engineer ecosystems and alter entire species, others regard such attitudes as unacceptable. Genetic engineering provokes strong moral, spiritual and ethical debates about the right of scientists and companies to alter life. Many cultures, particularly indigenous spiritual traditions, emphasise an intrinsic sanctity for the integrity of living beings and the web of life, but their traditional lands and waters may be impacted by gene drive releases.

Governments are under international obligations to protect and respect indigenous knowledge relevant to conservation of biodiversity,[23] to consult when making decisions that could impact lands and waters traditionally occupied or used by indigenous peoples and local communities,[24] and to ensure that assessments of the impacts of synthetic biology applications such as gene drives include full participation of indigenous and local communities.[25]

22 The research group developing Gene Drives at MIT call themselves the "Sculpting Evolution" group. www.sculptingevolution.org

23 Article 8J of the Convention on Biological Diversity states "Each contracting Party shall, as far as possible and as appropriate, Subject to national legislation, respect, preserve and maintain knowledge, innovations and practices of indigenous and local communities embodying traditional lifestyles relevant for the conservation and sustainable use of biological diversity."

24 UN Convention on Biological Diversity COP 7 Decision VII/16 adopted the Akwé: On voluntary guidelines for the conduct of cultural, environmental and social impact assessments regarding developments proposed to take place on, or which are likely to impact on, sacred sites and on lands and waters traditionally occupied or used by indigenous and local communities.

25 Decision UNEP/CBD/COP/DEC/XII/24 3c of the UN Convention on Biological Diversity urges parties to "To carry out scientific assessments concerning organisms, components and products resulting from synthetic biology techniques with regard to potential effects on the conservation and sustainable use of biodiversity, taking into account risks to human health and addressing, as appropriate, and according to national and/or regional legislation, other issues such as food security and socioeconomic considerations with, where appropriate, the full participation of indigenous and local communities;"

Official and Scientific Statements in support of precaution

Ecologists: "We caution that without a regulatory framework that provides a mechanism to work through these issues with clarity and transparency for CRISPR-Cas9 gene drive, this putative silver bullet technology could become a global conservation threat."

Source: Bruce L Webber *et al* (CSIRO Australia) in PNAS, August 2015

CBD Experts: "Applications that are aimed at altering and replacing natural populations (for example, gene drive systems) may have adverse effects at the ecosystem level, and vis-a`-vis the other two objectives of the Convention."

Source: CBD AHTEG on Synthetic Biology – September 2015. UNEP/CBD/SYNBIO/AHTEG/2015/1/3, p9

IUCN: "CALLS UPON the Director General and Commissions with urgency to assess the implications of gene drives and related techniques and their potential impacts on the conservation and sustainable use of biological diversity as well as equitable sharing of benefits arising from genetic resources, in order to develop IUCN guidance on this topic, while refraining from supporting or endorsing research, including field trials, into the use of gene drives for conservation or other purposes until this assessment has been undertaken."

Source: IUCN Motion 095 – Hawaii, September 2016

Conservation Leaders: "Given the obvious dangers of irretrievably releasing genocidal genes into the natural world, and the moral implications of taking such action, we call for a halt to all proposals for the use of gene drive technologies, but especially in conservation."

Source: A Call for Conservation with a Conscience – statement issued by 30 international conservation and environmental leaders including Dr Jane Goodall, Dr David Suzuki, Dr Vandana Shiva. Hawaii, September 2016.

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