# A Constitutional Moment

## Gene Drive and International Governance

Sustainability Council of New Zealand

The Law Foundation NEW ZEALAND
SUPPORTING INDEPENDENT LEGAL THINKING.

# Contents




Auckland law firm LeeSalmonLong provided legal analysis in support of this study

*The Sustainability Council gratefully acknowledges the support of the New Zealand Law Foundation*

September 2018, Sustainability Council of New Zealand, www.sustainabilitynz.org

# Preface

## Narrow Seas

*Who observed*
*the rat scaling the bow-lines and another*
*lodged in the forward hold?*[1]

Many New Zealanders' introduction to a new genetic engineering technique that offers "extinction to order" has been through the ambitious vision to rid the country of invasive introduced species which wreak havoc on our indigenous flora and fauna.

That vision rightly has strong backing from New Zealanders. But the question of how to get there – and whether technologies such as 'gene drive' should play any part in that effort - is another matter.

Gene drive is no ordinary technology. It is not, as the EPA has tried to convince tangata whenua, "simply a mechanism to spread a trait into a target population by changing its pattern of inheritance."[2] There is nothing simple about gene drive, technologically or ecologically. It has been dubbed 'ecological engineering' because it allows genetic engineering to reach beyond cultivated crops and livestock to engineer or eliminate wild species in their habitats. And, in the short time since the technical possibility was articulated, its potential ecological consequences have led the scientist first proposed the gene drive concept to admit it should probably never be used in the form in which it was originally conceived. Since then, ideas for curbing the power of gene drives or reversing their effects have been mooted, but all remain theoretical and some, ecologically fanciful.

The creation of gene drive possums and stoats is some years away, if it ever takes off. Meanwhile, New Zealand needs to accustom itself to the idea that a gene drive release is not the country's decision to make alone. Whether targeted at possums, rats or Argentine stem weevil, a gene drive release here could have regional or global implications.

The imperative to act as a global community on this issue may seem like a handbrake for those who want to use the technology, but it is not. It is in New Zealand's interests to ensure that the governance of the technology is international, as this report details, and that it has a seat at the table when other countries are contemplating outdoor uses of the technology - particularly as developer interest in gene drive technology extends well beyond conservation objectives. Riding on its coattails is the use of gene drive in agriculture[3], and there is the potential for an agriculture-focussed gene drive release elsewhere to impact on New Zealand's food and fibre production. This is a technology that requires us to think and act globally.

---

[1] Curnow A. 1937. Rats in the Bilge. First versions of Not In Narrow Seas. Tomorrow 1937-38.

[2] Environmental Protection Authority. 2017. *Genetic technologies, genetically modified organisms and the spectrum of genetic modifications in the context of Predator Free NZ 2050.* Briefing for Ngā Kaihautū, November 17. Obtained under the Official Information Act.

[3] Dearden D K, Gemmell N J, Mercier O M, Lester P J, Scott M J, Newcomb R D, Buckley T R, Jacobs J M E, Goldson S G and D R Penman. 2017. The potential for the use of gene drives for pest control in New Zealand: a perspective. *Journal of the Royal Society of New Zealand.*

# Summary

'Gene drive' offers the power to deliver "extinction to order" or the permanent reengineering of wild species. Since this new genetic engineering technique was first mooted in 2014, calls to place the technology under global governance have quickly followed.

The recognition that gene drive is no ordinary technology - one that "knows no political boundaries" - has bolstered that call.

Yet existing international agreements are inadequate to deal with the technique because it is not a mere extension of genetic engineering in its ambitions or capacity.

Gene drive technology has the potential to rapidly alter ecosystems in irreversible and damaging ways, where the removal of a species or population could trigger unintended cascades through the environment.

## Fundamental Governance Requirements

A critical building block for international governance over gene drive is **"collective consent"** whereby countries in which a gene drive release is proposed would need to gain the consent of other countries whose territory might be affected by that release. This reflects the potential for a gene drive release in one jurisdiction to have far-reaching impacts on another and that unilateral decision-making is quite inappropriate for this technology.

Other fundamental requirements for the international governance of gene drives include:

- **Precaution:** The precautionary principle lies at the heart of the international governance of GMOs under the Cartagena Protocol, and the additional risks posed by gene drive GMOs make precaution even more central for this technology.
- **Coverage:** Governance of all activities involving gene drive organisms is required. Field trials should be considered a form of full release as the escape of even one individual carries the potential for severe consequences.
- **Containment Standards:** Biological security standards for research need to be specified for gene drive activities as current standards are not designed to meet the technology's specific environmental hazards.
- **Assessment Against Alternatives:** An alternative approach that carries less risk and can achieve the same outcomes should be preferred by the regulator, other things being equal.
- **Risk Analysis:** Existing risk assessment models for GMOs are too narrow for evaluating gene drives and new models will need to address wide societal perspectives in addition to standard environmental and health issues.

- **Monitoring***:* Monitoring systems would be required to track the movement of gene drive organisms and the potential spread of introduced traits, through populations and across borders, and identify unintended harmful impacts.
- **Liability:** Operators should be strictly liable for any harm resulting from a gene drive release, as a condition of approval.

## The Governance Challenge

However, responding to the gene drive challenge will require more than regulatory action. In its ambition and potential for far reaching effects, gene drive technology triggers what has been called "a constitutional moment" - one that is both civilisational and ecological.

The fundamental ethical question it presents is under what circumstances, if ever, is it acceptable to wipe a species off the face of the earth.

Gene drive development also raises significant distributive justices issues. Most development and sponsorship is centred in the Global North, but many of the applications are intended for the Global South. Beyond ensuring that these distributive justice issues are squarely dealt with regionally and internationally, lie significant questions of who determines technology pathways.

Meeting the challenges that gene drive technology presents will require open-ended "constitutional conversations" within and across communities to deliberate common values and goals, and to explore the range of pathways before significant political and economic commitments are made to any gene drive applications.

## Existing International Agreements

A number of treaties could potentially cover aspects of gene drive use and releases, but would not provide a clear and coherent base for regulation. The Convention on Biodiversity (CBD) and its protocols could however be adapted to this and offer the best structure currently in place on which to build gene drive governance.

The Cartagena Protocol to the CBD is a potential natural home for gene drive governance as its purpose is protecting biodiversity and human health from impacts arising through the transboundary movement of living GMOs, such as gene drives. Central to the protocol is the concept of a receiving country having the right to decide in advance whether to accept any shipment of a living GMO. Yet the Cartagena Protocol has serious gaps, including:

- *Membership:* Although 171 countries have ratified the Cartagena Protocol, a key challenge to it providing effective governance is that the US, Canada, Argentina and Australia (all GM food exporting nations) and Russia are not party to the protocol.
- *Unintended Migration:* Although the protocol specifies prior informed consent for intended shipments, no such consent is required (only notification) if a release by one country risks unintended spread to another.

- *Enforcement and Monitoring:* The protocol lacks enforcement provisions and is weak on accountability generally.
- *Physical containment:* No special standards for containing a gene drive or similar organism have been specified in the protocol.
- *Assessment of Alternatives:* The protocol does not require the consideration of alternative ways of achieving the same outcomes.
- *Liability:* A supplementary protocol provides for nations to develop civil liability rules in their own legislation but does not require that this be a strict liability standard that would avoid the socialisation of risk.

## Pathways to an International Governance Regime

Credible international governance could be established through a number of different arrangements including: an amendment to the Cartagena Protocol, a new annex under that protocol, or a new protocol. Issues influencing the choice include: the treaty structures, the need to ensure GMO exporting nations participate, and the time and resources required to deliver gene drive governance.

Key operational issues requiring specification under any instrument are:

- *Collective consent of affected parties:* The most obvious grounds for a country to have standing in the process are if it is habitat to the same or related species that is the target of a gene drive release in another jurisdiction, or if that country could experience ecological, public health or other negative consequences as a result of the gene drive organism. It would be reasonable to expect countries to provide evidence that qualifies them to take part in such decisions.
- *Coordination:* While the parties given standing would hold authority to support or oppose a release proposal, delegating certain functions to a coordinating body would be efficient. It would provide facilitation and oversight for Information distribution and monitoring any release.

Until fit-for-purpose governance arrangements are adopted and operational, a globally-agreed restraint period prohibiting the outdoor use of gene drives is necessary.

## Governance of Gene Drive in New Zealand

To date, New Zealand government officials have been reluctant to concede that the existing international governance of genetic modification is inadequate to regulate gene drives.

Yet a country that is otherwise vigilant to biosecurity risks should be alive to the ways in which gene drive releases in other countries could prove a significant biosecurity threat. New Zealand needs to fundamentally reappraise gene drive's risk and benefit profile and reset policy in line with this.

While aspects of the law governing GMOs – the Hazardous Substances and New Organisms Act (HSNO) - could effectively regulate gene drive organisms, there are three important deficiencies: the exercise of precaution is optional rather than

required, there are significant gaps in the liability arrangements, and it is unclear to what extent effects beyond New Zealand are to be counted in an assessment.

It will be preferable for the new international governance rules to be known before considering changes to HSNO. In the meantime, New Zealand should set a constraint period during which no releases, field trials and outdoor GM development activities that involve gene drive organisms may be undertaken.

As gene drives contemplated for New Zealand - wasps, possums, stoats and rats - are generally agreed to be years away, the constraint period would not materially affect any local research and development.

The greater effect of taking this position would be to set an example globally and lay the foundations for the commitment needed to develop a global governance regime.

## No Case for Regulatory Discounts

Ultimately, gene drive is just one technology option for meeting societal objectives. A process of collective consent is a baseline requirement for gene drive governance. If there is not sufficient political will to establish such governance processes, that is not grounds for a regulatory discount: it is a signal to gene drive developers that the technology is at least not sufficiently mature.

Diluting regulatory requirements that would properly protect against risk does not advantage society as the risks are simply shifted from developers and users on to the environment and third parties.

There is real urgency to meet this governance challenge. A commitment by all countries not to allow gene drives until proper governance is in place is a first critical step and would be a signal that the international community recognises the enormous challenge this technology presents.

# 1. Enter Gene Drive

Evolutionary timescales – often measured in the millions of years over which species evolve - can defy human comprehension. Suddenly in the 21st century, however, six years is no longer a long time in biology. In 2014 - just two years after a new genetic engineering pathway (CRISPR/Cas9[4]) was discovered - gene drive was proposed[5], promising humans the technological power to collapse the hitherto evolutionary timescales of genetic change in species.

Gene drive is a technology that, in theory, can drive certain genetic traits through populations rapidly, leapfrogging the laws of inheritance that have regulated life on earth over the millennia.

Almost as soon as the CRISPR/Cas9-based gene drive proposition had been articulated, it was harnessed to efforts to tackle some of the most pressing global crises in public health and environment. This rapid elevation of a powerful but potentially uncontrollable technology, about which so little is understood, has had a shot-gun wedding effect with researchers and some patron governments seeking support from communities and citizens to apply the technology, even when it remains aspirational and years away from a functional product.

Meanwhile, gene drive lurches between extremes: between the possibility that it could save threatened species and the prospect that it becomes 'a global conservation threat'[6]; between being the most efficient biological killing machine ever directed to disease and pest eradication, to a technology that quite simply wont work.

This chapter provides a brief description of the technology; canvasses its mooted uses in conservation, public health and agriculture; the potential for its weaponisation; and the calls for governance.

## 1.1 The Technology and its Proposed Uses

A gene drive is a genetic engineering method for driving a trait through a population or species far more pervasively than the laws of natural inheritance allow. If it functions as intended, this "system of biased inheritance"[7] would broadcast a trait through 99% percent of an organism's offspring – twice the rate when inheritance is governed by natural laws of biology.[8] Use of the novel CRISPR technique is intended to allow the desired change or mutation – female sterility, for example, or

[4] CRISPR - "Clusters of Regularly Interspaced Short Palindromic Repeats" – is one of the so-called gene editing techniques.

[5] Esvelt K M, Smidler A L, Catteruccia F and G M Church. 2014. Concerning RNA-guided gene drives for the alteration of wild populations. *eLife.*

[6] Webber B L, Raghuc S and O R Edwards. 2015. Opinion: Is CRISPR-based gene drive a biocontrol silver bullet or global conservation threat? *PNAS* 112(34)

[7] US National Academy of Sciences. 2016. Gene Drives on the Horizon, p. 14.

[8] Regalado A. 2016. *The Extinction Invention*. *MIT Technology Reivew,* April 13.

susceptibility to specific toxins - to be introduced to both sets of chromosomes. This ensures all versions of the gene are modified,[9] and increases the likelihood that both copies come from only one of the parents.

Significantly, the technology allows genetic engineers to reach beyond domesticated species and into wild species. Nature can now be engineered *in situ* with a view to eradicating a species (so-called "population suppression" or "reduction") or changing its genetics to make it susceptible to human control (so-called "population replacement").[10] Because of these capacities, it has variously been described as setting off a "mutagenic chain reaction"[11], "the extinction invention"[12], and "ecological engineering".[13]

**Public health:** The most high-profile applications of gene drive technology are projects that tackle human diseases such as malaria, dengue fever and Lyme disease. Investment in and promotion of this area of gene drive research is significant. Private philanthropy is a key player in funding the research (The Gates Foundation has reportedly poured more than $75 million into gene drive mosquito research[14]), promoting the technology, and in supporting initiatives seeking to influence public policy discussions about how gene drive is to be governed.[15]

A great deal of gene drive research in this field is focussed on eliminating or reengineering vectors that transmit these diseases to humans – *such as* mosquitoes and mice - rather than on the disease itself,[16] although some labs are working on gene drives that would disable the malaria in the gut of mosquitoes.[17]

**Conservation:** The possibility that gene drives could be used to eliminate or bring invasive species under control has generated considerable interest among developers.

Under the banner of an international consortium, gene drive mice research is progressing, funded by the US military.[18] The consortium - Genetic Biocontrol of Invasive Rodents (GBIRd) - is made up of research institutions from the US, Australia and New Zealand along with US federal agencies, and is convened by US NGO, Island

[9] Norwegian Biotechnology Advisory Board. 2017. Statement on Gene Drives. February 14.
[10] US National Academy of Sciences. 2016. *Gene Drives on the Horiz*on, p. 15.
[11] Gantz V M and E Bier. 2015. The mutagenic chain reaction: A method for converting heterozygous to homozygous mutations. *Science* 348(6233): 424-444.
[12] Regalado A. 2016. *The Extinction Invention*. *MIT Technology Reivew,* April 13.
[13] Esvelt K M, Smidler A L, Catteruccia F and G M Church. 2014. Concerning RNA-guided gene drives for the alteration of wild populations. *eLife.*
[14] Regolado A. 2016. Bill Gates Doubles His Bet on Wiping Out Mosquitoes with Gene Editing. *MIT Technology Review,* September 6.
[15] https://www.gatesfoundation.org/How-We-Work/Quick-Links/Grants-Database/Grants/2017/07/OPP1174273
[16] Macias V M, Ohm J R and J L Rasgon. 2017. Gene Drive for Mosquito Control: Where Did It Come from and Where Are We Headed? *International Journal of Environmental Research and Public Health* 14.
[17] Mechanic M. 2017. This Technology Could Stop the World's Deadliest Animal. *Mother Jones,* August 14.
[18] Neslen A. 2017. US military agency invests $100m in genetic extinction technologies. *The Guardian,* December 4

Conservation.[19] GBIRd is focussed on releasing gene drive mice into island ecologies, and has been exploring islands off Western Australia and New Zealand as possible trial sites.

In Australia, gene drives have been mooted for rabbits, mice, cane toads, feral cats and a range of other invasive species.[20]

In New Zealand, gene drives are being considered for possums, stoats, rats and ferrets to achieve an ambitious goal of making the country "Predator Free" by 2050. While there is wide support for the "Predator Free" vision, the use of gene drives as a method is highly controversial. It is understood that no gene drive research is currently being conducted in New Zealand for the Predator Free programme, however the company had previously indicated that it had directed funds to gene drive mice research and development in Australia as a stepping stone to develop gene drives for rats, possums and stoats.[21]

**Agriculture:** Riding on the coattails of proposals to harness gene drive for public health and conservation purposes is use of the technology in agriculture.

Interest in using gene drive in agriculture has been piqued by the prospect of engineering wild species that affect production. The first indications of how the technology might be brought to bear in food and fibre production were set out in a key patent, which foresees gene drive "to control, reduce, or eliminate weeds and pests associated with agriculture", including "vermin, weed, plant and animal parasites and pathogens".[22] That is, gene drive would be harnessed for a new venture for genetic engineering in agriculture. Instead of the primary focus to date - crops - it would focus on the engineering of insects and plants that are agricultural pests and in so doing, to create "wild GMOs"[23].

Among the anticipated uses are "sensitizing drives" that are inserted into the genomes of target species, making them susceptible to external stimuli such as herbicides and pesticides. A scenario described is the introduction of gene drive to colonise a local population or species to reverse herbicide or pesticide resistance such as glyphosate resistant horseweed and pigweed, or Bt-resistant corn borer worm. Usage includes releasing in areas where herbicides and pesticides are not applied to create "reservoirs of sensitizing drives".

[19] http://www.geneticbiocontrol.org

[20] Moro D, Byrne M, Kennedy M, Campbell S and M Tizard. 2018. Identifying knowledge gaps for gene drive research to control invasive animal species: The next CRISPR step. *Global Ecology and Conservation* 13.

[21] In November 2017, the Predator Free NZ Science Strategy listed mouse 'proof of concept' gene-drive as a programme of work it was funding, noting that: "If the fundamental premise of gene-drive cannot be shown to work in mice, it will have little potential to contribute to a 2025 science solution. This will be explored overseas with the 'Genetic Biocontrol of Invasive Rodents' partnership."

[22] Esvelt K M and A L Smidler. RNA-Guided Gene Drives WO 2015/105928 A1. Example VII. Agricultural Safety and Sustainability

[23] Courtier-Orgogozo V, Morizot B and C Boëte. 2017. Agricultural pest control with CRISPR-based gene drive: time for public debate. Should we use gene drive for pest control? *EMBO Reports* 18(6)

Actual or anticipated research targets for the use of gene drives include the fruit fly[24] and Argentine stem weevil.[25]

While the dominant focus has been agricultural pests, gene drive has also been canvassed for use in livestock breeding.[26]

Fears that agricultural interests could use public-good oriented applications as a Trojan Horse for introducing the technology to agriculture have led patent holders, such as the US-based Broad Institute (jointly run by Harvard University and the Massachusetts Institute of Technology), to restrict the scope of the licensing of its IP holdings so that gene drives cannot be developed for agriculture.[27] Its current license to Monsanto for agricultural applications of CRISPR precludes the use of the technique for gene drives.[28] Whether there is any formal or informal arrangement to lift it at a later date has not been publicly declared.

Researchers warn that agricultural gene drive is not being given sufficient attention and that "[t]he spontaneous match between extractivist agriculture and gene drive could lead to multiple and uncoordinated releases of gene drives into the wild".[29] To the extent that the Broad Institute patent covers uses of gene drive in agriculture, the arrangement may place a handbrake on the commercialisation of agricultural gene drives. At best it provides time to get governance arrangements in place before any commercialisation is allowed.

## 1.2 Dual Use – Gene Drive Biological Weapons

The prospect that the same technological capacities might be used as a biological weapon is well recognised. Collapsing pollinator populations or other species critical to a country's food security, or engineering insects to carry disease or toxins lethal to humans, are two visions of 'weaponised' gene drives.[30] This possibility is one reason the US National Intelligence Agency has rated genome editing - the technology that gene drive rests upon - a national security threat.[31] It is also a prompt for a US$65 million investment by the US Federal Defence Advanced Research Projects Agency

[24] Buchman A, Marshall J M, Ostrovski D, Yang T and O S Akbari. 2018. Synthetically engineered Medea gene drive system in the worldwide crop pest Drosophila Suzuki. *PNAS* April 17.

[25] Dearden D K, Gemmell N J, Mercier O M, Lester P J, Scott M J, Newcomb R D, Buckley T R, Jacobs J M E, Goldson S G and D R Penman. 2017. The potential for the use of gene drives for pest control in New Zealand: a perspective. *Journal of the Royal Society of New Zealand.*

[26] Gonen S, Jenko J, Gorjanc G, Mileham A J, Whitelaw C B A and J M Hickey. 2017. Potential of gene drives with genome editing to increase genetic gain in livestock breeding programs. *Genetics Selection Evolution* 49(3).

[27] Begley S. 2016. Monsanto licenses CRISPR technology to modify crops — with key restrictions. *Statnews*, September 22.

[28] Rozen I. 2016. Licensing CRISPR for Agriculture: Policy considerations. *Broad Institute News*, September 29.

[29] Courtier-Orgogozo V, Morizot B and C Boëte. 2017. Agricultural pest control with CRISPR- based gene drive: time for public debate. Should we use gene drive for pest control? *EMBO Reports* 18(6), p. 880.

[30] Begley S. 2015. Why the FBI and Pentagon are afraid of this new genetic technology. *Statnews*, November 12.

[31] Clapper J R. 2016. Worldwide Threat Assessment of the US Intelligence Community. Statement for the Record to the Senate Armed Services Committee by the Director of National Intelligence. February 6.

