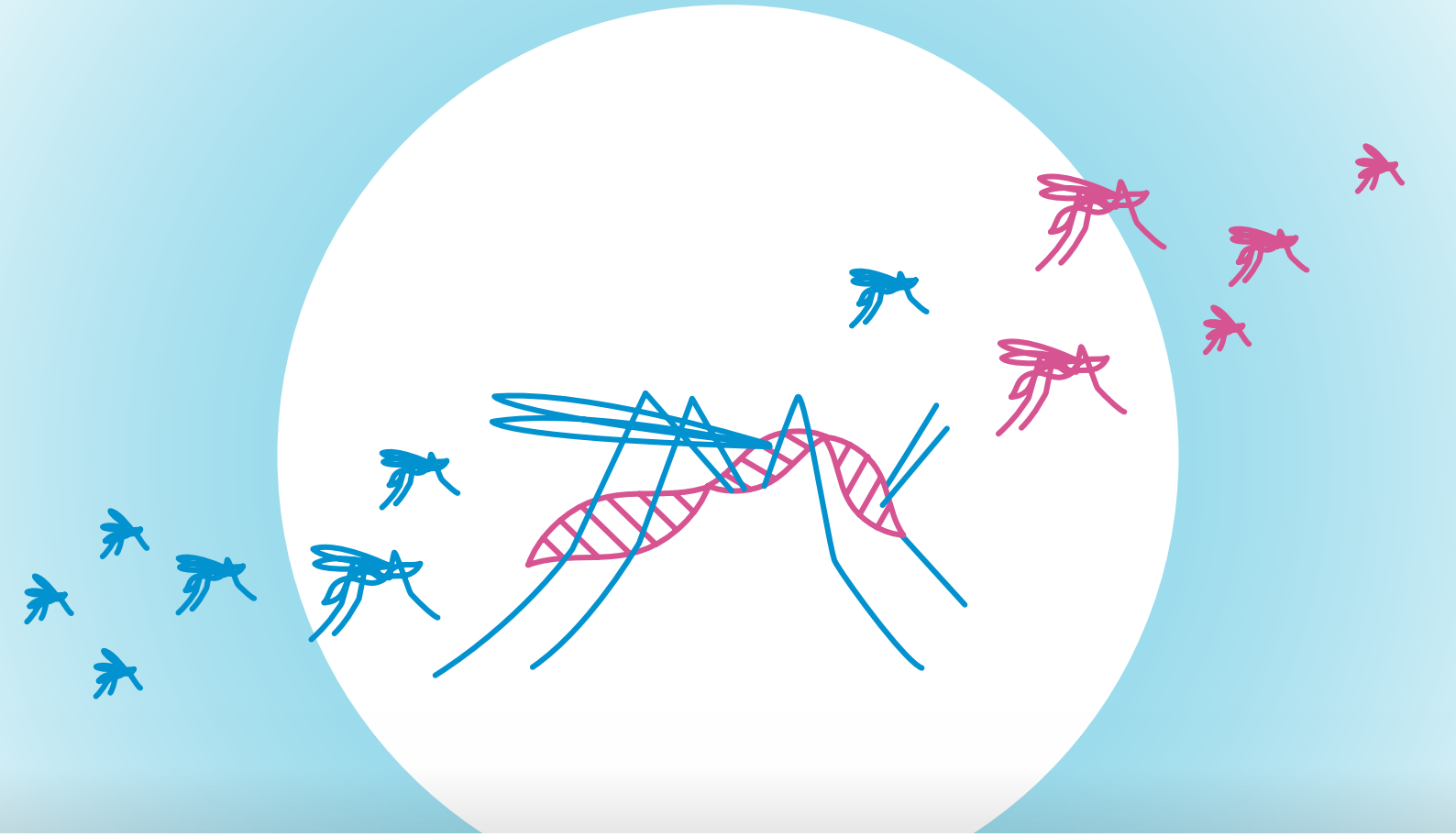

GENE DRIVES

A report on their science, applications, social aspects, ethics and regulations

CSS Critical Scientists Switzerland

European Network of Scientists for Social and Environmental Responsibility

VDW Vereinigung Deutscher Wissenschaftler

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Summary

The science, biology and techniques of Gene Drives

Engineered Gene Drives are a new form of genetic modification that provides the tools for permanently modifying or potentially even eradicating species or populations in the wild. Unlike the previous genetically modified organisms (GMOs), gene drive organisms (GDOs) are not meant to stay where they are released, but instead are designed and purpose-built to spread and to drive their modified genes far and wide into wild populations. The first chapter of this report provides an overview of the technology of gene drives, its history and the present body of scientific knowledge about them.