(DARPA) into research attempting to attenuate or reverse accidental or hostile gene drive releases.[32]

## 1.3 Timescales and Pace of Development

Investment in gene drive research is high-paced and it the technology is described as "moving faster than anyone dreamed".[33]

In 2015, when the US National Academy of Sciences published its report on the technology, just four proof-of-concept studies had been published, two involving mosquitoes, one fruit flies, and another yeast.[34] Now just three years later, as this report is being completed, the first demonstration of the technology in a mammal was announced: a mouse, engineered to alter coat colour.[35] Nevertheless, for many of the species for which gene drive has been mooted – for example, marsupials (such as possums, rats and stoats) and wasp species in New Zealand – there are significant barriers and technological distances to overcome before gene drive is even feasible.[36]

It is uncertain when a gene drive organism might be ready for trialling or full release in the environment, due to the extent of R + D underway globally and the potential for breakthroughs that accelerate progress or, conversely, the possibility that greater complexity delays development. Some reports suggest that it will be years before a gene drive targeting malaria transmitting mosquitoes will be ready for field trialling.[37] However, the scientist leading development of gene drive focused on disabling malaria in the gut of the South Asian mosquito *Anopheles stephensi* reports it could be ready for field trialling outdoors before the end of 2020.[38]

Meanwhile, gene drive marsupials and wasps in New Zealand remain "highly theoretical", with "years of technical development ahead" before trialling might begin.[39]

Gene drive mice are considered to be among the earliest candidates for release. In the US, gene drive mice that have been engineered with antibodies to Lyme disease are targeted by the developer for release in the US as early as 2024.[40]

---

[32] DARPA. 2017. Building the Safe Genes Toolkit. Media release, July 19.

[33] McFarling U L. 2017. Could this zoo of mutant mosquitoes lead the way to eradicating Zika? *Statnews,* December 13.

[34] US National Academy of Sciences. 2016. *Gene Drives on the Horizon*, p. 1.

[35] Williams S. 2018. CRISPR Gene Drive Used to Alter Mouse Coat Color. *The Scientist,* July 9.

[36] Dearden D K, Gemmell N J, Mercier O M, Lester P J, Scott M J, Newcomb R D, Buckley T R, Jacobs J M E, Goldson S G and D R Penman. 2017. The potential for the use of gene drives for pest control in New Zealand: a perspective. *Journal of the Royal Society of New Zealand.*

[37] Swetlitz I. 2917. In a remote West African village, a revolutionary genetic experiment is on its way — if residents agree to it. *STAT,* March 14.

[38] Mechanic M. 2017. This Technology Could Stop the World's Deadliest Animal. *Mother Jones,* August 14.

[39] Morton J. 2017. Science: What is gene drive technology and what does it mean for New Zealand? *New Zealand Herald,* December 4.

[40] Temperton J. 2017. Gene drives could wipe out diseases – but we need to understand the risks. *Wired Magazine,* April 24. Bouchard S. 2017. Gene 'editing' on mice tested in war on ticks. *Island Institute,* November 17.

## 1.4 "Governance must be international from the start"

Alert to the risks and far-reaching implications of the technology, academics, science institutions and civil society have called for gene drive to be under civil and global governance. From the elite science community through to the free market press, the call has been similar and unusually clear: "A decision by one nation, or one group, to release them might eventually affect every country where the species exists. Governance arrangements must be international from the start".[41]

### Calls for International Governance

The **US National Academy of Science** identifies "the need for international policies or regulation that build agreements between countries" and that:

> Research on gene drives is global. Responsible governance will need to be international and inclusive, with clearly defined global regulatory frameworks, policies, and best practice standards for implementation.[42]

**Georgetown University Law Center and Medical Center** academics set out the case in respect of applications involving GM mosquitoes:

> The current practice whereby private companies, researchers, or states make unilateral decisions without transparency and accountability is unacceptable. The benefits and harms of release will accrue not only to those actors, but also to entire regions of the world. Consequently, fair and dispassionate decision making processes, with broad international agreement, are vital.[43]

**Professor of zoology at the University of Manchester**, Matthew Cobb similarly argues an international regulatory regime is required:

> the only sustainable and safe way of applying this potentially transformative technology will involve international regulations, based on careful study and continual ecological monitoring, coupled with the rights of local communities to veto such projects if they so desire. This is an urgent task that an accepted international structure such as the United Nations needs to address as soon as possible.[44]

Some gene drive developers also argue that the permission of all potentially affected countries is required (for at least certain types of gene drive releases):

> moving forward without the permission of every other country harboring the target species would be highly irresponsible.[45]

**Australian scientists** have urged for immediate action to ensure adequate regulation:

> without a regulatory framework that provides a mechanism to work through these issues with clarity and transparency for CRISPRCas9 gene drive, this putative silver bullet

[41] Anon. 2016. Extinctions to Order. *The Economist,* September 17.
[42] US National Academy of Sciences. 2016. *Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values,* p. 6 and 149.
[43] Ostera G E and L O Gostin. 2011. Biosafety Concerns Involving Genetically Modified Mosquitoes to Combat Malaria and Dengue in Developing Countries. Georgetown Public Law and Legal Theory Research Paper No. 11-28. 305 JAMA 930-931.
[44] Cobb M. 2016. Gene drives need global policing. *The Guardian,* February 9.
[45] Esvelt K M and N J Gemmell. 2017. Conservation demands safe gene drive. PLoS Biol 15(11): e2003850.

> technology could become a global conservation threat. The time to develop this regulatory framework is now.[46]

The **Norwegian Biotechnology Advisory Board** has also stressed the need to "establish [] international regulations for gene drives":

> Because gene drives do not respect geographical boundaries, because the consequences of releasing them could potentially be significant, because there is disagreement about whether they should be used and because the technology is developing rapidly, there is an urgent need for international debate. Any decision about the application of the technology requires international cooperation and grounding in a common framework.[47]

In guidance on GM mosquitoes, including those involving gene drive, the **WHO** notes that:

> A regional notification and agreement process may be advisable for planned introductions capable of autonomous international movement beyond the scope of provisions in the Cartagena Protocol and may best involve a multilateral organization in a coordinating capacity.[48]
>
> If it is known or expected that introduced traits will have transboundary effects, then the need for multilateral regulatory approval by all countries, not separated by species barriers, subject to introduction of a specific GMM should be considered. To engage a multilateral regulatory process may involve international agreements, treaties, covenants, conventions, protocols, or county approvals prior to introduction to one country within a contiguous ecozone.

Most recently, the **Ad Hoc Technical Expert Group** (AHTEG) to the Convention on Biological Diversity

> **a precautionary approach and cooperation with all countries and stakeholders that could be affected,** taking into account the need for the free, prior and informed consent of indigenous peoples and local communities, might be warranted in the development and release of organisms containing engineered gene drives, including experimental releases, in order to avoid potential significant and irreversible adverse effects to biodiversity.[49]

There is real urgency to secure appropriate international governance for gene drives:

- Although completion of gene drives for most likely target species is some years off, laboratory contained work is gathering pace and field trialling (which should be treated as a release) will be much closer.
- Resistance to the required governance may increase as individual actors and states become more committed to the technology or particular gene drive applications on the basis of the current, inadequate regulatory requirements.

[46] Webber B L, Raghuc S and O R Edwards. 2015. Is CRISPR-based gene drive a biocontrol silver bullet or global conservation threat? Opinion, *PNAS* 112(34): 10565–10567.
[47] Norwegian Biotechnology Advisory Board. 2017. Statement on Gene Drives. February 14.
[48] WHO. 2014. Guidance framework for testing of genetically modified mosquitoes. ISBN 978 92 4 150748 6
[49] Ad Hoc Technical Expert Group on Synthetic Biology. 2017. Report. Montreal Canada. 5-8 December. CBD/SYNBIO/AHTEG/2017/1/3, para 25.

- Setting out governance requirements in advance is important so that would-be developers are well appraised of the expectations they must meet.
- Achieving consensus on international governance arrangements will be a lengthy process.

Developing appropriate governance over gene drive requires understanding that nature of the technological risk and the broader challenges that the technology poses – questions that the following two chapters explore.

# 2. A New Order of Technological Risk

The defining characteristics of gene drive technology are proliferation and irreversibility.[50] This technological capacity is new, in that, "humanity has no experience engineering systems anticipated to evolve outside of our control".[51]

Indeed, set against the past thirty years, where environmental release of GMOs has been primarily cultivated crops within agricultural systems, gene drive is a wholly different proposition. In addition to use in agriculture, developer ambitions for the technology include engineering wild species, including insects, plants and mammals, for their permanent eradication or modification. This "change in the spectrum of organisms and environments" that GM is now targeting poses daunting challenges to predict or understand the consequences of such proposals.[52]

The combination of technological power and potential uncontrollability was underscored in November 2017 when the creator of the gene drive concept disavowed his previous promotion of certain forms of the technology, stating that what he terms "universal drives" should probably never be used because they would be uncontrollable and their effects irreversible.[53]

This section provides an overview of the risks gene drive entails: methodological risks; proliferation and irreversibility; and the potential effects of gene drives on non-target species and ecosystems as a whole. The consequences of gene drive technologies failing are also discussed as this scenario is considered likely and itself entails a number of ecological risks.

## 2.1 Methodological uncertainty

Gene drive technology rests upon a new method of genetic engineering, CRISPR/Cas9 (dubbed 'gene editing' by developers). The approach is novel and its application still preliminary and lab-based. Research pointing to unintended genetic changes caused by use of CRISPR/Cas9 underscores the complexities that remain to be resolved, and challenges proponents' assertions that the technique is 'precise' and 'easy to use'.[54] By July 2018, new research revealed that the technique causes many more unintended changes than previously thought, with hundreds of large unintended deletions or changes (some of them with potentially serious or fatal

[50] US National Academy of Sciences. 2016. *Gene Drives on the Horizon*, p. 139.
[51] Esvelt K M and N E Gemmell. 2017. Conservation demands safe gene drive. *PLoS Biol* 15(11): e2003850.
[52] Simon S, Otto M and M Engelhard. 2018. Synthetic gene drive: between continuity and novelty. *EMBO reports* 19: e45760 | 2018.
[53] Esvelt K M and N E Gemmell. 2017. Conservation demands safe gene drive. *PLoS Biol* 15(11). e2003850.
[54] Schaefer K A et al. 2017. Unexpected mutations after CRISPR–Cas9 editing in vivo. Nature Methods 14, 547–548. Shin HY et al. 2017. CRISPR/Cas9 targeting events cause complex deletions and insertions at 17 sites in the mouse genome. Nature Communications 8, Article number: 15464.

consequences).[55] At least some CRISPR applications, stated a leading science writer, "may not be quite as safe as we thought".[56] The field can be characterised both as a highly sophisticated area of scientific research and an immature technology - as new forays into the unknown, and the unexpected, continue to reflect.[57,58]

This is more so the case with CRISPR-based gene drives, where understanding of the full implications of using the system to engineer life forms is embryonic even in laboratory-contained conditions.

## 2.2 Gene Drive Approaches

Since the CRISPR gene drive system was first described, theoretical approaches have diversified. This has led to a new classification of approaches, with 'universal' or 'self-propagating' gene drives on the one hand, and 'local' or 'self-limiting' drives on the other (see box below).

The most significant revision of the universal CRISPR-based gene drive proposition is the proposal to place biological limitations on the extent to which a gene drive will spread through populations in the wild. 'Local' gene drive proponents argue that their approach would allow for greater control over the use of the technology and would not require the same level of regulation as 'universal' drives, so that decisions about their use can be left to the communities where a 'local' gene drive is to be released.[59]

The terminology - coined to distinguish these different models - should be treated with caution, firstly because all gene drives are self-propagating (the question is one of extent). Further, as proponents of 'local' gene drives acknowledge, it has yet to be demonstrated that the self-limiting functions will perform as intended – even in one species, let alone every species into which gene drives are introduced.[60]

[55] Kosicki M, Tomberg K and A Bradley. 2018. Repair of double-strand breaks induced by CRISPR–Cas9 leads to large deletions and complex rearrangements. *Nature Biotechnology,* doi:10.1038/nbt.4192. The standard practice to identify unintended effects has been for researchers to predict the unintended changes and then search for those alone.

[56] Le Page M. 2018. CRISPR gene editing is not quite as precise and as safe as thought. *New Scientist,* July 16.

[57] Simon S, Otto M and M Engelhard. 2018. Synthetic gene drive: between continuity and novelty. *EMBO reports* 19: e45760 | 2018.

[58] Ihry R J, Worringer K A, Salick M R, Frias E, Ho D, Theriault K, Kommineni S, Chen J, Sondey M, Ye C, Randhawa R, Tripti Kulkarni T, Yang Z, McAllister G, Russ C, Reece-Hoyes J, Forrester W, Hoffman G R, Dolmetsch R and A Kaykas. 2018. p53 inhibits CRISPR–Cas9 engineering in human pluripotent stem cells. *Nature Medicine,* Letters.

[59] Esvelt K. 2016. 'Daisy drives' will let communities alter wild organisms in local ecosystems. *MIT Media Lab,* June 10.

[60] Esvelt K M and N E Gemmell. 2017. Conservation demands safe gene drive. *PLoS Biol* 15(11). e2003850.

## Technological responses to limit the impacts of gene drives

Technological proposals to dilute the potential impact of gene drive include:

- **Reversal drives,** which are proposed for introduction if the original gene drive does not operate as intended or causes greater harm than foreseen. A reversal drive would "overwrite one or all genomic changes spread by the first drive"[61]. Release of a third, successive drive, it is proposed, "could restore the exact wild-type sequence".[62]
- **"Split drives"** or **"Daisy chain drives",** where the components of a gene drive are separated and spaced to limit their active life and heritability. A daisy drive comprises "serially dependent, unlinked drive elements which are on separate chromosomes" and "are lost over time which limits the time and location of the gene drive spread."[63]
- **Immunizing drives,** which would block the spread of other gene drives that have been released, and, it is theorised, provide immunity to a species or sub-species that could otherwise be vulnerable to a gene drive targeting a related species. A combined "immunizing reversal" drive could be spread through both wild-type individuals and those affected by an earlier gene drive.

Such approaches remain highly speculative, if not fanciful, and are accompanied by similar risks and uncertainties to universal drives. These include:

- **Efficacy:** Secondary or alternate gene drives would also be vulnerable to natural resistance or suppression, so that their in-field ability to limit the effects of the original gene drive is uncertain. In respect of split drives, for example, a rare or unforeseen biological response could "undo the separation that prevents indefinite spread"[64].
- **Limited repair or reversibility:** Fully redressing ecological and environmental effects of the original gene drive could be impossible.[65] As exponents of the reversal drive note, "even if a reversal drive were to reach all members of the population, any ecological changes caused in the interim would not necessarily be reversed."[66]
- **Compounding biological risk:** Introduction of secondary or tertiary gene drives to populations (reversal or otherwise) could compound biological risk. Reversal drives, for example, "may also introduce their own sets of wider ecological effects.[67]
- **Genetic pollution:** Additional genetic material could remain within an individual or in a population, with the potential to mutate and trigger other unanticipated, off-target genetic changes.[68]

[61] Esvelt K. 2016. 'Daisy drives' will let communities alter wild organisms in local ecosystems. *MIT Media Lab,* June 10.
[62] Ibid.
[63] Australian Academy of Science. 2017. *Synthetic Gene Drives in Australia: Implications of Emerging Technologies.*
[64] Esvelt K. 2016. 'Daisy drives' will let communities alter wild organisms in local ecosystems. *MIT Media Lab,* June 10.
[65] US National Academy of Sciences. 2016. *Gene Drives on the Horizon,* p. 6. Prywes N. 2014. On the Irreversibility of Gene Drives. *The Scientist*, September 16.
[66] Esvelt K. 2016. 'Daisy drives' will let communities alter wild organisms in local ecosystems. *MIT Media Lab,* June 10.
[67] US National Academy of Sciences. 2016. *Gene Drives on the Horizon*, p. 111. Esvelt K. 2016. 'Daisy drives' will let communities alter wild organisms in local ecosystems. *MIT Media Lab,* June 10.

A more error-friendly technology might warrant a "benefit of the doubt" approach, but as the outcomes of failed self-limiting mechanisms could be as severe as if a functioning universal drive had been released, all gene drive models should be assumed to carry the same potential for universal release and proliferation.

## 2.3 Irreversibility and Uncontrollability

Gene drives rely on proliferation for their success. It is widely accepted that a gene drive organism "can spread indefinitely, potentially affecting every population of the target species throughout the world."[69] The intended rate at which a gene drive construct can colonise a population is a further feature that indicates the technology carries a different order of risk than classical biological control.[70] It is for this reason that gene drives are considered to pose "a global conservation threat".[71]

Geographical isolation – such as that enjoyed by island nations - is not a guarantee that 1) a country can release gene drive organisms with the expectation their further spread will be prevented by natural physical barriers or 2) that a country is fully insulated from gene drive organisms released in other countries. The Ad Hoc Technical Expert Group to the United Nations Convention on Biological Diversity (CBD) has firmly cautioned against such assumptions, stating: "Islands are not ecologically fully contained environments and should not be regarded as fulfilling the conditions in the definition of contained use as per Article 3 of the Cartagena Protocol unless it is so demonstrated"[72]. Noble et al underscore this possibility, warning that "any development efforts looking ahead toward field trials […] should be aware that there could be a high likelihood of unwanted spread across international borders, even from ostensibly isolated islands"[73].

Extreme weather events – which are becoming more commonplace globally – further erode geographical barriers that have traditionally been relied upon as protection against invasive species from other countries. The tsunami that followed the 2011 earthquake in Japan triggered what has been described as a "transoceanic biological rafting event with no known historical precedent"[74]. Plastic debris in the ocean is thought to have allowed species to passenger safely to land, and the rate of drift to have allowed biotic adaptation of those species.

---

[68] Esvelt K. 2016. 'Daisy drives' will let communities alter wild organisms in local ecosystems. *MIT Media Lab,* June 10.

[69] Ibid.

[70] Netherlands National Institute for Public Health and the Environment. 2016. Gene Drives. Policy Report, pp. 19-20.

[71] Webber B L, Raghuc S and O R Edwards. 2015. Opinion: Is CRISPR-based gene drive a biocontrol silver bullet or global conservation threat? *PNAS* 112(34)

[72] Ad Hoc Technical Expert Group (AHTEG). 2017. Report of the Ad Hoc Technical Expert Group on Synthetic Biology. Montreal, Canada, 5-8 December 2017, para 51(c)

[73] Noble C, Adlam B, Church G M, Esvelt K M and M A Nowak 2018. Current CRISPR gene drive systems are likely to be highly invasive in wild populations. *eLife* 2018;7:e33423. DOI:

[74] Carlton J T, Chapman J W, Geller J B, Miller J A, Carlton D A, McCuller M I, Treneman N C, Steves B P and G M Ruiz. 2017. Tsunami-driven rafting: Transoceanic species dispersal and implications for marine biogeography. *Science* Sep 29;357(6358):1402-1406.

## 2.4 Gene drive impacts on non-target species and wider ecosystem

Gene drive technology has "the potential to rapidly alter ecosystems in irreversible and damaging ways".[75] Any species targeted by a gene drive will have a myriad of interactions with the wider biological community it forms a part of, opening up the possibility that it could "pass the gene-drive construct to closely related individuals".[76]

The possibility that the gene drive and/or its elements could be transferred to non-target species via a mechanism known as horizontal gene transfer (HGT) has been flagged by the National Academy of Science as a particular concern.[77] While it may take place at a slower evolutionary pace, it is now recognized to be a more common occurrence than initially assumed and that this mechanism could "exact more profound changes in natural populations, perhaps contributing to major evolutionary transitions".[78]

Ecosystem-level impacts from gene drive releases are also possible – a reason the approach has been dubbed "ecological engineering".[79] Among the potential risks are that the removal of a species or population could trigger "unintended cascades that may represent a greater net threat than that of the target species".[80]

Population genetics and ecosystem dynamics are essential disciplines for trying to map the potential consequences of a gene drive release, but work on developing gene drives has outpaced study in these critical areas.[81] Ecosystem-level impacts are difficult to predict and require extensive mathematical modelling to estimate.[82]

Even then, some scientists question whether it will be possible to accurately predict how gene drive organism releases will impact on ecosystems and so whether proper risk assessment will be possible.[83] This is because "the potential breadth of a gene drive impact and the duration of its effects would be hard to model" and such modeling might not show up species that have been lost.[84]

This will particularly be the case for "keystone" species, so named because they play a number of roles that many other species depend on for survival. Rodents, which are the target of gene drive research, "can be keystone species in many ecosystems",

[75] Lunshof J. 2015. Regulating gene editing in wild animals. *Nature* (52) May 14, p. 127.
[76] US National Academy of Sciences. 2016. Gene Drives on the Horizon, p. 111.
[77] Horizontal gene transfer, as the Academy describes, is a pathway for the asexual movement of genetic material between otherwise distinct species and even across biological domains, for example, from bacteria to plants. Ibid.
[78] US National Academy of Sciences. 2016. *Gene Drives on the Horizon*, p. 36.
[79] Esvelt K M, Smidler A L, Catteruccia F and G M Church. 2014. Concerning RNA-guided gene drives for the alteration of wild populations. *eLife.*
[80] Webber B L, Raghuc S and O R Edwards. 2015. Opinion: Is CRISPR-based gene drive a biocontrol silver bullet or global conservation threat? *PNAS* 112(34): 10565–10567.
[81] US National Academy of Sciences. 2016. Gene Drives on the Horizon, p. 3
[82] Lunshof J. 2015. Regulating gene editing in wild animals. *Nature* (52) May 14, p. 127.
[83] Norwegian Biotechnology Advisory Board. 2017. Statement on Gene Drives
[84] Lunshof J. 2015. Regulating gene editing in wild animals. *Nature* (52) May 14, p. 127.

notes one leading academic, "as you would find if you could remove them to see what effects occur at the community and ecosystem level."[85]

Eliminating the mosquito species, *Aedes aegypti,* as a means of wiping out malaria – a widely publicized project for gene drive – raises significant questions about potential ecological cascades: what effect will this have on other species that depend upon that mosquito; what species will fill the niche left by an extinguished *Aedes aegytpi;* and what implications will the resulting cascades in the ecological community have on specific human and non-human communities? Will the effects of deliberate extinction end with the species' removal, or will it trigger a series of ecological disruptions that create new and unforeseen troubles? Malaria afflicts hundreds of millions of people, often the most economically vulnerable on the planet, and it is incumbent on the international community to make its eradication a priority. But only by understanding the full scope of potential negative consequences of such a gene drive response can it be properly evaluated against alternative ways of preventing the spread of malaria.

Monitoring and detecting ecosystem consequences, including the spread of gene drives beyond national borders presents a raft of difficulties – including the technical ability to identify the presence of a gene drive in a natural population. The greater challenge may be identifying any population decline and isolating gene drive as a cause (particularly when a gene drive has passed on to a non-target species).

## 2.5 Should Gene Drives Fail

From a risk perspective, it is also prudent to factor in the possibility that gene drive technology and/or a particular gene drive release may simply not work as intended – a scenario that carries its own ecological, societal and economic risks and costs.

This possibility arises because of the technical challenges of engineering gene drives as well as the complexity of species they are targeting, and the ecosystems they are to be released into – "challenges [that] should not be underestimated."[86]

The development of genetic resistance to the gene drive within a target species is the most commonly cited failure scenario and has been judged "inevitable"[87]. Indeed, it is rated as a "severe limitation to the effectiveness of current CRISPR gene drive approaches, especially when applied to diverse natural populations."[88]

There are several mechanisms by which resistance may develop within a species. Genetic diversity within a target species is one that "could have wide-ranging and sometimes severe consequences on the efficiency of drive propagation in a wild population"[89].

[85] Krebs C. 2014. Rodent biology and management. In: *Integrative Zoology* 2014 (9), p. 230.
[86] Australian Academy of Science. 2017, *Synthetic Gene Drives in Australia: Implications of Emerging Technologies,* p. 6.
[87] Unckless R L, Clark A G and P W Messer. 2016. Evolution of resistance against CRISPR/Cas9 gene drive. *Genetics:* Early Online.
[88] Champer J, Reeves R, Oh S Y, Liu C, Liu J, Clark A G and P W Messer. 2017. Novel CRISPR/Cas9 gene drive constructs reveal insights into mechanisms of resistance allele formation and drive efficiency in genetically diverse populations. PLoS Genet 13(7).
[89] Drury D W, Dapper A L, Siniard D J, Zentner, G E and M J Wade. 2017. CRISPR/Cas9 gene drives in

A further scenario for failure arises from the technique itself. It is plausible that the target organism's cells repair the cuts made in the DNA to introduce the gene drive trait in ways that are not recognisable by the CRISPR system, bringing the gene drive to a halt.[90] Some researchers consider this the most likely route to the evolution of resistance.

Proposals to overcome resistance (releasing several gene drives targeting the range of genetic variants within a population or species; targeting genetic locations in a species that tend to be less variable across the population; or attempting to shut down other DNA repair systems in an organism[91]) are biologically and technologically complex and their efficacy cannot be guaranteed. Resistance may still evolve despite these efforts.[92] Similarly, the potential for so-called off-target effects remains.

### *Persistence, mutation of failed gene drives*

Some potential consequences of a failed gene drive release are similar to the effects of a gene drive release that does not perform as intended. Even with limited effect on a local population, the gene drive trait could still persist and spread "around the world", developers predict.[93] Further, the foreign genetic material may mutate, bringing about unpredicted and unpredictable biological changes that are broadcast through a wild species.[94]

## 2.6 Concluding

The above has provided an overview of what might be called the generic technological risk landscape and focuses on the ecological risks arising from the technology. Clearly, the spectrum, nature and severity of the potential impacts will depend on what species gene drives are targeted at, and for what purpose. Agricultural gene drive applications, for example, may have a set of impacts that are largely distinct from those arising from other applications. Further, the reverberations of ecological effects will extend well beyond non-human communities and could have profound economic, social, ethical and cultural impacts on certain human communities.

As significant as the ecological implications of gene drive are, these are not the only governance challenges the technology presents society.

genetically variable and nonrandomly mating wild populations. ci. Adv. 2017;3:e1601910

[90] Callaway E. 2017. Gene drives thwarted by emergence of resistant organisms. *Nature,* 542:15.

[91] Australian Academy of Science. 2017. *Synthetic Gene Drives in Australia: Implications of Emerging Technologies,* p. 6.

[92] Unckless R L, Clark A G and P W Messer. 2016. Evolution of Resistance Against CRISPR/Cas9 Gene Drive. *Genetics,* p. 3.

[93] Hesman Saey T. 2017. Resistance to CRISPR gene drives may arise easily. *ScienceNews,* July 20.

[94] Ledford H. 2015. CRISPR, the Disruptor. *Nature* (522), p. 24.

# 3. The Governance Challenge

A technology that confers the ability to rapidly eliminate or reengineer entire species that have evolved over millions of years poses profound ethical and governance challenges for societies and the global community.

In this chapter, we review some of those governance challenges, including: ethical issues around wild species extinction and modification; distributive justice and the risk that the costs of gene drive projects will disproportionately fall on vulnerable communities; and the need for deep and broadly framed societal discussion about technology pathways.

The weightiness of these challenges does not diminish the imperative for proper governance in the form of binding regulation, but underscores that regulatory processes alone are not sufficient to confront the issues gene drive presents.

## 3.1 A "Constitutional Moment"

Human societies have long sought to control species that have threatened harvests, caused disease, or predated on native species. Gene drive, however, is not a mere addition to or extension of those efforts. Indeed, in both its ambition and its potential for severe unintended or unanticipated outcomes, the technology precipitates what has been called "a constitutional moment".[95] We refer here not to the codified constitutions of nation states, which set down the fundamental principles by which a country is governed through the rights of individuals and the limits of state power. We mean here a constitutional moment that is both civilisational and ecological in its dimensions, and brought about by the prospect of a technology that radically exceeds the existing boundaries of human power over nature. It is that technological power surge that propels society to examine its relationship to, and interdependence with, other species in the biological community and the biosphere. "An ethical debate on the right of humans to domesticate almost any species is needed", urge Orzogozo and colleagues.[96]

The fundamental ethical question that gene drive presents society is this: under what circumstances, if ever, it is acceptable to deliberately wipe a species off the

[95] The term, originally used in respect of science and technology by Sheila Jasanoff in 2003 and has been put forward by Jennifer Kuzma of North Carolina State University and picked up in a publication edited by Iva Braverman. Jasanoff S. 2003. In a Constitutional Moment: Science and Social Order at the Millennium. In: Joerges B and H Nowotny (eds) *Social Studies of Science and Technology: Looking Back, Ahead. Sociology of the Sciences,* vol 23. Springer, Dordrecht; Kuzma J. 2016. Governance for Gene Drives in Historical and Systems Context. Presentation to an OECD-sponsored workshop on 'Environmental Release of Engineered Pests: building an international governance framework'. North Carolina State University, Raleigh, October 5-6. Braverman I (ed). 2017. *Gene Editing, Law, and the Environment: Life Beyond the Human.* Routledge Press.

[96] Courtier-Orgogozo V, Morizot B and C Boëte. 2017. Agricultural pest control with CRISPR- based gene drive: time for public debate. Should we use gene drive for pest control? *EMBO Reports* 18(6), p. 880.

face of the earth? Hochkirch and colleagues put it clearly. Accepting the moral imperative for eliminating diseases such as malaria:

> "What determines the value of species and which legal instruments provide the basis to depart from conservation and turn towards eradication? Is there any threshold of impact a species must pass to fall under the human verdict of eradication? And, are there environmentally more friendly methods available to successfully control a vector or disease without eradicating it?"[97]

The question in the case of some proposed gene drive applications goes further: whether it is legitimate to wipe out the vector of the disease in order to target the disease.

Intrinsic value – "that each species may have a right to exist, independent of its value to human being"[98] - lies at the heart of this question. At a minimum, it prompts serious consideration of alternative methods for achieving societal goals, such as preventing disease and protecting biodiversity.

At bottom is a question that three French academics have usefully explored more deeply: what constitutes a pest?

> If manipulating other species to our benefit sounds at first like a humanitarian project, we should keep in mind that gene drive can also be used to serve the economic interests of particular groups with little concern for the general interest. There is no such thing as a "pest" *per se*: a population is only a pest with respect to specific interests, which does not mean these interests are illegitimate, only that they are *relative*. The species some call 'pests' may be the pollinators and the food of others species or may play an important ecological role for the local economy. [99]

Absent regulation, they argue that commercial incentives would deliver high-risk outcomes:

> Given the lack of reliable modeling, it is safe to assume that normalizing the use of CRISPR-based gene drive could lead to an ecological cacophony: every interest group in the agro-food industry editing the genome of those they call pests, spreading various mutations through gene drive, and causing long-term effects on the ecological dynamics of ecosystems—and on the human populations depending on them.
>
> One of the main concerns over gene drive is its potential long-term effects. The designated effects on the targeted populations will be fast—within a few years—while long-term effects on ecosystems may take decades to appear and are extremely unpredictable. The time frame of gene drive perfectly fits the economic development strategies dominant today in agribusiness, with a focus on short-term return on investments and disdain for long-term issues. The current economical system based on productivity, yields, monoculture, and extractivism is a perfect match for the operating mode of gene drive.

[97] Hochkirch A, Beninde J, Fischer M, Krahner A, Lindemann C, Matenaar D, Rohde K, Wagner N, Wesch C, Wirtz S, Zink A, Lötters S, Schmitt T, Proelss A and M Veith. 2017. License to Kill? – Disease eradication programs may not be in line with the Convention on Biological Diversity. *Conservation Letters.*

[98] Ibid.

[99] Courtier-Orgogozo V, Morizot B and C Boëte. 2017. Agricultural pest control with CRISPR- based gene drive: time for public debate. Should we use gene drive for pest control? *EMBO Reports.*

They also stress the need to consider how early examples of gene drive for purposes that stand a better chance of attracting public support could lead down a dangerous path:

> the eventual success of such a strategy against human pests [mosquitoes] might become a Trojan horse to legitimate gene drive to control diverse pests without questioning to whom or to what they are harmful.

In addition to the weighty question of intrinsic value, other ethical considerations loom large. These include the acceptability of using powerful technologies whose consequences are difficult to predict or control and which may have severe unintended impacts on certain communities, even as the technology might deliver benefits for others. Together, this suggests that while public good outcomes may form a greater moral imperative, it does not diminish the fundamental challenge, which is the acceptability of eliminating or permanently changing the genetics of an entire species. Instead, as above, the imperative is to fully explore the feasibility and relative efficiency of other methods.

## Technological uncertainty, ignorance and humility

Humility has been advocated by many science and technology commentators when faced with scientific uncertainty from new technological capabilities.[100] Humility may seem a soft currency when set against the bodies of knowledge typically called upon to inform decisions about technological risk and the clarity of purpose a new technology is directed to (disease prevention). Yet humility is a mature scientific reflection on the limits of human knowledge and control – a means of "accommodating the partiality of scientific knowledge and for acting under the inevitable uncertainty it holds".[101]

The immense and converging pressures that the biosphere is now experiencing (in the domains of climate, biodiversity, pollution and waste, water scarcity, among others) should encourage great caution in respect of a technology with the potential for far-reaching unforeseen consequences. Even as gene drive technology is proposed to tackle biodiversity loss, it has emerged during the sixth major species extinction event on the Earth[102], which has been described in its scale as "biological annihilation" and considered to be largely caused by human activity.

Hubris awaits if the limits of knowledge and control are not recognized. And there is, unfortunately, no shortage of past examples of unforeseen, severe ecological harm accompanying the deliberate introduction of alien species, and no shortage of events where limited understanding of a technological advance has had profound consequences.[103]

[100] See for example, Courtier-Orgogozo V, Morizot B and C Boëte. 2017. Agricultural pest control with CRISPR- based gene drive: time for public debate. Should we use gene drive for pest control? *EMBO Reports* 18(6): 878-880.

[101] Jasanoff S. 2007. Technologies of humility. *Nature*. 450: 33.

[102] Ceballos G, Ehrlich P E and R Dirzo. 2017. Biological annihilation via the ongoing sixth mass extinction signaled by vertebrate population losses and declines. *PNAS* 114 (30).

[103] Harremoes P, Gee D, MacGarvin, Stirling A, Keys J, Wynne B and S G Vaz (eds). 2002. *The Precautionary Principle in the 20th Century: Late Lessons from Early Warnings.* European Environmental Agency. Earthscan Publications.

## 3.2 Gene Drives and Distributive Justice

The social, economic and cultural implications of gene drive technology loom large for communities and countries located far beyond a release site, as well as those within its intended range. Certain communities - particularly those, which are economically vulnerable or have little political influence – may feel those impacts the most but may have little standing in decisions about gene drive releases.

The emerging geography of gene drive technology heightens this potential for distributive injustice. Characterised as a "global endeavour"[104], the technology system tracks well-trodden North-South divides. Gene drive development, along with its intellectual property and funding streams, are currently circulating and accumulating predominantly in the Global North, with the US dominating the landscape. Key patents are held by US researchers and institutions and the bulk of R+D funds are being provided by US military interests and billionaire philanthropists.[105] Use of the technology is likely to occur in other countries,[106] including those that have not developed the technology or might have inadequate regulatory and other governance provisions in place. Projects such as the Genetic Biocontrol of Invasive Rodents (GBIRd) is one such example, where research institutions from the US, New Zealand, and Australia are developing gene drive rodents, but trials and later release are envisioned for a greater number of countries. This dominance of control, unless counterbalanced properly in international governance arrangements and other ways, could see certain interests dictating technology pathways to other communities and parts of the world.

It is not only deliberate technology export that could affect the Global South but the unintended spread of gene drive releases in the North. For example, gene drive has been proposed as a way of eliminating Palmer Almaranth, a significant agricultural weed in the US, but which can interbreed with a related species which is grown for food in Central America, Africa, India and China.[107] Similarly, in Australia, gene drive has been mooted to tackle barnyard grass (*Echinochloa colona*), which poses real challenges for Australian farmers but is highly prized in India, where seeds of the grass are grown for a dish consumed on festival fasting days.[108] It is easy to foresee that without proper governance, the interests of more powerful countries (and sectors within them) will prevail.

The nature of distributive justice issues will depend on a specific gene drive proposal but there is potential for these to be significant and any assessment of gene drive technology must properly account for the harm that could fall on different communities, cultures and countries. More fundamental, however, is the question of choice of technology pathways, and which communities get to determine them.

[104] US National Academy of Science. 2016. Gene Drives on the Horizon, p. 151.
[105] Regalado A. 2016. Bill Gates Doubles His Bet on Wiping Out Mosquitoes with Gene Editing. *MIT Technology Review,* September 6.
[106] US National Academy of Science. 2016. *Gene Drives on the Horizon,* p. 151.
[107] Ibid*.,* p. 53.
[108] Australian Academy of Science. 2017, *Synthetic Gene Drives in Australia: Implications of Emerging Technologies*, p. 7.

## 3.3 Self-Regulation Inappropriate

The general retreat from regulation and biotechnology's rapid rate of invention has left much to be self-regulated, allowing those undertaking the activity to determine the level of protections and accountability they are prepared to provide. This is particularly the case in the US – the home of genetic engineering and where patents are held for the prime tool used to carry gene drives. There, regulatory authority has withered to the point that for gene drives "[i]n place of state regulations, what seems to be emerging is a form of self-regulation by the gene drive scientists themselves" as "… the responsible scientist also ends up representing the public interest in place of the incompetent state".[109]

While developers may not have been the authors of the deregulatory zeal of recent decades that led to more dependence on self-regulation, and scientists have been among those calling for effective gene drive governance, there is still a strong self-regulation culture, which varies in its expression.

In a paper reviewing the findings of an international workshop directed at assessing the security implications of genome editing, there is mention of gene drives as a special risk but no separate remedy proposed to meet this, and the essential recommendation offered is:

> Committing to self-regulation, while minimizing bureaucracy, helps to address a common concern within the scientific community that additional governance measures would hamper responsible research without diminishing the likelihood of intentional misuse.[110]

The inference from local gene drive developers, for example, is that while universal drives require global governance, their technology does not.

A self-regulation model that places scientists and those who commercialise the work at the heart of decision-making is simply not appropriate when gene drive is recognised as having the capacity to do serious harm to the global environment. The public interest in its public estate is too great to be subjugated to the judgement of private actors.

[109] Braverman I. 2017. Gene Drives, Nature, and Governance: An Ethnographic Perspective, in Braverman I (ed). 2017. *Gene Editing, Law, and the Environment: Life Beyond the Human.*

[110] Fears R and V ter Meulen. 2018. Assessing Security Implications of Genome Editing: Emerging Points From an International Workshop, *Frontiers in Bioengineering and Biotechnology,* March 28.

### 'Local Consent' is a Form of Self-Regulation

Some developers are proposing 'local consent' as sufficient for gene drives that are engineered to have a narrow geographical range and limited life span. That is, the ultimate decision-makers are the communities within the intended ecological range of the drive. For example, MIT developers working on a gene drive mouse to prevent transmission of Lyme disease to humans - a serious affliction for communities in certain parts of the US - and has set up a project with locals on the islands of Nantucket and Martha's Vineyard.[111] Independent boards govern the project and the scientists have stated that they will accept the community's decision, if it goes against pursuing gene drive.

While the tip to local democracy is welcome, in bringing the community into decisions about the science, gene drive is simply not suited to a local consent model:

- The proposition rests upon the assumption that the drive will reliably terminate before it reaches too far (an aspiration that has yet to be demonstrated and could have a high cost if it proves to be wrong)
- The idea that island geographies offer sufficient containment for gene drive organisms has been dismissed, so a project designed to be local could go national, if not global, and would need governance to match.[112]

## 3.4 The Need for Open-ended Constitutional Conversations

This study advocates for the international governance of gene drive technologies, and specifically for all affected countries to be party to decisions about gene drive releases. However, ensuring that nation states have a seat at the table will likely be insufficient on its own to provide proper democratic governance over a technology with significant ethical, intergenerational ecological and distributive justice implications. Essentially, the consensus required about the place, use or avoidance of this technology should not be constrained to nation states but must also be secured within and across communities.

It is not the purpose of this report to set out in detail how this should occur, as that will be best determined in consultation with those communities. We do, however, underscore, as do other commentators, that if the oft-stated pledges to democratize science and to earn a social licence are made in earnest, this will require: 1) moving beyond standard consultation that takes place after a technology pathway has been selected by developers and sponsored by governments, and 2) an open-ended enquiry into societal values and goals and which technology paths are best to achieve those.

[111] Bouchard S. 2017. Gene 'editing' on mice tested in war on ticks. *The Working Waterfront,* Island Institute. November 17.

[112] Ad Hoc Technical Expert Group on Synthetic Biology. 2017. Report. Montreal Canada. 5-8 December. CBD/SYNBIO/AHTEG/2017/1/3, para 51(b).

### *"Constitutional conversations"*

For gene drives, simply consulting with the public about the desirability and acceptability of using gene drives within the confines of a regulatory risk assessment process that many countries have adopted as part of their GM regulatory regimes will not be sufficient. Such consultation, when done with real agnosticism to the outcomes, has its place but in practice is often performed and/or experienced as a check-box exercise. It also significantly curtails public involvement in the choice of technology pathways and can silence certain communities because:

- It privileges specialised knowledge and creates barriers to public involvement through resourcing and expertise requirements. As such, it does not ensure due representation.
- Formal public consultation processes also tend to circumscribe what analysis and perspectives are acceptable and "may not admit novel viewpoints, radical critiques, or considerations lying outside the taken-for-granted framing of the problem"[113].
- It comes "too late to identify alternatives to dominant or default options"[114]. In many countries, GMO regulatory approval processes invite public participation only once a GMO is ready for trialling or release in the environment, by which time significant political, financial and institutional investment has been channelled into that product. For this reason, consultation is typically an exercise in working out whether the proposal on offer meets basic hurdles, rather than a genuinely open consideration of options. As Stirling notes, "regulatory appraisal is mainly about justifying policy".[115]

How to address these questions properly within and across societies is a significant challenge and will require "a new architecture for democratic debate"[116], but there is a wealth of experience on participatory decision-making to draw upon and some promising proposals for how to move this forward for new era genetic engineering technologies.[117]

### *Open-ended enquiry*

What is clear is that properly democratising science decision-making will involve much more than simply asking communities whether one or another gene drive

[113] Jasanoff S. 2003. Technologies of Humility: Citizen Participation in Governing Science. *Minerva:* 41, p. 238.
[114] Ibid., p. 237.
[115] Stirling A. 2016. "Challenges in the Governance of Engineered Life: research policy, innovation dynamics and the politics of progress." Presentation to an OECD-sponsored workshop on 'Environmental Release of Engineered Pests: building an international governance framework'. North Carolina State University, Raleigh, October 5-6.
[116] Burall S. 2018. Don't wait for an outcry about gene editing. Comment. *Nature* (555): 438-439.
[117] Jasanoff and Hurlbut propose a global observatory for gene editing, which would constitute an international network of scholars and organizations with a goal of helping determine how the potential of science can be better steered by the values and priorities of society. Proposed roles of the observatory would include 1) providing a clearinghouse for the global range of ethical and policy views on gene editing; 2) tracking and analysis of developments around gene editing and responses to these; and 3) convening meetings and seeding international discussion. Jasaonoff S and J B Hurlbut. 2018. A global observatory for gene editing. *Nature* 555: 435-437.

application is acceptable. Meeting the constitutional moment that gene drive technology generates will require what has been called "constitutional conversations"[118], where communities can deliberate about societal values and goals and explore the range of pathways (technological or otherwise) to achieve these.

To be clear, it is not simply a question of developers and proponents talking to communities early as a step along a pre-ordained technology pipeline. Further, developers will need to relinquish the 'deficit model' mindset that has typified science establishment attitudes towards the public on questions of science and technology: namely, that the public is scientifically illiterate; that pushback against technologies is simply a failure in communications; that lay qualms about new technologies are generally misguided; and that consultation is an exercise in 'education' that will deliver the intended result: public backing for a specific technological pathway.