The realisation of functional gene drive mechanisms has only become possible with the arrival of the genome editing tool CRISPR/Cas. This tool offered a sense of simplicity and ease and this in turn inspired hopes, projections, claims – and funding. However, intentions and promises must be submitted to a reality check, meaning an in-depth understanding of the tools and mechanisms involved, including a focus on their risks and limitations.

The most advanced type of CRISPR/Cas-based gene drive is characterised by its potential capacity to modify or eliminate all targeted organisms. This means that no mistakes must be made, neither concerning the target species nor the affected ecosystems. They must not go where they are not intended to go, nor accidentally escape from cages in laboratories, nor have any unintended effects on the target species, ecosystems, biodiversity or human health. Many risks of this type of gene drive are being voiced in the literature as well as at the Convention on Biological Diversity (CBD) and other bodies. Moreover, there are also serious limitations with the functioning of this technology, such as its inefficacy in many organisms, the quick emergence of resistance, and with its control, such as irreversibility and the impossibility of containment or recall once released.

This technology, as it stands, is not fit for application. Are the above issues addressed? Are they being solved? Major efforts are being undertaken to circumvent or overcome resistance. The other issues of concern, so far, are stuck at the stage of theoretical models and designs, such as the various daisy drive designs, or the "anti-gene drive"-drives, e.g. immunisation drive, reversal drive, drive catchers etc. All these efforts are still lacking proof of concept and often merely exist in the form of mathematical modelling, which carries its own limitations. It is, however, important to recognise that any new layer of 'solutions' will also carry, and needs to be assessed for, their own risks and limitations. These include the utilisation of highly conserved genes as disruption targets that are also found in other species.

These developments have considerably expanded knowledge at the genetic level. There is, however, a sad lack of knowledge about the complexities of real-life settings, with completely different surrounding conditions, high genetic variation in wild populations and a complex network of interactions with other species. The behaviour of gene drives and gene drive organisms in the real world may be very different from any laboratory experiments and modelled predictions, thus adding an extra layer of risk. This powerful technology so far has not proven to be reversible or containable. This means, as pointed out above, we must not make any mistakes.

Potential applications

The usual categorisation of gene drives based on fields of applications and desired or claimed benefits betrays an excitement about the technical advances and a focus on the benefits only. The underlying

causes of the problems gene drives are intended to solve have often been created by current unsustainable practices which could be discontinued and/or replaced or solved by less hazardous means. For instance, modern agriculture is vulnerable to pests because of the biological and genetic simplification of industrial practices, which destroy the balance between pests and their natural enemies, e.g. by pesticides and habitat loss. More diverse farming systems based on agroecology provide a substantive defense against pests. Choices are a matter of information about different options, political will and economic support.

This second chapter therefore places the organism itself and the ecosystems linked to it at centre stage. Fully understanding the biology of an organism and its ecosystems is essential for understanding the impacts and identifying the negative consequences that may arise from the release of a GDO. Three case studies are presented, focusing on taxonomic categories, namely mosquitoes, mice and Palmer amaranth. In all three, the data are insufficient and the complexities too intricate to presently (if ever) allow for clear and reliable predictions of the outcomes and the impacts from a release of invasive gene drives. Given the high level of unpredictabilities, the lack of knowledge and the potentially severe negative impacts on biodiversity and ecosystems (including agroecosystems), the authors and publishers of this study recommend that any releases of GDOs (including experimental releases) be placed on hold until there is sufficient knowledge on gene drives or other solutions to the problem are chosen. For each of the case studies, the search, development, availability and support of other sustainable approaches are elaborated.

Last but not least, the dual use potential of this powerful technology should not go unmentioned. The fact that civilian gene drive technology can also be used for military and harmful purposes needs urgent attention.

The spectrum of organisms discussed as gene drive targets is already broad and continuously growing. The intention of developers is to make the technology quickly and widely applicable for small mammals and for any type of insect, which we regard as alarming, both as an approach to deal with problems, as well as with regards to the impacts of such practices. This exacerbates all the problems discussed above.

There is no solid scientific basis for performing an adequate and robust risk assessment that would cover all the points we have raised, and that we regard as essential for safeguarding biodiversity and human health. The wisdom of strictly applying the Precautionary Principle may be our best guide when facing this new and potent technology.