Proper deliberation on the technology will need a commitment from governments and the science community to open such conversations before significant political and economic commitments have been made to gene drive or specific applications, so that communities are involved at "the front-end of scientific and technological production – a place from which they have historically been strictly excluded."[119] It will mean science institutions need to be open to responses from communities that might be unwelcome: for example, that use of the technology might not be acceptable in some, many or all cases and that other methods to achieve a certain outcome are preferred.

While the prospect may seem daunting, commitment to such a process should contribute – alongside dispassionate risk assessment – to deeply considered technology choices that are backed by an involved, supportive citizenry.

[118] Hilgartner S. 2018. Afterword: Governing Gene Editing. A Constitutional Conversation. In: *Gene Editing, Law, and the Environment: Life Beyond the Human.* Irus Braverman (ed). Routledge Press.
[119] Jasaonoff S and J B Hurlbut. 2018. A global observatory for gene editing. *Nature* 555: 435-437.

# 4. Fundaments of Gene Drive Governance

The imperatives for international governance of gene drive release have been identified by academics, research institutions and civil society (see section 1). The power of the technology makes unilateral decision-making inappropriate and the international community will be required to step up to meet the governance challenge.

This chapter outlines principles and essential elements for a governance framework, including: consensus decision-making, precaution, governance of all stages of development, comparison against alternatives, availability of appropriate risk assessment tools, monitoring, and liability.

## 4.1 Collective Consent

As gene drives are purpose-built to spread through ecological niches and these may well not coincide with political borders, affected parties beyond the country of release have a stake in any release decision.

Gene drive developers Esvelt and Gemmell consider permission from affected countries to be essential. They put the issue squarely: "Do we want a world in which countries and organizations routinely and unilaterally alter shared ecosystems regardless of the consequences to others?" As they observe:

> moving forward without the permission of every other country harboring the target species would be highly irresponsible. Even assuming that national sovereignty is morally irrelevant, the social and diplomatic consequences of an unconstrained release should give us pause. [120]

Other authors join this call, stating that "regulatory approval must be obtained from every country that would be affected by an eventual deployment."[121]

"Collective consent" is a concept that recognises that decision-making for certain activities should involve all affected parties. It has been advocated for other new technologies that have been identified to carry population-wide effects (including novel medical treatments such as xenotransplantation):

> The risks […] potentially include the whole community and, as such, individual consent […] is insufficient. [...] There is an argument that if it is unethical to subject individual patients to procedures, which they have not consented to, then it is also unethical to subject the public to risks […] without having obtained collective

[120] Esvelt K M and N J Gemmell. 2017. Conservation demands safe gene drive. PLoS Biol 15(11): e2003850. Note that Esvelt and Gemmell's argument for international consensus decisions on gene drives appears to apply to so-called self-replicating or universal gene drives and not necessarily to so-called self-limiting gene drives. However, as the authors acknowledge, the self-limiting functions have yet to be demonstrated and it is our view that a precautionary approach requires all gene drives, irrespective of the mechanism, to be subject to international governance.

[121] Min J, Smidler A L, Najjar D and K M Esvelt. 2018. Harnessing gene drive, Journal of Responsible Innovation, 5:sup1, S40-S65.

consent.[122]

Collective consent has also been used in the health sector to reflect the different cultural values and approaches to decision-making and permission-giving, for example amongst indigenous communities, where the focus on individuality may be inappropriate.

At the intergovernmental level, collective consent is best implemented through each nation holding the right for its approval to be required for a gene drive release in another jurisdiction that could impact upon its territory, directly or indirectly.

At first glance, this may seem to impose a significant restraint on a country's ability to determine the use of gene drive technology. It is, however, the application of a principle already well grounded in the governance of international environmental commons: states must act as members of a linked and interdependent community, and so accept constraints on their sovereignty that are required for successful co-management.[123]

The United Nations Convention on Biological Diversity (CBD) itself firmly adjudicates the balance between the rights and responsibilities of states with respect to biodiversity. Article 3 sets down a fundamental principle that the international community adopted for the treaty:

> States have, in accordance with the Charter of the United Nations and the principles of international law, the sovereign right to exploit their own resources pursuant to their own environmental policies and **the responsibility to ensure that activities within their jurisdiction or control do not cause damage to the environment of other States or of areas beyond the limits of national jurisdiction**. (Emphasis added)

The principle that states have a responsibility to ensure that activities within their jurisdiction or control do not cause damage to the environment of other states has been described as a principle of customary international law and is affirmed also in a number of other International Agreements including the 1972 Stockholm Declaration, 1992 Rio Declaration, and the Convention on the Law of the Sea.[124]

Other international environmental agreements under which states agree to forego the use of particular technologies, or apply internationally set standards for them, include the UN treaty on Persistent Organic Pollutants (which bans the use of listed substances) and the Montreal Protocol (under which all parties agree not to use certain ozone-depleting substances, nor to import them from countries not party to the agreement).

---

[122] New Zealand Health and Disability Commissioner. 2005. Submission on the Bioethics Council discussion document, The Cultural, Spiritual and Ethical Aspects of Xenotransplantation: Animal-to-human Transplantation, p. 5.

[123] Kiss A and D Shelton. 2007. Strict Liability in International Environmental Law. In: Ndiaye T M and R Wolfrum (eds). *Law of the Sea, Environmental Law and Settlement of Disputes: Liber Amicorum Judge Thomas A Mensah.* Brill Academic Publishers.

[124] See, for example, the discussion of International Court of Justice decisions in Marte Jervan "The Prohibition of Tansboundary Environmental Harm, An Analysis fo the Contribution of the International Court of Justice to the Development of the No-harm Rule", although the author of this paper notes that the legal status of the principle is not without controversy.

## Global Regulator Not Appropriate for Gene Drive Decisions

The inherent transboundary risk associated with gene drives also raises the question of whether governance should be placed with a global regulator, rather than each country making an assessment. The potential benefit of such an arrangement is that a global regulator could look at the overall pattern of benefits and if they were sufficient, determine that a release should go ahead even if it generated lesser negative effects in certain nations.

However the creation of such a regulator would depend on there being trust that the institution would not be captured by any particular nation or groups, would be consistently and sufficiently funded, and would have adequate assessment tools. There are grounds for reservations on each of these counts, based on the experience of other global bodies. More problematic is that its existence would depend on governments of the world supporting its utilitarian ethos and giving away their right to decide themselves on any particular gene drive release proposal – including ones that would have a negative impact on their individual territory.

Governments are beginning to understand that they may have no choice but to cooperate on climate change responses that will have uneven distributional impacts, as there is no alternative in many cases. But where gene drive is just one method for achieving outcomes, and alternatives don't pose nearly the same risk profile, there may be no obvious net gain globally (and so no compelling benefit to persuade governments to give up their current rights). The appropriate decision making structure at this time at least remains one in line with the Cartagena Protocol framework - leaving each state the right to decide on the merits of any release that would risk damaging its territories.

An international treaty governing genetically modified organisms – the Cartagena Protocol on Biosafety – aligns with both the CBD principle and the collective consent model by requiring a country intending to export GMOs to gain the prior consent of the proposed recipient country. That right of advance informed agreement, applying to intended shipments, is exercised at the border.

Environmental release of gene drives differs from conventional GMOs in that the appropriate point of control for this unintended export is not the border, but the point of release - where the risk of transboundary movement originates. This distinguishing feature of gene drive technology requires a revised interpretation of the principle of prior consent to reflect the fact that the control point must be when a release is being contemplated in another country, not after the fact. In other words, those proposing a release should be required to seek the prior consent of those nations that are vulnerable to the effects of a gene drive GMO in another jurisdiction or to the flow on effects of a gene drive release elsewhere.

For decision-making via collective consent to be accepted by the international community, there would likely need to be some grounds for determining whether a country or other stakeholder is eligible to participate in decisions about releases of gene drive organisms in another state.[125] There are complex issues to resolve in

[125] Norwegian Biotechnology Advisory Board. 2017. Statement on Gene Drives. February 14: "It will be important to include various stakeholders in the discussions on the use of gene drives. However, it may be difficult to define who these should be. Which groups are affected geographically, and is it

order to devise rules for participation and these are discussed in section 6.2, while section 4.2 addresses what type of activities should be covered by international governance.

## 4.2 Precaution

The precautionary principle has become the internationally agreed response to scientific uncertainty and ignorance. This approach is well warranted for gene drives: "systems anticipated to evolve outside of our control", and systems for which humanity has no experience.[126]

The principle first gained recognition in international law in 1987 when the Second International Conference on the Protection of the North Sea agreed that the discharges of substances that are "persistent, toxic and liable to bioaccumulate" should be prevented at source, "even where these is no scientific evidence to prove a causal link between emissions and effect".[127] It subsequently gained a more formal definition when set out in the Rio Declaration in 1992:[128]

> Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation.

A European Environment Agency review of past unpleasant surprises from technology drew lessons for regulators from these case studies in support of adoption of the precautionary approach.[129] It describes the principle in the following terms:

> The precautionary principle is an overarching framework of thinking that governs the use of foresight in situations characterised by uncertainty and ignorance and where there are potentially large costs to both regulatory action and inaction.

The principle lies at the heart of the international governance of GMOs and their transboundary movement, which is regulated under the Cartagena Protocol (further described in section 5.2).[130] It is also central to Euopean GMO regulaiton.[131] The grounds for its application to biosafety in general are clear and include the:

- Potential irreversibility of effects arising from living GMOs;
- Capability for living GMOs to spread across borders;
- Potential scale and scope of the effects; and
- Likelihood of unexpected impacts from novel technologies.

necessary to be directly affected to be heard?"

[126] Esvelt K M and N E Gemmell. 2017. Conservation demands safe gene drive. PLoS Biol 15(11): e2003850.

[127] Thornton J. 2000. *Pandora's Poison: Chlorine, Health and a New Environmental Strategy*, p 344;

[128] Principle 15 of the Rio Declaration on Environment and Development (the Rio Declaration).

[129] *The Precautionary Principle in the 20th Century,* European Environment Agency, March 2002, p 187.

[130] The protocol puts the precautionary principle into operation in Articles 10(6) and 11(8).

[131] Court of Justice of the European Union, 25 July 2018, Case C-528/16 http://curia.europa.eu/juris/document/document.jsf?text=&docid=204387&pageIndex=0&doclang=EN&mode=req&dir=&occ=first&part=1&cid=783263

As gene drive orgnaisms have the potential to carry significantly greater risks, the case for applying precaution is stronger still.

## 4.3 Governance of All Stages of Gene Drive Development

### *Environmental Release*

International governance must cover all outdoor uses of gene drives, including field trials. Indeed, field trials involving gene drives should be regarded as releases. Firstly because of the potential for severe consequences should a gene drive organism escape: "initiating contained field trials," warn Noble at al, "[…] could potentially result in unintended spread to additional populations"[132] while Simon et al point out, "releasing even some individuals can be considered a full release". As such, trials of universal drives (and we would argue, local gene drives at this point) contradicts the whole rationale of a field trial.[133]

Further, the outdoor field trialling of organisms is prone to breaches of containment controls. The number of incidents involving experimental GMOs contaminating food products demonstrates the risks of accidental release from experimental activities. These incidents, which have thus far been restricted to agricultural GMOs, have exacted a huge toll on affected sectors and their supply chains.[134] Notably, such events have occurred under regimes with strict controls on the conduct of outdoor field trials.[135]

Indeed, the notion of field trialing needs to be reconceptualised for gene drives because, as the NAS notes (despite its cautious advocacy for phased trialing process), attempts at containment may be 'irrelevant' in some cases:

> Gene drives do not fit well within the existing regulatory logic of confinement and containment because they are designed to spread a genotype through a population, making confinement and containment much more difficult (or even irrelevant) and the environmental changes introduced by release potentially irreversible.[136]

Some gene drive organisms may be more amenable to physical containment than others. However, outdoor trials of certain species – such as insects – will always present high levels of risk of escape beyond the trial site.

---

[132] Noble C, Adlam B, Church G M, Esvelt K M and M A Nowak 2018. Current CRISPR gene drive systems are likely to be highly invasive in wild populations. *eLife* 2018;7:e33423.

[133] Simon S, Otto M and M Engelhard. 2018. Synthetic gene drive: between continuity and novelty. *EMBO reports* 19: e45760.

[134] Contamination by experimental GM wheat, rice and flax has had significant impacts on North American farmers. The "Triffid" flax contamination of Canada's flax industry is a standout, requiring close to a decade to eliminate the unauthorised GM flax from seed stocks and collapsing Canadian flax exports to Europe.

[135] New Zealand has, by international standards, a relatively strict regime for field trials, which requires that reproductive material not be allowed to form on plants and that all heritable material is removed at the end of a trial. Despites this and that the fact that few trials have been conducted in New Zealand, there has been more than one breach of controls, involving a GM brassica. See Stevens P, Ashby N, Griffin W, Lewis D and I Ferguson. 2009. Internal review of procedures in relation to HSNO Act approval controls: ERMA Approval GMF06001 *Bt Brassica* Field Test. A report prepared for MAF – Biosecurity New Zealand. Plant & Food Research Report SPTS No 2146 Milestone number: 29581.

[136] US National Academcy of Sciences. 2016. Gene Drive on the Horizon,. 167.

As noted above, it is not appropriate to assume that use of attenuated gene drive systems – such as so-called daisy chain or local gene drives - can make safe the outdoor field trialing of gene drives because their efficacy has yet to be demonstrated, let alone their ability to perform reliably under environmental stresses.[137]

In consequence, anything beyond contained use must be subject to international regulation and treated as if it is a release.

### *Laboratory-contained Development*

Laboratory-contained R+D of gene drives is also not without risk. For example, Esvelt and Gemmell warn that with 'universal' gene drives:

> Even building such a construct in laboratory containment within a region harboring the target species poses the risk that an accidental escape might eventually affect everyone who shares an ecosystem with that species[138]

Containment standards for first generation agricultural GMOs may differ widely across countries. Simon et al advise that the safe handling of gene drives in containment requires attention, "since even a small unintended release can already lead to an extensive spread of the gene drive." As they note, biological security standards for research activities have been developed principally to manage pathogens, resulting in some protections that are unnecessary for gene drives while not delivering on safeguards needed to regulate contained use of the technology - environmental hazards in particular.[139] Further, previous incidences - such as breaches of anthrax from US military research centres testing defence systems against biological and chemical weapons[140] – underscore why standards should be agreed and adopted by the international community.

At a minimum, internationally agreed standards for containment, as advocated by the Ad Hoc Technical Expert Group on Synthetic Biology, should be developed to guard against accidental release of gene drive organisms as other countries are stakeholders in the management of such activities.[141]

## 4.4 Comparison Against the Alternative

Where an activity involves significant risk to the global environment, it is not sufficient to set what will be an arbitrary risk threshold and declare "safe" any proposal that clears it. Ultimately, gene drive will be just one of a range of possible options for delivering an outcome, whether in public health, conservation, food production or another sphere. Comparison against the alternatives is critical, as if an alternative approach that carries less risk can achieve the same outcomes then,

[137] Esvelt K M and N E Gemmell. 2017. Conservation demands safe gene drive. PLoS Biol 15(11): e2003850.
[138] Ibid
[139] Simon S, Otto M and M Engelhard. 2018. Synthetic gene drive: between continuity and novelty. *EMBO reports* 19: e45760 | 2018.
[140] Trevan T. 2015. Rethink biosafety. Comment. *Nature,* November 12. 527: 155-158.
[141] CBD. 2017. Report of the Ad Hoc Technical Expert Group on Synthetic Biology. Montreal, Canada, 5-8 December 2017.

other things being equal, the regulator should prefer the alternative. To this end, Simon et al recommend:

> a technology assessment approach that goes beyond mere risk assessment and that is generally not foreseen in legislation. On a basic level, this approach could discuss the appropriateness of the technique in comparison with other means to achieve the goal.[142]

The comparator to be set up in each case is known as the "least harmful alternative" or the "best practicable alternative" (BPA) and this concept is well established in regulatory practice.[143]

The discipline of considering the alternative is of course most appropriately applied at the outset, when first considering a gene drive as a possible response, and throughout any research and development. This guards against sinking investment into risky gene drive strategies if less harmful alternatives are available, or could be developed.

The Australian Academies of Science is among those advocating for decision-making that opts for the least harmful alternative:

> Such considerations should include a thorough and quantitative investigation of alternative methods to address the experimental problem. Not all problems that can be addressed by a gene drive modified organism should be: if there is an alternative available that will achieve the same outcome while presenting fewer hazards then it should be prioritised over new technologies.[144]

This approach has also been suggested for decisions involving GMOs that do not utilise gene drives: "the genetic or biological innovations with the lowest ecological risks" should be chosen and "genetically or biologically modified arthropods should be released into the environment only as a last resort."[145]

## 4.5 Risk Assessment

It is widely recognised that existing risk assessment models for GMOs are insufficient to address gene drives, due to the purpose of the technology, its novelty, and "the complexity of the potential impacts on the environment".[146] Directing genetic modification to engineer species in the wild is, scientists note, a fundamental "change in the spectrum of organisms and environments" affected, and one that will

[142] Simon S, Otto M and M Engelhard. 2018. Synthetic gene drive: between continuity and novelty. *EMBO reports* 19: e45760.

[143] For example, the federal guidelines for US floodplains and wetlands management requires that 'In all cases, the 'best practicable alternative' test must be met". Economic Development Administration Directives System. 1992. EDA Program to implement Execuive Orders 11988 "Floodplain Management" and 11990, "Protection of Wetlands" Directive No. 17.04.

[144] Australian Academy of Science. 2017. *Synthetic Gene Drives in Australia: Implications of Emerging Technologies.*

[145] Ostera G R and L O Gostin. 2011. Biosafety Concerns Involving Genetically Modified Mosquitoes to Combat Malaria and Dengue in Developing Countries. *JAMA* 305(9): 930-931.

[146] Convention on Biological Diversity. 2017. Report of the Ad Hoc Technical Expert Group on Synthetic Biology. Montreal Canada, 5-8 December.

challenge risk assessors.[147]

Broadly speaking, the issue is still at the stage of problem recognition. The US National Academy of Sciences recommends the adoption of a theoretical assessment model that it describes, as "the study and use of probabilistic decision-making tools to evaluate the likely benefits and potential harms of a proposed activity on the wellbeing of humans and the environment, often under conditions of uncertainty".[148]

However, others caution the extent to which "hypothesis-driven" modelling of gene drive impacts can reliably and accurately predict the nature and scope of real world outcomes of a release, saying this is limited because too little is known about the parameters that might affect the outcomes.[149]

As noted above, gene drives are likely to have significant and wide-ranging social, cultural and economic impacts, which should also be the subject of detailed assessment and inform decisions concerning any gene drive release, as the NAS also specifies:

> a comprehensive approach to the development and governance of gene-drive modified organisms will need to go beyond considerations for public health and the environment, and must also consider the benefits of technological innovation, the implications of intellectual property arrangements, public engagement, and economics, among other valued societal commitments.[150]

## 4.6 Monitoring

Monitoring systems would be required to:

- Track the movement of gene drive organisms and the potential spread of the trait through populations, and across borders and ecosystems; and
- Identify unintended, harmful impacts during and after a gene drive release programme that could lead to a change in or revocation of a gene drive approval.

A critical element of a monitoring programme would be the capability to detect the spread of gene drive organisms. The ready availability of detection methods should be a prerequisite for any gene drive development in the laboratory.

Detection of the gene drive construct itself should generally be possible and a test made publicly available as a condition of any release.[151] However, detection of the partial transfer of gene drives or unintended effects of the presence of the gene drive (functional or not) that could result in sublethal changes to populations may

[147] Simon S, Otto M and M Engelhard. 2018. Synthetic gene drive: between continuity and novelty. *EMBO reports* 19: e45760 | 2018. DOI 10.15252/embr.201845760.
[148] US National Academies of Sciences. 2016. *Gene Drives on the Horizon,* p. 9.
[149] Norwegian Biotechnology Advisory Board. 2017. Statement on Gene Drives. February 14.
[150] US National Academies of Sciences. 2016. *Gene Drives on the Horizon*, p. 9.
[151] Min J, Smidler A L, Najjar D and K M Esvelt (2018) Harnessing gene drive, Journal of Responsible Innovation, 5:sup1, S40-S65.

not be so readily detectable.[152] This concern applies to as yet theoretical approaches, such as so-called local or daisy-chain drive, and to successive releases of a range of organisms targeting the genetic diversity of a population/species (to overcome resistance). In these gene drive models, residual components may continue to be transmitted down through generations or across populations even when the full drive system is no longer active and is no longer capable of delivering the intended effect.

Such limitations on the reach of detection and monitoring must be clearly acknowledged if a gene drive release is contemplated and should reinforce the consideration of alternatives to gene drive technology that can achieve the desired outcome.

Monitoring should also be built into reviews of any releases that go ahead. If the successive release of gene drive organisms is likely, then monitoring for any unforeseen negative consequences will inform future decisions, including the potential cessation of a current release. Appropriate monitoring arrangements would need to be set in advance, in consultation with countries at risk of a cross-border gene drive incursion.

## 4.7 Liability

Arguably the greatest risks presented by a gene drive release are those to the global environment – to the public estate's biodiversity and to the health of ecosystems. While it may not be possible to fully rectify the harm that a gene drive release could impose on the public estate, it is imperative that the assumed cost of any damage is incorporated in the international governance regime and forms part of the decision making process. Without that, the risk of harm is not internalised and so not made a meaningful part of the assessment. It is instead externalised – removed from the count, and by default socialised rather than resting with the actors who propose undertaking the release and collecting its potential benefits.

Ensuring that those who stand to benefit are also fully exposed to the potential costs – and not just the private costs but also the public costs – is therefore critical to good decision making as well as fairness and sustainable governance. Anything less, particularly where the risks are significant, provides an uneven basis for alternatives to compete on, as gene drive would receive a form of subsidy relative to less risky options. And as that socialisation involves risks to the health of the global environment, rather than simply a financial subsidy, and the global environment is under significant stress, this reinforces the importance of liability not being attenuated by monetary caps and coverage gaps.

One example of strict liability for damage caused by a dangerous activity is the regime governing liability for oil pollution damage. The 1969 Convention on Civil Liability for Oil Pollution Damage reflects a consensus that:[153]

- The worldwide maritime carriage of oil in bulk poses danger of pollution;

[152] Simon S, Otto M and M Engelhard. 2018. Synthetic gene drive: between continuity and novelty. *EMBO reports* 19: e45760.
[153] International Convention on Civil Liability for Oil Pollution Damage 1969, preamble.

- There is a need to ensure that adequate compensation is available to persons who suffer damage caused by pollution resulting from the escape or discharge of oil from ships; and
- It is desirable to have uniform international rules and procedures for determining questions of liability and providing adequate compensation.

The 1992 Convention reflects these principles by providing for strict liability for damage for the shipowner, a fixed monetary cap for liability based on the ship's tonnage and requirements for insurance.[154] It also provides that the ship owner's entitlement to limited liability will not apply if it is proven that the damage resulted from the owner's personal act or omission, committed with the intent to cause such damage, or recklessly and with knowledge that such damage would probably result.

It is worth noting that the alternative to a negotiated agreement on liability for the release of dangerous substances under a state's control is a potential open-ended liability arising from the principle of international law noted above - that states have a responsibility to ensure that activities in their territory do not cause harm to other states.

There are a number of parallels between the risks associated with gene drive and with the carriage of oil, as both have the potential to cause large-scale and potentially irreversible damage to ecosystems. There are also, however, differences in that (given its ubiquity as an energy source) setting terms for the commercial carriage of oil had a presumptive benefit to all states; it meant that they could also ship or receive shipments of oil. Gene drive has no such presumptive general benefit, meaning that compared to carriage of oil, the case for capped liability is weak.

The release of gene drive may benefit one country, or one developer, but have negative environmental and economic costs in others who stand to gain nothing from the release. An international regime on release of gene drive ought to properly allocate the risk of negative consequences to those that promote the release (be it developers or states). As in the case of oil pollution this could be done by imposing strict liability and requiring minimum levels of insurance. Thus if any release is approved, it must be on condition that those operating the release are strictly liable for harm resulting from it, not just in the originating country but globally.

[154] International Convention on Civil Liability for Oil Pollution Damage, 1992; International Convention on the Establishment of an International Fund for Compensation for Oil Pollution Damage, 1992, and 2003 Supplementary Fund Protocol.

# 5. Existing International Agreements and Gene Drive

This section reviews existing international agreements for their suitability as a platform for building comprehensive gene drive governance. It then examines the Cartagena Protocol in greater detail as this treaty is targeted at the transboundary movement of living GMOs, and assesses the gaps it presents in relation to gene drives.

## 5.1 The landscape

International agreements relevant to the current and potential future regulation of gene drives include:

- The Convention on Biological Diversity (CBD)[155]
- The Cartagena Protocol on Biosafety (a protocol under the CBD)[156]
- The Nagoya Protcol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity (a protocol to the CBD)[157]
- The Agreement on the Application of Sanitary and Phytosanitary Measures (SPS)[158], administered by the World Trade Organisation
- The Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction (the Biological Weapons Convention, BWC)[159]
- The Environmental Modification Convention (ENMOD)[160], and
- Guidelines issued by the World Health Organisation (WHO)[161].

These agreements and instruments differ widely in their purpose, scope and the extent to which they could contribute to an international governance regime for gene drives.

The Norwegian Biotechnology Advisory Board notes, “none of the existing frameworks are ideal for regulating gene drives”.[162] However, analysis of these frameworks suggests that the Convention on Biological Diversity (hereafter the CBD) provides the framework that would be most naturally suited to inclusion of a governance regime for gene drive.

The other treaties and instruments identified above (and profiled briefly in box below) cover only some gene drive applications or a limited range of gene drive

[155] https://www.cbd.int
[156] http://bch.cbd.int/protocol/
[157] http://bch.cbd.int/protocol/supplementary/
[158] https://www.wto.org/English/tratop_e/sps_e/spsagr_e.htm
[159] https://www.un.org/disarmament/wmd/bio/
[160] http://www.un-documents.net/enmod.htm
[161] http://www.who.int/maternal_child_adolescent/guidelines/about-guidelines/en/
[162] Norwegian Biotechnology Advisory Board. 2017. Statement on Gene Drives. February 14.

release scenarios, and are not grounded on the principles needed to underpin gene drive governance.

This does not remove the imperative, nor the urgency, for the possible use of gene drives as biological weapons to be dealt with under the Biological Weapons Convention. Further, other international treaties could still prove a useful tool to respond to a gene drive release in some instances. In addition, as discussed in box 3, the SPS requirements might also offer assistance when a government looks to take steps to protect its territories from risks caused by gene drive.

However, a patchwork of possibly applicable conventions does not properly address the governance issues raised by the technology. Proper governance of gene drive requires a regime that is international, comprehensive and fit-for-purpose. The CBD and its protocols represent the best structure currently in place to house such a regime.

## Other Agreements Relevant to Gene Drive

### *The Sanitary and Phytosanitary Measures Agreement (SPS)*

The World Trade Organisation Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement) governs the use of sanitary and phytosanitary measures that may, directly or indirectly, affect international trade.[163] It entered into force in 1995 and is part of the multilateral trade rule system under the World Trade Organisation and has 164 member countries.[164] The agreement is aimed at preventing countries adopting unjustified barriers to trade disguised as health and safety measures.[165] That is, member states may act to protect human, animal or plant life or health pests, diseases, disease-carrying organisms or disease-causing organisms, but only as far as these measures meet standards set out under the Agreement and do not unjustifiably restrict trade, directly or indirectly.

The SPS Agreement has already been confirmed to cover GMOs through the landmark dispute led by the US against European Union rules governing GM crops (EC-Biotech). The Agreement has more recently been deemed by commentators (including the CBD Secretariat) to have some potential application to new genetic engineering technologies (including gene drives), should they, for example, be classified as pests, diseases, disease-carrying organisms or disease-causing organisms, and present a risk to human, animal or plant life or health among others.[166] The SPS Agreement recognizing, albeit weakly, the precautionary principle and scientific uncertainty (Article 5.7), allows States

[163] Agreement on the Application of Sanitary and Phytosanitary Measures, art 1, para 1.
[164] https://www.wto.org/english/thewto_e/whatis_e/tif_e/org6_e.htm
[165] See The WTO Agreements Series: Sanitary and Phytosanitary Measures (WTO, Switzerland, Revised 2010) at 10. See also Robert Cunningham "The ABC of GMOs, SPS and the WTO: an analysis of the application of the Agreement on Sanitary and Phytosanitary Measures within the context of biotechnology and international trade" Southern Cross University Law Review vol 9, p 19 at 24.
[166] Schiele, S., Scott, D., Abdelhakim, D., Garforth, K., Gomez Castro, B., Schmidt, L. and Cooper, H.D. 2015. Possible gaps and overlaps with the applicable provisions of the Convention, its Protocols and other relevant agreements related to components, organisms and products resulting from synthetic biology techniques. Part II of: *Synthetic biology*. Secretariat of the Convention on Biological Diversity. Montreal, Technical Series No. 82.

to introduce provisional measures until a proper risk assessment can be undertaken "within a reasonable period of time."

SPS, however, is silent on whether or not a particular risk should be accepted by any member state. It is concerned only with whether a protective measure (such as a prohibition on importation of goods that might harbour gene drive organisms) is justifiable. States set their own "Acceptable Level of Protection" or ALOP, and provided that the protective measures they put in place are consistent with their ALOP, are consistent with measures applied to like risks, and have a proper scientific foundation, then the measures are justified, and there is no right of recourse to the WTO for their imposition. SPS is concerned only with whether a state's regime for protecting against biosecurity risks arising from trade is functioning properly to protect risk, or whether it is an impermissible non-tariff trade barrier. Normative assessments of risks remain for states to determine.

### *The Biological Weapons Convention (BWC)*

The Biological Weapons Convention of 1975 prohibits the development, production, acquisition, transfer, retention, stockpiling and use of biological agents and toxins for non-peaceful purposes. There are 180 State Parties and 6 Signatory States.[167]

The Convention has been described as the "cornerstone of the bioweapons nonproliferation regime"[168] and considered an appropriate forum to address weaponised uses of gene drive[169]. Three review conferences to the BWC have confirmed that synthetically generated microbial or other biological agents or toxins are covered by the Convention. Among them, the 2006 Conference confirmed that "Article I [the prohibition on biological agents and toxins] applies to all scientific and technological developments in the life sciences and in other fields of science relevant to the Convention"[170]. New gene technologies have been discussed at several meetings of the State Parties in 2012 and 2013[171] and policy briefings on gene drive specifically occurred in 2014 and 2015. Despite this, there have been "no concrete steps towards the development of an oversight framework, guiding principles, or models to inform risk assessment and oversight of scientific research." There is no formal mechanism to deliver security risk assessments for new technologies such as gene drives. Further governance gaps include the absence of formal implementation and compliance measures within the Convention itself and the lack of mandate to respond to serious violations by member nations.[172]

---

167 https://www.unog.ch/80256EE600585943/(httpPages)/77CF2516DDC5DCF5C1257E520032EF67?OpenDocument

168 Lentzos F and G D Koblentz. 2016. It's time to modernize the bioweapons convention. *Bulletin of the Atomic Scientists,* November 4.

169 Tarini G and R A Zilinskas. 2016. Gene Drives: Panacea or Pandora's Box? *The Nuclear Threat Initiative.* November 21.

170 BWC/CONF.VI/6. 2006. Final Report of the Sixth Review Conference of the States Parties to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction.

171 Schiele S, Scott D, Abdelhakim D, Garforth, K, Gomez Castro B, Schmidt L and H D Cooper. 2015. Possible gaps and overlaps with the applicable provisions of the Convention, its Protocols and other relevant agreements related to components, organisms and products resulting from synthetic biology techniques. Part II of: *Synthetic biology*, p. 92.

172 Lentzos F and G D Koblentz. 2016. It's time to modernize the bioweapons convention. *Bulletin of the Atomic Scientists,* November 4.

The most recent five-yearly review of the Convention was considered to be a failure[173], as parties could not agree to a reform agenda. The next, in 2021, is an opportunity the parties must seize to bring use of gene drive as a biological weapon under the prohibition agreed by the global community and – just as importantly – to establish a moral consensus to underpin this.

### *Environmental Modification Convention (ENMOD)*

The ENMOD Convention prohibits the use of military or other hostile use of environmental modification techniques. Environmental modification "includes any technique for deliberate manipulation of natural processes – the dynamics, composition or structure of the earth, including its biota". The Convention arose from bilateral talks between the US and the USSR[174], and entered into force in 1978. There are 48 State Signatories (16 of which are still to ratify) and 78 State Parties.

There has been some interest in whether the Convention could provide governance over hostile uses of gene drive, however a number of factors suggest that the Biological Weapons Convention would be the more appropriate forum for this purpose. These include the high-threshold to trigger the provisions (the so-called troika of widespread, long-lasting or severe effects) as well as the Conventions' dormant state. Five-yearly conferences of the parties are specified under its rules, but the most recent review conference was held in 1992[175] and a call in 2013 by the Secretary-General of the United Nations to bring the parties together did not receive the necessary number of affirmative responses to convene a conference.[176]

### *World Health Organisation (WHO) Guidelines*

The World Health Organisation (WHO) is the principle international authority in the promotion and protection of public health. Established in 1948, it is governed by the World Health Assembly, made up of Member States, and the executive, under the Director General.

Applications of gene drive that would come under the general remit of the WHO include gene drives targeting human diseases - the most frequently discussed being a gene drive that would eliminate malaria-transmitting mosquitoes.

The chief instrument at the WHO's disposal are guidelines - non-binding instruments that set out recommendations for clinical practice or public health policy.[177] Guidelines are developed at the request of WHO country offices, external experts or other stakeholders ask for guidance and are approved by the Guidelines Review Committee following a consultative process involving WHO member states, experts, industry and civil society, depending on the nature of the guideline.[178]

[173] Rhodes C. 2017. Make the bioweapons treaty work. *Bulletin of the Atomic Scientists,* May 8.
[174] https://www.unog.ch/enmod
[175] https://www.unog.ch/80256EDD006B8954/(httpAssets)/639911CFE7D2087EC1257B82005B713A/$file/13-099nve.pdf
[176] https://www.unog.ch/80256EDD006B8954/(httpAssets)/6AE93F4C89FEF143C1257C740055C00B/$file/UNSG+NV+re+ENMOD.pdf
[177] http://www.who.int/maternal_child_adolescent/guidelines/about-guidelines/en/
[178] World Health Organisation. 2014. *Handbook for Guideline Development.* Second Edition, p. 4.

In 2014, the WHO issued guidance on the field trialling of genetically modified mosquitoes for malaria control, that makes reference to gene drives.[179]

A key deficiency is that while WHO guidelines may become international standards, these are non-binding. The need for more comprehensive governance is noted by the WHO, which has recommended that "multilateral regulatory approval by all countries, not separated by species barriers […] should be considered", and that this may involve "international agreements, treaties, covenants, conventions, protocols, or county approvals prior to introduction to one country within a contiguous ecozone".[180]

## 5.2 Cartagena Protocol

### *Baseline Features*

The Cartagena Protocol on Biosafety (the Cartagena Protocol) seeks to protect biodiversity and human health from impacts arising through the transboundary movement of living GMOs. This protocol to the CBD was adopted in January 2000,[181] and as of April 2018 had been signed and ratified by 171 countries.[182]

The definition of a living modified organism (LMO) was framed to capture a broad range of techniques for producing GMOs, as it includes any technique not regarded as "traditional breeding". As a result, a technical body appointed to advise the protocol parties has concluded that essentially any form of gene drive will be covered.[183]

The Cartagena Protocol's key contribution was to establish a mechanism for nations to obtain notice of the first planned shipment of LMOs intended for intentional release into the environment of another country - under the Advance Informed Agreement Procedure (AIA).[184] This allows each nation to assess in advance whether it wishes to permit a particular living GMO to cross its border under the AIA procedure.[185] The movement requests are coordinated through the Biosafety Clearing House – an entity designed to provide a neutral platform and a repository to record prior decisions and information relevant to risk assessment.

[179] WHO. 2014. Guidance framework for testing of genetically modified mosquitoes. It is not the purpose of this report to review the adequacy of this guidance, however the rapid pace of development and insights since the recommendations were published would suggest such a review be conducted in the near term.
[180] Ibid, p. 99.
[181] Note that a related additional CBD protocol is the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization, adopted on 29 October 2010.
[182] http://bch.cbd.int/protocol/parties/
[183] See for example: Secretariat of the Convention on Biological Diversity. 2015. *Synthetic biology.* Montreal, Technical Series No. 82, p 12.
[184] The princple is set out in Article 7 and expanded on in subsequent articles.
[185] This includes four components: notification of an export (by the Party or the exporter), acknowledgment of receipt of notification, decision procedure, and review of decisions. http://bch.cbd.int/protocol/cpb_faq.shtml#faq13

Central to the Cartagena Protocol is the concept of a receiving country having the right to decide whether to accept any transfer of a living modified organism (including a gene drive organism), should an assessment show risk. A description of that risk assessment is set out in the CBD secretariat's guide to the Cartagena Protocol: "The Protocol empowers governments to decide whether or not to accept imports of GMOs on the basis of risk assessments. These assessments aim to identify and evaluate the potential adverse effects that a GMO may have on the conservation and sustainable use of biodiversity in the receiving environments."[186] The criteria relevant to a risk assessment under the Cartagena Protocol are biodiversity and human health (Article 2), and decision-making can also take into account socioeconomic effects (Article 26).[187]

A baseline process for risk assessment is set out in Annex 3 to the Cartagena Protocol, including a set of minimum standards. This acts as a default should member countries not have more specific procedures and/or higher standards for assessment. A ceiling of sorts on standards is created under Article 16(2).[188]

Underpinning the approach to risk assessment is the Cartagena Protocol's commitment to the precautionary principle. It incorporates principle 15 from the Rio Declaration and expresses this with respect to biosafety in Article 1, Article 10 and Annex 3.[189] "In the case of the Biosafety Protocol, this concept means that a government may decide on the basis of precaution not to permit a particular GMO to be imported across its borders", observes the CBD secretariat. "This is the case even if there is insufficient scientific evidence about the GMO's potential adverse

[186] CBD secretariat and UNEP, *Biosafety and the environment: An introduction to the Cartagena Protocol on Biosafety,* 2003, p 10.

[187] Art 2.2: "The Parties shall ensure that the development, handling, transport, use, transfer and release of any living modified organisms are undertaken in a manner that prevents or reduces the risks to biological diversity, taking also into account risks to human health". Art 26.1: "The Parties, in reaching a decision on import under this Protocol or under its domestic measures implementing the Protocol, may take into account, consistent with their international obligations, socio-economic considerations arising from the impact of living modified organisms on the conservation and sustainable use of biological diversity, especially with regard to the value of biological diversity to indigenous and local communities."

[188] "Measures based on risk assessment shall be imposed to the extent necessary to prevent adverse effects of the living modified organism on the conservation and sustainable use of biological diversity, taking also into account risks to human health, within the territory of the Party of import."

[189] Art 1: "In accordance with the precautionary approach contained in Principle 15 of the Rio Declaration on Environment and Development, the objective of this Protocol is to contribute to ensuring an adequate level of protection in the field of the safe transfer, handling and use of living modified organisms resulting from modern biotechnology that may have adverse effects on the conservation and sustainable use of biological diversity, taking also into account risks to human health, and specifically focusing on transboundary movements."
Art 10.2: "Lack of scientific certainty due to insufficient relevant scientific information and knowledge regarding the extent of the potential adverse effects of a living modified organism on the conservation and sustainable use of biological diversity in the Party of import, taking also into account risks to human health, shall not prevent that Party from taking a decision, as appropriate, with regard to the import of the living modified organism in question as referred to in paragraph 3 above, in order to avoid or minimize such potential adverse effects."

effects".[190] To date, decisions made under the protocol have principally involved the international movement of agricultural GMOs.

### *Gene Drive Governance Gaps in the Protocol*

The focus of the Cartagena Protocol on the transboundary movement of living GMOs, and the incorporation of features outlined above, has made this treaty a natural focus for discussion about international regulatory arrangements for gene drives. Yet the Cartagena Protocol has serious gaps in relation to this task and would require significant augmentation. Chief among the gaps are:

- Scope
- Membership
- Duties of GM exporting countries; rights of others
- Monitoring and Enforcement
- Risk assessment
- Physical containment and controls
- Liability

**Scope:** While all gene drive organisms are likely to qualify as an LMO, not all gene drive release scenarios will be adequately covered by the Protocol in its current form, as described below. Of note, the protocol's Advanced Informed Agreement procedures do not cover contained research involving living GMOs. This limited scope is of significance in the case of gene drives because the escape of an individual gene drive organism from laboratory containment (for example, as a result of human error or extreme weather events) has the potential to collapse local populations of the same species or even lead to regional or global extinction.[191]

**Membership:** Although 171 countries have ratified the Cartagena Protocol, a key challenge to its ability to provide effective governance is that the US, Canada, Argentina and Australia (all GM food exporting nations) and Russia are among the countries which are not party to the protocol. While these countries must still comply with the national legislation of Parties to the protocol, its effectiveness to govern gene drive use will be limited without the participation of nations at the forefront of GMO production. This is particularly the case with the USA, given that a great deal of gene drive R+D is centered there and and federal military agencies are currently the largest government funders of gene drive research in the world.[192] As the NAS notes:

> it is a major gap in international governance that the United States does not have a clear policy for collaborating with other countries with divergent systems of

[190] CBD secretariat and UNEP. 2003. *Biosafety and the environment: An introduction to the Cartagena Protocol on Biosafety,* p 6.

[191] Esvelt K M and N J Gemmell. 2017. Conservation demands safe gene drive. PLoS Biol 15(11): e2003850: "Even building such a construct in laboratory containment within a region harboring the target species poses the risk that an accidental escape might eventually affect everyone who shares an ecosystem with that species."

[192] Callaway E. 2017. US defence agencies grapple with gene drives. *Nature,* July 21.

> governance, especially when such countries may, in fact, lack the capacity to assess the safety of gene drive research, undertake public engagement and societal dialogue, and maintain regulatory institutions. This gap is also significant because many sites for field testing, and ultimately environmental release of gene-drive modified organisms are likely to be outside of the United States.[193]

**Duties of GM exporting countries, rights of others:** Under the protocol, obtaining the prior informed consent of other countries is required at the point there is a relevant intentional transboundary movement, such as a shipment of grain containing living modified material (Article 4 and 7).[194] No such consent is required if release of a GM organism by one country risks *unintended* migration of that GMO to another country.[195] Article 17 requires a party to provide only notification to other countries, rather than anticipate and seek agreement in advance, "when it knows of an occurrence under its jurisdiction resulting in a release *that leads, or may lead, to an unintentional transboundary movement* of a living modified organism *that is likely to have significant adverse effects* on the conservation and sustainable use of biological diversity" (emphasis added).[196] This reflects the focus of the regime on predecessor technology: GMOs that are relatively easily containable and intended to be contained and only released across borders in a controlled way. Most applications of gene drive are by definition intended *not* to be contained; they are intended to spread using natural patters of dispersal and genetic inheritance that ignore borders, or to lead to a hereditary dead end before crossing a border. So in order for the principle of Advance Informed Consent to be respected, consent would need to be sought before the release took place rather than at the border (as discussed in section 4.1).

Additionally, the protocol provisisons on unintended movement need not be complied with before a gene drive organism has been released and could be executed only after such organisms are found to have crossed a border.

**Enforcement and Monitoring:** The Cartagena Protocol also lacks enforcement provisions, and is weak on accountability generally. Article 25 puts the onus on parties to enact domestic legislation to address illegal transboundary movements and is generally silent on effective enforcement mechanisms (other than the liability provisions described below).

Monitoring is similarly weak, as parties monitor themselves. Only the implementation of their obligations, rather than a performance standard for

[193] US National Academy of Sciences. 2016. *Gene Drives on the Horizon,* p. 161.

[194] Art 4: "This Protocol shall apply to the transboundary movement, transit, handling and use of all living modified organisms that may have adverse effects on the conservation and sustainable use of biological diversity, taking also into account risks to human health."

[195] Art 17.1: "Each Party shall take appropriate measures to notify affected or potentially affected States, […] when it knows of an occurrence under its jurisdiction resulting in a release that leads, or may lead, to an unintentional transboundary movement of a living modified organism that is likely to have significant adverse effects …"

[196] Atricle 17 alsoe requires the Party to consult affected or potentially affected states to enable them to determine appropriate responses and initiate necessary action.

outcomes, is mentioned in Article 33, which addresses this issue.[197] The minimum standards for the risk assessment set out in Annex 3 does allow for effects based monitoring to be required by the regulator, but this is discretionary.[198]

**Physical containment:** As no special standards for containing a gene drive or similar organism have been specified in the protocol, this too would require attention. Article 18 is focused on safe handling in transit and describes a need for standards for identification, handling, packaging and transport practices.

**Assessment of alternatives:** An appropriate governance regime will have to go beyond a simple threshold approach to risk and also incorporate the assessment of alternatives, as highlighted in section 4.4.

The Cartagena Protocol currently acts as a mechanism to enable a transboundary movement, once it has been established that the movement would not exceed a threshold level of risk. There is no basis for assessing relative risks and benefits (although countries can mandate such an assessment process when implementing the protocol in national legislation). Such an approach does not match the potential magnitude of the risk and the difficulty in predicting outcomes that certain gene drive releases could pose. A requirement to consider alternative ways of achieving the same outcomes as allowing the transfer of an LMO would therefore be needed.

Further, risk assessment procedures and the information required to ensure thorough assessment would need to be augmented from the framework set out in Annex III and the separate Guidance on Risk Assessment of LMOs, which is inadequate for GM organisms intended to engineer entire species or local populations in the wild.

**Liability:** Another reform required is a strict liability regime. Article 27 recognises the importance of liability and redress with a placeholder paragraph, which was actioned in 2010 through the development of a supplementary protocol to the CP.[199]

The supplementary protocol applies to damage arising from a transboundary movement of living GMOs (Article 3).[200] However it is down to Parties to develop civil

[197] Article 33: "Each Party shall monitor the implementation of its obligations under this Protocol, and shall, at intervals to be determined by the Conference of the Parties serving as the meeting of the Parties to this Protocol, report to the Conference of the Parties serving as the meeting of the Parties to this Protocol on measures that it has taken to implement the Protocol."

[198] Annex 3, 8(f): "Where there is uncertainty regarding the level of risk, it may be addressed by requesting further information on the specific issues of concern or by implementing appropriate risk management strategies and/or monitoring the living modified organism in the receiving environment".

[199] The following description is in part adapted from https://bch.cbd.int/protocol/supplementary/about/#tab=1

[200] Under the supplementary protocol, 'damage' refers to an adverse effect on the conservation and sustainable use of biological diversity that is measurable or otherwise observable and significant, taking also into account risks to human health. It provides for an indicative list of factors that should be used to determine the significance of any effect. States must require operators to take response measures (Article 5), where the 'operator' is any person in direct or indirect control of the living GMO. The operator must also take response measures where there is a sufficient likelihood that damage will result if timely response measures are not taken. Response measures may also be taken by the regulator, such as when the operator has failed to do so. In such cases, the regulator may recover the expenses and costs of such measures from the operator. Damage is defined as reasonable actions to

liability rules in their own legislation to address damage. In this way the supplementary protocol provides a framework for nations to adopt domestic law capable of recognising, arresting, and seeking compensation for damage, and would allow a strict liability standard to be set but does not mandate strict liability.

As set out in section 4.7, given the potential scale of the risks and the difficulty in predicting outcomes, gene drive developers and operators should face strict liability for activities that could lead to large-scale, irreversible damage to ensure that the risk of negative consequences is properly allocated. The fact that there will invariably be lower risk conventional alternatives to gene drive applications which the developer or operator has chosen not to use, also supports the argument that the standard should be strict liability that is uncapped.

This is particularly the case for damage occurring in states that are not the origin of the release.

prevent, minimize, contain, mitigate or otherwise avoid damage, as appropriate, or reasonable actions to restore biological diversity.

## *Applicability of the Cartagena Biosafety Protocol to Gene Drive Releases*

*Traffic light colour coding rates provisions, with red indicating a complete gap, orange to yellow where upgrades are required, and green where current provisions suffice*

| Provision | Adequacy for Gene Drive Releases |
|---|---|
| Organisms Covered | Covers all gene drive organisms (Art 3) |
| Scenarios covered | Transboundary movement of LMOs for export (Art 4). If that movement is unintentional, states releasing GD must provide notification but no prior informed consent is required |
| Types of risk | Biodiversity, human health (Art 2), socioeconomic (Art 26) |
| Precautionary principle | Central; based on principle 15 of Rio Declaration (Art 1; Art 10 and Annex III) |
| Timing of notification | Duties to provide advance informed agreement are triggered at the time of planned shipment (Art 7), but may be after a release has been made that might unintentionally cross national boundaries (Art 17) |
| Containment standards | Basic standards expected but not defined (Art 18) |
| Risk assessment | Baseline methodology defined for assessment of living GMOs (Annex III) and guidance document |
| Accountability | Limited |
| Monitoring | Parties monitor themselves, annual report (Art 33) |
| Liability | Nagoya Protocol provides framework for domestic legislation implementation and this permits strict liability but does not require it as a standard |
| Consent requirements | Advanced Informed Agreement (AIA) is required, but limited to deliberate transboundary movement (Art 7). No AIA for natural migration, only notification (Art 17) |
| Membership | States. Significant non-signatories/ratifiers are US, Canada, Argentina, Australia and Russia |
| Alternatives assessment | No consideration of alternatives is provided for (Annex III) |
| Enforcement | None, essentially |

# 6. Pathways to An International Governance Regime

While the Cartagena Protocol is viewed as the most relevant existing agreement for governance of gene drives, the scale of the governance gaps prompts consideration of alternative pathways to deliver comprehensive arrangements. There are also a series of design issues that arise regardless of the instrument or pathway selected. These issues, and how to ensure there is time to resolve them before a gene drive organism is released, are the focus of this section.

## 6.1 International Instrument

Credible international governance could potentially be provided through a number of different arrangements. Here we discuss five options: 1) Amendment of the CBD, 2) amendment of the Cartagena Protocol; 3) a new annex under the Protocol; 4) a new protocol under the CBD; and 5) an entirely new convention. Each of these has the capability to offer legal force and so provide a hard discipline on gene drive activities.

### *Convention on Biological Diversity (CBD)*

A reason for considering the CBD is that while a number of nations that are significant to the regulation of GMOs have not ratified the Cartagena Protocol, most of these have ratified the CBD. The US however has ratified neither and while there is some advantage in being able to focus mainly on just bringing that nation inside a treaty, the US has fundamental objections to multiple elements of the CBD so it would be unlikely to join the CBD, especially if it includes governance of gene drives.

In any case, a regulatory regime for gene drive within the Convention proper would not be consistent with its overall approach and structure. The CBD sets out high-level principles and specifies steps that the Parties must take to meet its purpose of conserving biological diversity. It does not itself contain a governance regime for achieving this.[201]

### *Cartagena Protocol*

As noted in the previous chapter, while this protocol is a natural home for gene drive regulation, significant change would be needed to deliver adequate governance of gene drives.

A question of US participation again arises, namely whether it would need to ratify the CBD in order to become a party to the Cartagena Protocol, as would normally be required. While it is unusual to allow parties to sign up to a Protocol only, it is not unprecedented: the London Protocol to the Convention on the Prevention of Marine Pollution by Dumping of Wastes and Other Matter 1972 allows non-parties to the

[201] So while the discusisons about sythetic biology that gene drive comes under have been under the CBD, the best treaty in which to locate provisions is a separate question.

convention to join the protocol.[202] A case for non-convention state participation in the protocol could be made here on the basis that the protocol is the appropriate place for governance on gene drive and that a key player is not a Party to the CBD and is unlikely to become one. Even then, the US objects to multiple elements of the Cartagena Protocol so its will to join would remain an issue.

Further, there would still be a clutch of GMO exporting nations that stood outside the protocol along with the US. Having been resistant to join the protocol due to provisions applying to GMO shipments that they do not favour, those provisions would remain a barrier to these countries joining the protocol as a way to regulate gene drive organisms. This resistance would remain even if the more stringent provisions applying to gene drives were designed so that they did not affect the shipment of commodity crops.

### *New Annex to the Cartagena Protocol*

An alternative path would be to locate the provisions in a new annex to the protocol and clearly separate the new provisions from the rest of the protocol. However, it would not be consistent with the convention and protocol's current approach to annexes, which are restricted to procedural, scientific, technical or administrative matters already covered in the agreements (too narrow for the type of extensions to the protocol that are required for governance).[203]

Should the parties nonetheless consider the advantages of a separate annex sufficient, they could decide to amend Article 30(1) of the Convention to remove the restriction on the scope and function of annexes, and allow for stand-alone obligations.[204]

Limiting the scope of negotiations to the new text would mean that the new annex would need to be essentially standalone in character. The more this was the case, the more it would start to take on the form of a separate protocol and so weigh the scales more in favour of that pathway.

### *New Protocol Under the CBD*

As the negotiations for a new protocol would start from scratch, they would require more time and resources than amending an existing protocol, other things being equal. The Cartagena Protocol took ten years to negotiate and, at the time of its completion in 2000, was the most rapidly completed UN treaty.

The significance of any additional time demands from negotiating a new protocol will depend, among other factors, on whether there is a commitment to establish

[202] The London Protocol to the Convention on the Prevention of Marine Pollution by Dumping of Wastes and Other Matter 1972 is open for signature by any State and provides that the Protocol supersedes the Convention as between parties to the protocol that are also parties to the Convention.
[203] Article 30(1), CBD
[204] Note that separating new text in this way would not greatly reduce the prospect of the existing text being relitigated – as non-parties would still have to ratify the entire protocol in order to sign up to the new provisions for gene drive. To better protect against relitigation, the parties would need to also consider modifying the rules so that a nation could become a party to just an annex without having to become a party to the protocol, or even the CBD. This would confine the invitation to non-parties to join on the basis that they need only be bound by the new text covering additional regulation that is specific to gene drives.

comprehensive governance before any release occurs. If there is such a commitment, the additional time may not be important.

There is also a question of the overlap with the Cartagena Protocol and whether there is sufficent justification for an entrely new protocol. Ultimately it is a question of political will, and whether the international community feels strongly enough about the issue to give it the significance of a new and separate protocol.

### *New Convention*

A new instrument standing outside the CBD is a further possiblity. This option is similar in character to a new protocol under the CBD, but would require even greater resource in order to initiate a new arrangement without the benefit of an existing overarching framework, a secretariat or a meetings schedule to support the process. Given such a high hurdle, this option would likely require bundling gene drive governance with other issues of a similar nature in order to gain sufficient critical mass and political support. For example, if there were a will to focus on issues that: are transboundary, complex, pose serious risks, and are in need of global governance. Whether such aggregation would help or hinder progress on such issues individually and related complex questions are, however, beyond the scope of this study.

## 6.2 Key Structural Issues

Whatever instrument or pathway is chosen for gene drive governance, a series of structural and operational issues arise in addition to the key principles and disciplines discussed in section 4. Chief among them are: defining collective consent; evidence and the burden of proof; coordination; adjudication, and cost allocation.

### *Collective Consent of Affected Parties*

The Cartagena Protocol sets out a principle that a nation can claim the opportunity to veto any living GMO before it is introduced to its territory. If this core tenant of the protocol is to be maintained, and the collective consent of all affected countries will be required for any gene drive release, then identifying what determines whether a country would be affected becomes essential.

The most obvious indicators that a country will be affected include:

- If a country is habitat of the same or related species that is the target of a gene drive release in another.[205]
- If a country could experience ecological, public health or other negative consequences from the release of a gene drive elsewhere, even if the target species is not present in that country. Scenarios include the possibility that elimination of a local population or a species opens up ecological niches that are filled by other species and which create new pest pressures that spill across national borders.

[205] That species may be introduced or native; wild or cultivated; have a permanent or migratory presence; and considered beneficial or a pest

The international community may identify other factors it considers valid and it is vital that the scope for participation in decisions about gene drive releases is sufficiently broad to cover the range of ways in which countries may be impacted by a gene drive release.

An alternative basis for attempting to identify affected parties is a process whereby potentially affected states "opt in" if they wish to participate in a decision about a gene drive release.

The above assumes that all stakeholder interests are fairly and efficiently represented by states, and that promoters have a state as their sponsor. If those conditions do not apply - for example if promoters were permitted to operate without a sponsoring state; if governments chose to ignore the concerns of key constituents; or stakeholders operating across jurisdictions wished to act collectively but independent of a state - then the question of how best to give effect to collective consent would become considerably more complex.

### *Evidence and the burden of proof*

A further question is where the burden of evidence lies in relation to different aspects of decision-making. Any meaningful consideration of a proposed gene drive release will require a well documented and researched assessment of potential impacts (and the states in which they may occur) from the developer and sponsor state. For an "opt-in" collective consent process, it would be reasonable to expect that a state that wishes to be heard on whether release should occur sets out the basis upon which it considers the release may affect it. On more complex questions, such as the nature of the potential affects, the precautionary principle ought to be given full effect; uncertainty is pervasive in respect of gene drive technology. Independent assessment may also be desirable to ensure the best possible analysis is provided and to maintain trust in the process.

### *Coordination*

A key function within the governance architecture would be coordination, including facilitation and oversight. While the states with standing would continue to hold authority to support or oppose a release proposal, delegating certain functions to a coordinating body would be efficient.

Those functions could include:

- Information distribution
- Receiving proposals for release of a gene drive
- Receiving advice from states that wish to participate in a process for considering a release proposal, and dealing with any challenges to a state gaining standing
- Acting as a repository for documents exchanged during the collective consent process
- Contracting for any independent assessment of the proposal requested by states as a common resource, including a comparison to the best practicable alternative; and

- Overseeing the monitoring of any gene drive release and compliance with conditions.

## 6.3 Constraint Period

Remedying the serious governance gaps identified is a precondition to consideration of any release of gene drive organisms. While regulation can play catch up to technology when the stakes are low, gene drive presents an overwhelming case for precaution due to the potential scale and uncertainty of effects. It dictates withholding from any release or field trialling until governance arrangements are complete.

Although there is a clear need for more time to develop the tools that would allow an adequate assessment of effects across entire ecological systems, the first timetable consideration is governance arrangements.[206] The period during which the outdoor use of gene drives is prohibited would therefore be tied to the time it takes to have a full set of governance arrangements operational.

There is precedent for use of new technology being subject to a constraint period. A recent example within the CBD is the moratorium on climate-related geo-engineering activities, which was similarly founded on the precautionary principle.[207]

Meetings of the CBD parties are a natural forum to broker a constraint period, as nearly all significant nations are parties to the convention. Although the US has not ratified the convention it has signed it, and does participate in meetings under it.[208] While a gene drive moratorium proposal put to the CBD in 2016 was not adopted, the issue was immature at the time.[209] Since then, the threat of outdoor trials and a significant intentional release have become stronger, as has recognition of the case for international governance amongst all sectors - including the scientists at the forefront of developing the technology.

A constraint agreement would be founded on article 14 of the CBD (the precautionary principle) and would specify that for organisms containing engineered gene drives:

- No release or field trial may be undertaken during the period of the constraint
- All laboratory-based research is subject to strict containment standards
- All parties shall ensure domestic laws, including for liability and redress, are in place by a specified date to allow them to enforce the constraint period.

The trigger conditions for termination of the period could be achievement of a specified set of governance functions, so that partial delivery is recognised at the outset as insufficient. These could include:

[206] Having adequate tools for assessment then becomes an issue considered under the applications process and a failure on that count becomes a reason to refuse an application.
[207] Convention on Biological Diversity UNEP/CBD/COP/DEC/X/33/29 October 2010.
[208] https://www.cbd.int/information/parties.shtml
[209] Civil Society Working Group on Gene Drives. 2016. *The Case for a Global Moratorium on Genetically-engineered Gene Drives.*

- Specification of the information and commitments a project proponent needs to provide in order to trigger the collective consent process
- An entity available to: receive project proposals, confirm the interest of parties in the proposal, and register outcomes of inter-party dialogues
- Guidance to assist each party to make their assessment of impacts, including of risks to the environment and human health, and socio-economic, cultural and ethical impacts
- Arrangements to monitor the effects of any gene drive release
- Arrangements for liability and redress to deal with damage arising from a gene drive release

## 6.4 Conclusion

Whichever governance path the international community opts for, delivery of a credible governance regime for gene drives is urgent.

The starting point is the constraint period. For it to be effective, it will be important for the principal nations engaged in gene drive research and project development to be party to it.

One means of encouraging this would be for states that support a constraint period to announce that they expect to have their approval sought in advance of any gene drive release that could affect their territory.

## Key recommendations to the international community

It is recommended that:

- **A constraint period is established as soon as possible by the international community,** such that no gene drive release or field trial takes place until international governance that is fit-for-purpose is in place.
- The international governance regime:
  - **Provide for "collective consent",** requiring the approval of each country whose territory could be impacted, directly or indirectly by a gene drive release or field trial in another jurisdiction.
  - **Be founded on the precautionary principle** and recognise the CBD founding principle - that countries shall not cause damage to the environment of other countries.
  - **Set laboratory containment standards for research** to address gene drive's specific environmental hazards.
  - **Require gene drive proposals to be compared against alternative ways** of meeting the same objective with less risk.
  - **Require monitoring to be undertaken** to track the movement of gene drive organisms and the potential spread of introduced traits.
  - **Set a strict liability standard** for any harm resulting from a gene drive release, as a condition of approval.

# 7. Governance of Gene Drive in New Zealand

This section evaluates the adequacy of gene drive regulation and policy in New Zealand. It first examines the current position and then proposes interim reforms for the domestic governance arrangements, pending development of fit-for-purpose international rules.

## 7.1 Gene Drive as a Biosecurity Risk and the Need for Reform

To date, New Zealand government officials have been reluctant to concede that the existing international governance of genetic modification is inadequate to regulate gene drives. They have not supported additional regulation.[210] In advice prepared for ministers in advance of CBD and Cartagena Protocol negotiations in 2016, which included specific consideration of gene drive governance, officials have gone so far as to state that:

- The risk of transboundary spread of gene drive organisms "isn't an issue for New Zealand, being a remote island with no physical borders"; and
- Defining illegal and unintentional movements of GMOs across borders – a key consideration for international governance of GD technology - was "not considered … necessary".[211]

However, the assumption that traditional border protections are sufficient has been dismissed by various authorities. The Ad Hoc Technical Expert Group to the CBD cautioned that:

> Islands are not ecologically fully contained environments and should not be regarded as fulfilling the conditions in the definition of contained use as per Article 3 of the Cartagena Protocol unless it is so demonstrated"[212].

Most recently, Noble et al warned that "any development efforts looking ahead toward field trials […] should be aware that there could be a high likelihood of unwanted spread across international borders, even from ostensibly isolated islands.[213] This is consistent with New Zealand's experience of biosecurity generally, and its approach to it.[214]

[210] New Zealand Delegation Brief, CBD, 2016, p 269. "To resist calls to develop further instruments, until there is a clear case that a synthetic biology-specific instrument is needed to manage impacts on biodiversity".

[211] New Zealand Delegation Brief, Cartagena Protocol, 2016, p 46.

[212] Ad Hoc Technical Expert Group (AHTEG). 2017. Report of the Ad Hoc Technical Expert Group on Synthetic Biology. Montreal, Canada, 5-8 December 2017, para 51(c)

[213] Noble C, Adlam B, Church G M, Esvelt K M and M A Nowak 2018. Current CRISPR gene drive systems are likely to be highly invasive in wild populations. *eLife* 2018;7:e33423.

[214] In the last 10 years New Zealand has been subject to a number of significant incursions of unwanted pest species including varroa, , Psa, and Mycoplasma Bovis, despite an extensive biosecurity regime that does not presume that its geography eliminates risk.

Domestically, rather than recognising gene drive as a biosecurity threat, government departments have been more focused on facilitating the potential use of gene drive to exterminate conservation pests. When the previous administration set out its plan for a *Predator Free New Zealand*, it stated that "[t]he predator free goal is dependent on breakthrough science" and "[t]he use of gene drive and other techniques, could, for example … lead to an eventual collapse of the possum population".[215]

Yet the possum is a case in point for why international governance will be essential. The release of a gene drive designed to eliminate possums in New Zealand would raise significant issues for Australia where the possum is a protected species and because, as the Australian Academy of Science states: "Once gene drives are released into wild populations in other countries, they will inevitably reach Australia".[216]

The complacency that has previously typified official thinking needs to be set aside. Gene drive is at root a tool for major and potentially irreversible change to ecosystems. As a country that is otherwise vigilant to biosecurity risks, New Zealand should be alive to the ways in which gene drive releases in other countries could prove a significant biosecurity threat.

New Zealand needs to fundamentally reappraise gene drive's risk and benefit profile. It has taken an optimistic view of the risks in tandem with interest in local gene drive uses for conservation, but its geography will not protect it from unwanted gene drive organisms any more than it protects it from other biosecurity risks.

New Zealand's interests, like other nations, are ultimately served by the strong global governance of gene drive and it will benefit from championing this and abandoning stances that are no longer credible.

## 7.2 HSNO and Gene Drive

Regulation of the outdoor use of GMOs in New Zealand is centralised under the Hazardous Substances and New Organisms Act 1996 (HSNO). There is only a minor contribution to this regulatory regime from other statutes.[217]

The key structural features of HSNO include:

- Its orientation to protect New Zealand against risks arising through the introduction of new organisms – which includes those already existing but not in New Zealand, as well as ones newly created by genetic modification.
- Its purpose, which is "to protect the environment, and the health and safety of people and communities, by preventing or managing the adverse effects of hazardous substances and new organisms" (s4).

[215] New Zealand Government. 2016. *Accelerating Predator Free New Zealand*. Cabinet Paper, paras 8; 56.

[216] Fleischfresser S. 2017. Benefits and dangers in altering our evolutionary trajectory. *Cosmos Magazine,* May 2.

[217] Notably the Biosecurity Act with respect to border detection and to enforcement, and the Resource Management Act with respect to land use controls on GMOs set by individual councils.

- The requirement for regulatory approval for any proposed use of GMOs in the outdoors. This includes a release into the environment, and field trials (which must be contained) (Part 5).
- Identification of the Environmental Protection Authority (EPA) as the decision-making body under the Act (Part 5).
- Public notification of and consultation on applications involving outdoor use. Applications are open to submissions by any individual, group or entity and are subject to a public hearing (s53, s60).
- Assessment on a case-by-case basis, where all forms of effects are assessed (definition of effect, s5, s6, s38).
- Net benefit test: Positive effects must exceed adverse effects for a release to be approved (s 38(1)).
- Minimum standards that cannot be traded away, such that an application must be declined if the activity does not meet these (s36).

With respect to the fundamental requirements for the governance of gene drives identified earlier, HSNO has the potential to deliver on some, but key aspects are either missing or not sufficiently well provided for. Provisions under HSNO that could effectively regulate gene drives include:

> **Coverage:** The HSNO definitions for genetic modification are based on those in the Cartagena Protocol (s2) – thus covering all techniques not regarded as traditional use.[218] New Zealand has also separately determined that all gene editing and other new genetic engineering techniques are covered by HSNO. This was confirmed firstly by the courts and subsequently affirmed following a government review of the regulations.[219] Accordingly, any gene drive activity would be covered by HSNO, from a release through to any contained use.
>
> **Assessment:** The scope of effects that must be considered is unrestricted and specifies dimensions as broad as: the sustainability of all native and valued introduced flora and fauna, the intrinsic value of ecosystems, public health, how easily an organism could be eradicated, and all economic costs and benefits (s6, s37). This is important for assessment of a gene drive release as the potential impacts could involve many dimensions. The act also

[218] In addition, any organism not present in the country at the trigger date of 29 July 1998 is deemed a new organism and is also covered by the Act. Just as Cartagena exempts organisms created through "traditional breeding", HSNO exempts specified techniques in line with this approach under a white list.

[219] The court ruling was issued in response to an EPA decision that deemed two gene editing techniques (ZFN-1 and TALEs) not to be GMOs, as defined by the HSNO Act. The Sustainability Council, a charitable trust, appealed the regulator's decision to the High Court which quashed the EPA's decision. The court ruled that the techniques did meet the regulatory definition of a GMO – see [2014] NZHC 1067. A subsequent review by the government review considered whether to deregulate all or some of the new gene editing techniques and it decided to continue regulating all gene editing techniques as GM- see Minister for the Environment. 2016. GMO regulations clarified. Media release, April 5.

allows applications to be declined if there is inadequate information on which to make a decision (s38 (1)(b) iii). While it is clear that new tools would be required to assess the impacts of a gene drive (as identified in section 2), these are set at the operational level and are unlikely to require amendment to HSNO.

**Comparison against the alternative:** Details of how the EPA is to assess an application are contained in both HSNO and the Hazardous Substances and New Organisms (Methodology) Order 1998. While neither of these specify that a decision must be made with reference to alternatives, the relevant EPA guide specifies that: "the baseline should be considered to be the status quo, or what would happen if the application were to be declined".[220] It further notes that when assessing what would be different relative to that baseline, it expects the baseline to change over time and that other options could come into use in the time over which the approval is considered. In this way, the EPA sets out a basis for considering what the best practicable alternative would be, and counts benefits and costs of an application relative to this.[221]

**Containment and Monitoring:** There are strong provisions for the containment of organisms in transit and for experimental work. No standards for gene drive have yet been devised - a gap that needs to be addressed and can be remedied under existing provisions. There is also wide scope for the EPA to require that effects be monitored by the applicant and that records be supplied from this work (s38 (d)).

There are three important deficiencies in HSNO with respect to a gene drive assessment:

### *Precaution*

HSNO does not formally embrace the precautionary principle, nor does it mandate that the EPA be precautionary. Instead, s7 of the act specifies simply the following:

> "All persons exercising functions, powers, and duties under this Act, ... shall **take into account the need for caution** in managing adverse effects where there is scientific and technical uncertainty about those effects. " [Emphasis added]

In *Bleakley v Environmental Risk Management Authority,* the High Court did not accept submissions of the appellants that s7 embraced the precautionary

[220] Environmental Protection Authority (EPA). 2011. *Assessment of Economic Risks, Costs and Benefits: Consideration of impacts on the market economy,* p 10.

[221] Ibid. The document does note however that "Publications in this technical series are endorsed by the EPA Board but are not a required basis for decision making." Further, while the guide is not currently on the EPA website, and so it is not clear if it remains endorsed, there is clear precedent set by past decisions making use of this approach.

principle, partly as a result of the Court's reading of the parliamentary debates prior to HSNO's enactment.[222]

More recent rulings, including that relating to the scope of HSNO coverage of gene editing techniques, have been more open to interpreting s7 as conferring a duty on the EPA to act with a precautionary intent.

The important point of distinction here is not that the EPA is precluded from implementing the precautionary principle. HSNO grants the EPA relatively wide powers under s38(1)(b) to decline an application such that it is well within the scope of the act for the EPA to deliver precautionary outcomes, were it of a mind to do so. The key point is that rather than precaution being mandatory, HSNO makes it a matter for the EPA's discretion – something to be "taken into account". The need for precaution must be considered, but may be outweighed by other considerations.

But even as it has become clearer that the EPA has the ability to exercise precaution, the EPA has shown it is capable of ignoring this consideration on GMO matters. In its determination regarding whether two new genetic engineering techniques were covered by HSNO, the EPA decision-making committee made no reference to precaution, and failed to consult any affected parties during its decision-making process.[223]

### *Liability*

Economic harm resulting from use of gene drives forms part of the full cost of selecting this technology to meet a particular objective. If losses fall on third parties, it subsidises gene drive activities relative to alternatives, as the full costs are not carried by the developer or user. That type of subsidy is presently enshrined in HSNO.

Those who make or use gene drives are not liable under HSNO for any damage arising as a result of an activity if it is carried out in accordance with an EPA approval. Only if an operator undertakes a release without a permit, or breaks conditions of an EPA approval, would it be strictly liable for damages. Even then, damages payable are capped at a value that claims could readily exceed.[224]

HSNO instead places a heavy reliance on controls and penalties for breaching these. The problem with this approach is that the regulator must accurately foresee all the circumstances in which something could go wrong, and be able to prescribe for these in advance. Yet an important source of risk in respect of gene drives is unexpected adverse effects. A liability regime based on "perfect" foresight is therefore not suited to these risks.

---

[222] *Bleakley v Environmental Risk Management Authority,* 2001 3 NZLR 213 (HC), p.250; paras 160 - 164, McGechan J.

[223] Environmental Protection Authority (EPA). 2013. *Determination of whether or not any organism is a new organism under section 26 of the Hazardous Substances and New Organisms (HSNO) Act 1996*. See also Terry S. 2014. GM guardian's error a grave failing. *New Zealand Herald,* June 6.

[224] Parties who suffer damage to property have the option of pursuing a civil action via common law torts. However, this involves relying on law ill-suited for this purpose, and which makes daunting demands in terms of evidence, time and financial resources.

An effective liability regime should also ensure that liable parties have the means to pay for harm caused. HSNO sets no requirement for financial fitness on the part of the applicant, but it is capable of providing for this. In particular, any determination authorising a release could specify that the applicant would need to post a performance bond. Such financial assurance requirements can be imposed under s38D, as can requirements to monitor and to keep and provide records.[225]

In order to ensure that potential costs are tied to the release to the extent possible, the performance bond would need to cover scenarios for harm at the high end of the cost range that could result from a breach of HSNO conditions.[226]

If monitoring and record keeping was also required in a form that was general but in addition was clearly suitable for supporting claims for damages, this would enhance the effectiveness of the bond requirement.

### *International Obligations*

When assessing an application under HSNO, decision makers must take into account "New Zealand's international obligations" (s 6(f)). As any gene drive release carries a clear risk of transboundary impacts, it will be useful for the government to interpret how this obligation is likely to apply with respect to use of gene drive organisms.

As discussed in section 4.1, along with the CBD's article 3 principle, there is a general obligation in international law for states to ensure that activities within their jurisdiction and control do not cause harm to the environment of other states.[227] The risk of transboundary movement of gene drive organisms and their potential to cause environmental damage discussed in section 2 means that this obligation will be engaged when an application for approval of gene drive is assessed.

The HSNO decision-making methodology that sits under the Act but is also legally binding, requires assessment of the risks costs and benefits associated with the organism. The costs and benefits that may be considered are only those relating to New Zealand:

[225] While financial assurance requiremens can only be imposed if an applicaton is made for a conditonal release (s 38), as no gene drive organism woud qualify for release without condiitons (s34), it is a hypotehtical gap. As as a field trial under HSNO requires that altered genetic material be contained to the test site, a gene drive field trial is equally improbable.

[226] While HSNO's capping of liability would dilute the effect, requiring a performance bond would be significant in itself as, to date, the EPA has not utilised this mechanism.

[227] Schiele S, Scott D, Abdelhakim D, Garforth K, Gomez Castro B, Schmidt L and H D Cooper. 2015. Possible gaps and overlaps with the applicable provisions of the Convention, its Protocols and other relevant agreements related to components, organisms and products resulting from synthetic biology techniques. Part II of: *Synthetic biology*. Secretariat of the Convention on Biological Diversity. Montreal, Technical Series No. 82. See also Dina L Shelton and Alex Kiss "Strict Liability in International Environmental Law" *Law of the Sea, Environmental Law and Settlement of Disbutes,* 2007.

> 14. The costs and benefits are those that relate to New Zealand and that would arise as a consequence of approving the application.[228]

That methodology defines costs and benefits as follows:

> "Benefit" means the value of a particular positive effect expressed in monetary or nonmonetary terms:
>
> "Cost" means the value of a particular adverse effect expressed in monetary or nonmonetary terms:

However, "risk" is not limited in the same way as costs, but is defined in the Methodology as the combination of the magnitude of an adverse effect and the probability of its occurrence. HSNO s10 requires the risks relating to New Zealand's international obligations to be taken into account.

The assessment provided for in the methodology then feeds into one of the key sections of the Act which specifies that an application must be approved if, amongst other matters: "the positive effects of the organism outweigh the adverse effects of the organism".[229]

How the assessment is likely to play out in an application for release of gene drive is currently unclear. The combination of the obligation not to cause damage to other countries, the requirement to take into account international obligations, and the risks that gene drives pose, together could amount to an adverse effect of the organism which, in a particular case, might outweigh its positive effects. However, should the methodology be interpreted to mean that all adverse effects are to be monetised as a part of the decision-making process and only those relating to New Zealand may be counted as costs, then even in this case, it seems that the risks to other nations could be considered as secondary effects. That is, to the extent that the New Zealand government assesses that another nation could seek a remedy from New Zealand for harm caused, there is a risk that a cost will be incurred in this way. Even potential damage to New Zealand's reputation would count as such a cost.

To clarify the position, the government could obtain a legal opinion to help it specify what would be counted as an adverse effect of a gene drive, including the risk of claims against it and reputational harm.

## 7.3 A Constraint Period on Trials and Releases

If the global community agrees to a constraint on gene drive releases until a purpose-built international regime is developed, then it is reasonable to expect that New Zealand would be a party to this.

New Zealand's best response under this scenario would be to apply the constraint domestically until the form of the new regime is clear. When that is known, domestic governance arrangements can be reassessed to determine what, if any, change needs to be made to HSNO.

[228] Hazardous Substances and New Organisms (Methodology) Order 1998
[229] s38 (1)

However, if there is no internationally agreed constraint period, New Zealand needs to consider its position independently. The same logic that drives a constraint period at the international level applies to the nation state. Time is required to at least evaluate and remedy governance gaps, and to ensure that tools are available to properly assess any gene drive application. And it would still be preferable for the international governance rules to be known before considering what changes are needed to HSNO.

There is a domestic precedent for this approach. In 2000, when the government held a royal commission of inquiry into genetic modification and wanted to translate the recommendations into law before an application for GMO release was made, it set a constraint period covering three years during which no applications for release could be made. A first period of a year involved the government gaining agreement from GMO developers for a voluntary constraint, and this was followed by a regulated constraint period.

The new constraint on gene drive organisms would cover any application made to the EPA for release, field trialing or outdoor development of an organism containing an engineered gene drive.[230] It would either be aligned with the internationally agreed period or, in absence of this, it could specify an initial period (with provision for extensions) tagged to the completion of specific governance measures before it could lapse.

Such a constraint period would have little or no effect on the progress of any domestic gene drive research, particularly that targeting eradication of conservation pests, as it is widely acknowledged that field trials for this are many years away.[231] However, due to the potentially high consequences of a breach of work undertaken in containment, it is recommended that the Government review the sufficiency of laboratory containment standards for gene drive and that these are later upgraded if any international standards developed are stricter than domestic requirements.

The new constraint period could again be set essentially via a voluntary agreement with affected domestic developers. As there are only a small number of these developers, and gene drive research and development is heavily dependent on government funding if not its patronage (through its *Predator Free New Zealand* programme), the government is well placed to secure their cooperation. And as their research is at a relatively early stage, the likelihood of an application is low. However, as applications for release can also be made by parties overseas and there is a recent example of a consortium considering New Zealand offshore islands as an outdoor test area for a gene drive, additional arrangements may be important to establish.[232]

[230] These activities are covered in HSNO sections 34 and 38 (full and conditional releases) and section 39 (field trials and developments).

[231] Dearden D K, Gemmell N J, Mercier O M, Lester P J, Scott M J, Newcomb R D, Buckley T R, Jacobs J M E, Goldson S G and D R Penman. 2017. The potential for the use of gene drives for pest control in New Zealand: a perspective. *Journal of the Royal Society of New Zealand.*

[232] Neslen A. 2017. US military agency invests $100m in genetic extinction technologies. *The Guardian,* December 4. and Fisher D. 2017. Consortium eyes NZ islands for genetic trials on pests. *New Zealand Herald,* December 4.

An additional arrangement that could capture a 'rogue' developer would be for the government to "call-in" any application involving use of gene drives outside the laboratory. The call-in powers set out under HSNO s68 allow for the environment minister to assume the decision-making role for applications that will have "significant cultural, economic, environmental, ethical, health, international, or spiritual effects".[233] Given the potential large scale effects on the environment, any application to field trial or release a gene drive organism would readily qualify. Alternatively, the government could legislate specifically to mandate the constraint period, as it also did in 2001.

At the point the constraint period is announced, New Zealand should embark upon its own "constitutional conversation". As noted in section 3, that conversation will need to be widely framed to identify collective values and goals in areas such as conservation and agriculture where gene drive applications are mooted and consider the breadth of possible pathways to achieve those aspirations. Democratising this process so that New Zealanders have a seat at the table in choosing technology pathways is a key step in rising to the constitutional moment that gene drive governance presents.

The constraint period would not only shore up domestic governance arrangements for the time being, its wider effect would be to set an example globally and demonstrate New Zealand's commitment to global governance of the technology.

As the government gains greater understanding of efforts to develop international governance of gene drive, New Zealand can then begin to exercise a leadership role, in calling for a global constraint period and drawing attention to the need for the international governace gaps to be remedied.

While it is awaiting that global constraint period, New Zealand could also advise other states that it expects to be consulted in advance of any release or field trial of a gene drive organism in another country that could affect New Zealand, and expects that the activity would not proceed without its consent. It would in effect seek a collective consent arrangement with any country contemplating a release.

[233] The call-in process offers a way for the minister to ensure that the government's approach to environmental management is paramount for special cases, such as a gene drive release, rather than it being delegated to decision makers that the EPA board appoints under HSNO. Under the call-in provisions, the EPA's assessment process is similar to other application paths, but the Authority's reports go to the minister rather than an EPA appointed decision-making committee.

## Key recommendations for New Zealand government policy on gene drives

It is recommended that:

- **A constraint period is established for all releases, field trials and GM outdoor developments involving gene drive organisms**, until a fit-for-purpose international governance regime is in place. During this period, no applications to the EPA could be made for these activities.
- **A review of the adequacy of New Zealand law** is undertaken, with the purpose of ensuring that:
  - **The precautionary principle is explicitly applied** when evaluating gene drive as a technology, and assessing the risks of particular gene drive organisms.
  - **A strict liability standard is established** for activities involving gene drive organisms. Those making or using gene drives are also required to post a performance bond to demonstrate they are able to meet claims by third parties for any harm resulting from a gene drive activity.
  - **Monitoring of any outdoor activities** involving gene drive organisms is required to track effects for science purposes, and to provide records to support any claims for harm caused.
  - **The government seeks a legal opinion** on the extent to which, under a HSNO assessment, the costs to other countries of a gene drive organism release in New Zealand would be counted (including the risk of claims against it and reputational harm).
- **New Zealand exercises a leadership role internationally**, calling for a constraint period to apply to gene drive releases and field trials until the international governance that is fit for purpose is in place.

# 8. No Case for Regulatory Discount

Gene drive presents a 21st Century constitutional moment. The power to deliver "extinction to order" or the permanent reengineering of wild species needs to be clearly held within civil and international community control. It demands global governance commensurate with its risks.

Gene drive brings into question society's fundamental principles and values – such as humanity's relationship with the wider biological community and where are the acceptable limits of human manipulation and dominance of nature. It also challenges fundamental tenets the international community has established, such as the CBD duty for nations "not [to] cause damage to the environment" of others.

Existing international governance arrangements are inadequate to deal with gene drive because it is not a mere extension of genetic engineering in its ambitions or capacity.

## 8.1 Risk Shifting

This study has set out the fundaments of what is required to address a considerable governance gap. If the proposed regulatory response is proportionate to the risks, then opposition to it is a bid to have risks shifted from developers and users and on to the environment and third parties.[234]

That would not be a responsible – or an ethical - path forward. An international governance regime needs to ensure that if harm is caused, that the costs rest with developers and users.

Proponents may well argue that gene drive is a 'special case' because of the scale of benefits they believe are available. But the birth of the nuclear power industry in the US showed why high-risk activities should not be given special deals. There a technology that was to produce electricity "too cheap to meter" was able to commercialise because liability for an accident was capped to low levels and liability waived for manufacturers[235], while its costs today are uncompetitive with alternatives using no risk renewable energy sources.[236]

[234] As governments are loath to crystallise the costs of such special treatment, and proponents are equally loath to see a subsidy explicitly recorded, a key risk of such approaches is a weakening of regulation at the application stage and what happens when risks actually come to book. At the same time the regulator becomes co-opted to provide statutory endorsement for the use of the tech.

[235] The statement "too cheap to meter" was made in 1954 by Lewis Strauss, Chairman of the US Atomic Energy Commission: www.nrc.gov/reading-rm/doc-collections/fact-sheets/nuclear-insurance.html; Anthony Heyes and Catherine Liston-Heyes, 2000. Capping Environmental Liability: The Case of North American Nuclear Power, *The Geneva Papers on Risk and Insurance,* Vol. 25 No. 2 (April 2000) 196 ± 202.

[236] Anon. 2001. A Renaissance That May Not Come. *The Economist,* May 16.

## 8.2 Regulatory Discounts Make Us Poorer

If gene drive technology is not viable under proper governance, then this is evidence that it is not an appropriate technology.

Diluting regulatory requirements that would properly protect against risk does not advantage society. It simply socialises risks, including those, which may not be properly foreseen. Even in the case where the technology is directed at outcomes that benefit whole communities or populations, all costs need to be explicitly counted because it has the potential to trigger a cascade of complex and significant effects that are difficult to predict, let alone control. Society is poorer to the extent risks are not fully internalised in the costs faced by developers and users.

That cost can be thought of as a contingent liability on the books of the global environment and other affected communities. And with ecosystems across the earth already under multiple systemic pressures, the case for rejecting regulatory discounts is stronger still. Nature has less resilience available to recover from systemic threats of the form a gene drive could set off.

Ultimately, it is the outcome that gene drive is mooted for - not the means - that is the societal objective. Gene drive is just one technology option - competing against existing alternatives and others under development. As such, any advantages that are claimed for it in terms of cost, time or ease of application need to be properly compared against those of its competitors along with the risks applying to all options. In the case of gene drives, that means liability arrangements and the costs of regulation must be included in the equation to avoid the assessment being biased in its favour.

If one of the minimum standards for gene drive governance is a requirement for collective consent by affected states, then the onus is on its promoters to deliver the political support for a process that will facilitate this. If the benefits of gene drive are not enough to attract the political will necessary to even establish the required governance processes, that is not grounds for a regulatory discount. That is a signal to gene drive developers that the technology is at least not sufficiently mature.

Despite the compelling and urgent causes that gene drive is often recruited for – combating diseases that affects millions or eliminating pest to the conservation estate – short cuts should not be taken. Indeed, many of the crises that gene drive proposals are directed at are themselves cautionary tales of poor governance.

## 8.3 Resolution

Navigating a pathway to gene drive governance will be assisted by the following:

- Clearly recognising the precautionary principle and the CBD founding principle, along with relevant international law.
- Recognising that unilateral decisions on environmental release of this technology are inappropriate and that collective consent, with affected countries able to decide to reject a proposed gene drive release in another, is a fundamental requirement.

- Acting early before there is significant commercial investment in the technology to raise expectations that commercialisation is only a matter of haggling the conditions
- Challenging developers to assist with building good governance rather than looking for regulatory discounts.
- Ensuring the best practicable alternatives are compared to gene drive proposals at each step of the way.

There is real urgency to meeting this governance challenge, given the investment in the technology, the political sponsorship it has attracted and the risks that attend even contained development. The international community must quickly commit to that process, as it will take some time to complete. Among the advantages of early action is that clear signals to would-be developers about the regulatory requirements may assist in technology choices. Moreover, the longer fit-for-purpose governance is delayed, the more political resistance can be expected from developers and patron governments.

In the meantime, it is imperative that governments collectively commit to not allow gene drives outdoors – whether for trialling or release – until proper governance is in place. That pledge will be a first signal that the international community has recognised the enormous challenge that this technology presents.

# References

Ad Hoc Technical Expert Group on Synthetic Biology. 2017. Report. Montreal Canada. 5-8 December. CBD/SYNBIO/AHTEG/2017/1/3

Akbari O S, Bellen H J, Bier E, Bullock S L, Burt A, Church G M, Cook K R, Duchek P, Edwards O R, Esvelt K M, Gantz V M, Golic K G, Gratz S J, Harrison M M, Hayes K R, James A A, Kaufman T C, Knoblich J, Malik H S, Kathy A. Matthews K A, O'Connor-Giles K M, Parks A L, Perrimon N, Port F, Russell S, Ueda R and J Wildonger. 2015. *Safeguarding gene drive experiments in the laboratory.* 349 (6251): 927-929.

Ankeny R A and A Hoffmann. 2017. Gene drives may cause a revolution, but safeguards and public engagement are needed. *The Conversation,* May 5. https://theconversation.com/gene-drives-may-cause-a-revolution-but-safeguards-and-public-engagement-are-needed-77012

Anon. 2016. Gene-ocide. The promise and peril of "gene drives". *The Economist,* September 17. http://www.economist.com/news/leaders/21707211-promise-and-peril-gene-drives-gene-ocide

Anon. 2016. New Zealand's war on predators. *The Economist,* August 2. https://www.economist.com/science-and-technology/2016/08/02/new-zealands-war-on-predators

Anon. 2015. *Trojan Female Project User Needs Analysis.* A report for Landcare Research. The AgriBusiness Group. https://www.landcareresearch.co.nz/__data/assets/pdf_file/0012/99498/TFT_user_needs_analysis.pdf

Australian Academy of Science. 2017. *Synthetic Gene Drives in Australia: Implications of Emerging Technologies.* Discussion Paper. https://www.science.org.au/files/userfiles/support/documents/gene-drives-discussion-paper-may2017.pdf

Begley S. 2015. Why the FBI and Pentagon are afraid of this new genetic technology. *Statnews*, November 12. https://www.statnews.com/2015/11/12/gene-drive-bioterror-risk/

Begley S. 2016. Monsanto licenses CRISPR technology to modify crops — with key restrictions. *Statnews*, September 22. https://www.statnews.com/2016/09/22/monsanto-licenses-crispr/

Bouchard S. 2017. Gene 'editing' on mice tested in war on ticks. *The Working Waterfront,* Island Institute. November 17. http://www.islandinstitute.org/working-waterfront/%E2%80%8Bgene-'editing'-mice-tested-war-ticks

Braverman I (ed). 2017. *Gene Editing, Law, and the Environment: Life Beyond the Human.* Routledge Press.

Buchman A, Marshall J M, Ostrovski D, Yang T and O S Akbari. 2018. Synthetically engineered Medea gene drive system in the worldwide crop pest Drosophila suzukii. *PNAS*. https://doi.org/10.1073/pnas.1713139115.

Burall S. 2018. Don't wait for an outcry about gene editing. Comment. *Nature* (555): 438-439.

Callaway E. 2017. US defence agencies grapple with gene drives. *Nature,* July 21. https://www.nature.com/news/us-defence-agencies-grapple-with-gene-drives-1.22345

Callaway E. 2017. Gene drives thwarted by emergence of resistant organisms. *Nature,* 542:15. https://www.nature.com/news/gene-drives-thwarted-by-emergence-of-resistant-organisms-1.21397

Caplan A L, Parent B, Shen M and C Plunkett. 2015. No time to waste—the ethical challenges created by CRISPR. *Science and Society.* EMBO Reports DOI 10.15252/embr.201541337

Ceballos G, Ehrlich P E and R Dirzo. 2017. Biological annihilation via the ongoing sixth mass extinction signaled by vertebrate population losses and declines. *PNAS* 114 (30): https://doi.org/10.1073/pnas.1704949114.

Champer J, Reeves R, Oh S Y, Liu C, Liu J, Clark A G et al. 2017. Novel CRISPR/Cas9 gene drive constructs reveal insights into mechanisms of resistance allele formation and drive efficiency in genetically diverse populations. *PLoS Genet* 13(7): e1006796. https://doi.org/10.1371/journal.

Champer J, Buchman A and O S Akbari. 2016. Cheating evolution – engineering gene drives to manipulate the fate of wild populations. *Nature* (17): 146-159. doi:10.1038/nrg.2015.34

Civil Society Working Group on Gene Drives. 2016. *The Case for a Global Moratorium on Genetically-engineered Gene Drives.* http://www.etcgroup.org/sites/www.etcgroup.org/files/files/cbd_cop_13_gene_drive_moratorium_briefing.pdf

Clapper J R. 2016. Worldwide Threat Assessment of the US Intelligence Community. Statement for the Record to the Senate Armed Services Committee by the Director of National Intelligence. February 6. https://www.dni.gov/files/documents/SASC_Unclassified_2016_ATA_SFR_FINAL.pdf

Cobb M. 2016. Gene drives need global policing. *The Guardian,* February 9. https://www.theguardian.com/science/2016/feb/09/gene-drives-need-global-policing

Courtier-Orgogozo V, Morizot B & C Boëte. 2017. Agricultural pest control with CRISPR-based gene drive: time for public debate. Should we use gene drive for pest control? *EMBO Reports* 18(6): 878-880*. DOI 10.15252/embr.201744205*

Davison I. 2016. Tread carefully with GE pest control, Govt warned. *New Zealand Herald,* October 3 2016. http://www.nzherald.co.nz/nz/news/article.cfm?c_id=1&objectid=11721103

Dearden D K, Gemmell N J, Mercier O M, Lester P J, Scott M J, Newcomb R D, Buckley T R, Jacobs J M E, Goldson S G and D R Penman. 2017. The potential for the use of gene drives for pest control in New Zealand: a perspective. *Journal of the Royal Society of New Zealand,* DOI: 10.1080/03036758.2017.1385030

Defence Advanced Research Projects Agency (DARPA). 2017. Building the Safe Genes Toolkit. Media release, July 19. https://www.darpa.mil/news-events/2017-07-19

DeFrancesco L. 2015. Gene Drive Overdrive. *Nature Biotechnology* 33(10): 1019-1021.

Dowling D K, Tompkins D M and N J Gemmell. 2015. The Trojan Female Technique for pest control: a candidate mitochondrial mutation confers low male fertility across diverse nuclear backgrounds in Drosophila melanogaster. *Evolutionary Applications* (2015) 871-880. doi:10.1111/eva.12297

Drury D W, Dapper A L, Siniard D J, Zentner, G E and M J Wade. 2017. CRISPR/Cas9 gene drives in genetically variable and nonrandomly mating wild populations. ci. Adv.

2017;3:e1601910

Economic Development Administration Directives System. 1992. EDA Program to implement Execuive Orders 11988 “Floodplain Management” and 11990, “Protection of Wetlands” Directive No. 17.04
http://www.corporateservices.noaa.gov/grantsonline/Documents/EDA_DOO_17-04.pdf

Ely A, Van Zwanenberg P and A Stirling. 2014. Broadening out and opening up technology assessment: Approaches to enhance international development, co-ordination and democratization. *Research Policy* 43: 505– 518

Environmental Protection Authority (EPA). 2011. *Assessment of Economic Risks, Costs and Benefits: Consideration of impacts on the market economy.*

Environmental Protection Authority (EPA). 2013. *Determination of whether or not any organism is a new organism under section 26 of the Hazardous Substances and New Organisms (HSNO) Act 1996*.

Environmental Protection Authority. 2017. *Genetic technologies, genetically modified organisms and the spectrum of genetic modifications in the context of Predator Free NZ 2050.* Briefing for Ngā Kaihautū, November 17. Obtained under the Official Information Act.

Esvelt K M and A L Smidler. RNA-Guided Gene Drives WO 2015/105928 A1

Esvelt K M and N E Gemmell. 2017. Conservation demands safe gene drive. *PLoS Biol* 15(11): e2003850. https://doi.org/10.1371/journal.pbio.2003850

Esvelt K M, Smidler A L, Catteruccia F and G M Church. 2014. Concerning RNA-guided gene drives for the alteration of wild populations. *eLife.* DOI: 10.7554/eLife.03401.001

Federal Ethics Committee on Non-Human Biotechnology (ECNH). 2018. *Precaution in the Environmental Field. Ethical requirements for the regulation of new biotechnologies.* Swiss Federal Office for Buildings and Logistics FOBL, Bern

Fisher D. 2017. Consortium eyes NZ islands for genetic trials on pests. *New Zealand Herald,* December 4. https://www.nzherald.co.nz/nz/news/article.cfm?c_id=1&objectid=11952909

Fleischfresser S. 2017. Benefits and dangers in altering our evolutionary trajectory. *Cosmos Magazine,* May 2. https://cosmosmagazine.com/biology/benefits-and-dangers-in-altering-our-evolutionary-trajectory?utm_source=Today+in+Cosmos+Magazine&utm_campaign=09557a5b6b-RSS_EMAIL&utm_medium=email&utm_term=0_5f4ec2b124-09557a5b6b-180014249

Gantz V M and E Bier. 2015. The mutagenic chain reaction: A method for converting heterozygous to homozygous mutations. *Science* 348(6233): 424-444. doi: 10.1126/science.aaa5945

Gantz V M, Jasinskiene N, Tatarenkova O, Fazekas A, Macias V M, Bier E, and A A James. 2015. Highly efficient Cas9-mediated gene drive for population modification of the malaria vector mosquito *Anopheles stephensi.* PNAS 112(49). E6736–E6743, doi: 10.1073/pnas.1521077112

Garthwaite J. 2016. U.S. Military Preps for Gene Drives Run Amok. *Scientific American.* https://www.scientificamerican.com/article/u-s-military-preps-for-gene-drives-run-amok/

Gonen S, Jenko J, Gorjanc G, Mileham A J, Whitelaw C B A and J M Hickey. 2017. Potential of gene drives with genome editing to increase genetic gain in livestock breeding programs. *Genetics Selection Evolution* 49(3). DOI: 10.1186/s12711-016-0280-3.

Harremoes P, Gee D, MacGarvin, Stirling A, Keys J, Wynne B and S G Vaz (eds). 2002. *The*

*Precautionary Principle in the 20th Century: Late Lessons from Early Warnings*. European Environmental Agency. Earthscan Publications.

Heitman E, Sawyer K and J P Collins. 2016. Gene Drives on the Horizon, Issues for Biosafety. *Applied Biosafety,* 1535676016672631. http://journals.sagepub.com/doi/full/10.1177/1535676016672631

Hesman Saey T. 2017. Resistance to CRISPR gene drives may arise easily. *ScienceNews,* July 20. https://www.sciencenews.org/article/resistance-crispr-gene-drives-may-arise-easily

Hilgartner S. 2018. Afterword: Governing Gene Editing. A Constitutional Conversation. In: *Gene Editing, Law, and the Environment: Life Beyond the Human.* Irus Braverman (ed). Routledge Press.

Hochkirch A, Beninde J, Fischer M, Krahner A, Lindemann C, Matenaar D, Rohde K, Wagner N, Wesch C, Wirtz S, Zink A, Lötters S, Schmitt T, Proelss A and M Veith. 2017. License to Kill? – Disease eradication programs may not be in line with the Convention on Biological Diversity. *Conservation Letters,* https://doi.org/10.1111/conl.12370

International Union for the Conservation of Nature (IUCN). 2016. 095 - Development of IUCN policy on biodiversity conservation and synthetic biology. Declaration adopted at Planet at the Crossroads Congress. Hawaii, 1-10 September 2016. https://portals.iucn.org/congress/motion/095

Jasaonoff S and J B Hurlbut. 2018. A global observatory for gene editing. *Nature* 555: 435-437.

Jasanoff S. 2003. Technologies of Humility: Citizen Participation in Governing Science *Minerva:* 41: 223-244.

Kiss A and D Shelton. 2007. "Strict Liability in International Environmental Law". In: Ndiaye T M and R Wolfrum (eds). *Law of the Sea, Environmental Law and Settlement of Disputes: Liber Amicorum Judge Thomas A Mensah.* Brill Academic Publishers. https://scholarship.law.gwu.edu/cgi/viewcontent.cgi?article=2046&context=faculty_publications

Kuzma J, Gould F, Brown Z, Collins J, Delborne J, Frow E, Esvelt K, Guston D, Leitschuh C, Oye K and S Stauffer. 2018. A roadmap for gene drives: using institutional analysis and development to frame research needs and governance in a systems context, *Journal of Responsible Innovation*, 5:sup1, S13-S39, DOI: 10.1080/23299460.2017.1410344

Lash A. 2016. With New Program, DARPA To Encourage Safety "Brakes" For Gene Editing. *Xconomy.* http://www.xconomy.com/national/2016/10/05/with-new-program-darpa-to-encourage-safety-brakes-for-gene-editing/

Ledford H. 2015. CRISPR, the Disruptor. *Nature* (522): 20-25.

Lunshof J. 2015. Regulating gene editing in wild animals. *Nature* (52) May 14, p. 127.

McFarling U L. 2017. Could this zoo of mutant mosquitoes lead the way to eradicating Zika? *Statnews,* December 13. https://www.statnews.com/2017/12/13/gene-drive-mosquitoes-darpa/

Marshall J, Buchman A, Sanchez H M and O S Akbari. 2016. Overcoming evolved resistance to population-suppressing homing-based gene drives. doi: https://doi.org/10.1101/088427. http://biorxiv.org/content/early/2016/12/07/088427

Min J, Smidler A L, Najjar D and K M Esvelt. 2018. Harnessing gene drive, Journal of Responsible Innovation, 5:sup1, S40-S65, DOI: 10.1080/23299460.2017.1415586.

Minister for the Environment. 2016. GMO regulations clarified. Media release, April 5. https://www.beehive.govt.nz/release/gmo-regulations-clarified

Moro D, Byrne M, Kennedy M, Campbell S and M Tizard. 2018. Identifying knowledge gaps for gene drive research to control invasive animal species: The next CRISPR step. *Global Ecology and Conservation* 13. https://doi.org/10.1016/j.gecco.2017.e00363

Morton J. 2017. Science: What is gene drive technology and what does it mean for New Zealand? *New Zealand Herald,* December 4. https://www.nzherald.co.nz/nz/news/article.cfm?c_id=1&objectid=11952878

Nature. 2015. *Driving test. Gene drive' techniques have the potential to alter whole populations. Regulators must catch up.* Editorial. *Nature* 524:5.

Neslen A. 2017. US military agency invests $100m in genetic extinction technologies. *The Guardian,* December 4. https://www.theguardian.com/science/2017/dec/04/us-military-agency-invests-100m-in-genetic-extinction-technologies

Netherlands National Institute for Public Health and the Environment (RIVM). 2016. Gene Drives. Policy *Report. Authors: J. Westra, C.J.B. van der Vlugt, C.H. Roesink, P.A.M. Hogervorst and D.C.M. Glandorf*

New Zealand Government. 2016. *Accelerating Predator Free New Zealand*. Cabinet Paper.

Nuffield Council on Bioethics. 2016. *Genome Editing. An Ethical Review.* http://nuffieldbioethics. .org/wp-content/uploads/Genome-editing-an-ethical-review.pdf

New Zealand Government. 2016. Accelerating Predator Free New Zealand. Cabinet: Minute of Decision. CAB-16-MIN-0335

Noble C, Adlam B, Church G M, Esvelt K M and M A Nowak 2018. Current CRISPR gene drive systems are likely to be highly invasive in wild populations. *eLife* 2018;7:e33423. DOI: https://doi.org/10.7554/eLife.33423.001

Norwegian Biotechnology Advisory Board. 2017. Statement on Gene Drives. February 14. http://www.bioteknologiradet.no/filarkiv/2017/02/Statement-on-gene-drives.pdf

Ostera G R and L O Gostin. 2011. Biosafety Concerns Involving Genetically Modified Mosquitoes to Combat Malaria and Dengue in Developing Countries. *JAMA* 305(9): 930-931.

Owens B. 2017. The Big Cull. Can New Zealand pull off an audacious plan to get rid of invasive predators by 2050? *Nature* 541: 148-150.

Oye K A, Esvelt K, Appleton E, Catteruccia F, Church G, Kuiken T, Lightfoot S B-Y, McNamara J, Smidler A and J P Collins. 2kl014. Regulating gene drives. *Science* 345 (6197), 626-628. doi: 10.1126/science.1254287.

Prywes N. 2014. On the Irreversibility of Gene Drives. *The Scientist*, September 16. http://www.the-scientist.com/?articles.view/articleNo/41027/title/Opinion--On-the-Irreversibility-of-Gene-Drives/

Regalado A. 2016. The Extinction Invention. *MIT Technology Reivew,* April 13. https://www.technologyreview.com/s/601213/the-extinction-invention/

Regalado A. 2016. Bill Gates Doubles His Bet on Wiping Out Mosquitoes with Gene Editing. *MIT Technology Review,* September 6. https://www.technologyreview.com/s/602304/bill-gates-doubles-his-bet-on-wiping-out-mosquitoes-with-gene-editing/

Rosen I. Licensing CRISPR for Agriculture: Policy considerations. *Broad Institute News*, https://www.broadinstitute.org/news/licensing-crispr-agriculture-policy-considerations.

Simon S, Otto M and M Engelhard. 2018. Synthetic gene drive: between continuity and novelty. *EMBO reports* 19: e45760 | 2018. DOI 10.15252/embr.201845760

Stirling A. 2016. "Challenges in the Governance of Engineered Life: research policy, innovation dynamics and the politics of progress." Presentation to an OECD-sponsored workshop on 'Environmental Release of Engineered Pests: building an international goverenance framework'. North Carolina State University, Raleigh, October 5-6. https://research.ncsu.edu/ges/files/2016/06/Stirling-s16j-raleigh-OECD-GM-workshop.pdf

Swetlitz I. 2016. College students try to hack a gene drive — and set a science fair abuzz. *STAT,* December 14. https://www.statnews.com/2016/12/14/gene-drive-students-igem/

Swetlitz I. 2917. In a remote West African village, a revolutionary genetic experiment is on its way — if residents agree to it. *STAT,* March 14. https://www.statnews.com/2017/03/14/malaria-mosquitoes-burkina-faso/

Taning C N T, Van Eynde B, Yu N, Ma S, Smagghe G. 2017. CRISPR/Cas9 in insects: Applications, best practices and biosafety concerns. *Journal of Insect Physiology.* DOI: http://dx.doi.org/ 10.1016/j.jinsphys.2017.01.007

Tarini G and R A Zilinskas. 2016. Gene Drives: Panacea or Pandora's Box? *The Nuclear Threat Initiative.* November 21. http://www.nti.org/analysis/articles/gene-drives-panacea-or-pandoras-box/

Temperton J. 2017. Gene drives could wipe out diseases – but we need to understand the risks. *Wired Magazine,* April 24. http://www.wired.co.uk/article/kevin-esvelt-mit-genetic-engineering

Terry S. 2014. GM guardian's error a grave failing. *New Zealand Herald,* June 6. https://www.nzherald.co.nz/nz/news/article.cfm?c_id=1&objectid=11268377

United Nations Convention on Biological Diversity.

United Nations Cartagena Protocol on Biosafety.

Unckless R L, Clark A G and P W Messer. 2016. Evolution of Resistance Against CRISPR/Cas9 Gene Drive. *Genetics, Early online December 10. https://doi.org/10.1534/genetics.116.197285*

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

Webber B L, Raghuc S and O R Edwards. 2015. Opinion: Is CRISPR-based gene drive a biocontrol silver bullet or global conservation threat? *PNAS* 112(34): 10565–10567. doi/10.1073/pnas.1514258112

Williams S. 2018. CRISPR Gene Drive Used to Alter Mouse Coat Color. *The Scientist,* July 9. http://www.the-scientist.com/news-opinion/crispr-gene-drive-used-to-alter-mouse-coat-color-64461

World Health Organisation. 2014. *Guidance framework for testing of genetically modified mosquitoes.* http://www.who.int/tdr/publications/year/2014/Guidance_framework_mosquitoes.pdf

Xue K. 2014. Synthetic Biology's New Menagerie Life, reengineered. *Harvard Magazine,* September-October 2014, pp. 42-49.