Social issues

Social issues are important from the start of the research process, upstream of the whole life cycle of innovation (from R&D to outcomes), beginning with the science of gene drives itself. The chapter describes the political economy of GDOs, including how research is patented and funded, and how this leads to unrealistic claims about what researchers can deliver. While gene drive R&D is still in its infancy and no field trials have been attempted yet, many claims about future benefits of gene drives portrayed in the media, scientific publications and patent applications seem premature. The chapter explores how exaggerating effectiveness can lead to opportunity costs when alternative solutions are neglected, and how it can close down public debate about the best ways to develop salient knowledge collectively, to tackle societal problems. The chapter discusses open releases of genetically modified (GM) mosquitoes into the environment (currently without gene drive, but with some plans to include it in the future). It highlights serious limitations in the process of obtaining prior informed consent and discusses how power imbalances may affect the regulatory framework, who is liable if anything goes wrong, and who is asked for their input in decisions.

The chapter concludes that public engagement has to take place at the very beginning of the process, when funders, innovation stakeholders and researchers define what a problem is and set R&D priorities. Social issues regarding GDOs can only be

addressed by broadening the processes of public engagement with prevailing R&D and commercial interests and by taking a properly precautionary approach, which acknowledges uncertainty and ignorance. Genuine empowerment of all affected parties in the interests of making better choices must not be conducted with the premise that the technology will be accepted. The choice of alternative pathways of development for the future must be available.

Ethics and governance

The development of engineered gene drives raises a broad range of ethical questions and considerations. GDOs do not emerge in a vacuum and so the chapter begins by providing a brief sketch of the social and technological background context from which they come and how this context helps shape questions of ethics and governance. The chapter grants that assessing consequences through a risk/benefit lens is important, but insists that this is far from the only lens through which the ethical aspects of a technology as powerful as gene drives should be considered. To widen the ethical viewpoint, the chapter is organised around three categories of concern. These represent concerns connected to 1.) Impacts, 2.) Intervention and 3.) Intention. In the section describing ethical issues connected to impacts, the focus is on describing the uncertainties that plague the current state of knowledge about the impacts of GDOs on organisms and environments, before turning to questions concerning the impacts of GDOs on international, intergenerational, and interspecies justice. Beyond questions about the impacts of GDOs on the physical and social environment, though, are a different set of questions about the type of intervention into the world a GDO represents. The chapter consequently moves on to explore ethical questions connected to the level of interference with the world a gene drive displays and the 'naturalness' of the technology. How a person feels about both the type of intervention and the impacts of the technology will often depend on the intention being embodied and enacted. The chapter therefore turns next to describing some of the worldviews and attitudes that can be associated with engineered gene drives and identifies some of the characteristics of non-relational thinking that GDOs appear to display. With the broad range of ethical considerations about impacts, intervention, and intention outlined and in hand, the chapter closes by making recommendations for how these diverse issues may be addressed through implementing five broad principles for responsible governance of this controversial technology.

Legal and regulatory issues

There is an urgent need for effective international and legally binding regulation of GDOs, as the final chapter of this report shows. Existing biosafety rules, established for 'conventional' GMOs, are deficient and not fully equipped to manage the unique risks of GDOs. With GDOs, spread and persistence are their raison d'être, posing different legal and regulatory challenges, because of their high potential to spread beyond national borders, particularly in the case of GDOs containing 'global' gene drives.

This chapter's review of existing instruments and processes relevant to gene drives and GDOs shows that there are serious gaps. In our assessment, the Convention on Biological Diversity (CBD) and its Protocols, whose aims include the protection of biological diversity, whose scopes include GDOs and which have begun substantive work specific to GDOs, are currently the best home for their international governance.

We consider the following elements as fundamental in a legal and regulatory regime for GDOs:

- Strict contained use standards specific to GDOs to regulate its laboratory research, as well as strict containment measures for transport
- Joint decision-making, in terms of operationalising prior informed consent for all potentially affected countries concerning a particular environmental release
- Effective measures for dealing with unintentional transboundary movements

- Genuine public participation and obtaining the free, prior and informed consent of indigenous peoples and local communities

- Adapted risk assessment and risk management approaches for GDOs, including acknowledgment when such approaches are not possible

- Full assessment of socio-economic impacts, including ethical concerns

- A technology assessment approach, including consideration of alternatives

- Rigorous monitoring and detection

- Stringent liability and redress rules

These elements are not fully in place and urgent efforts need to be undertaken to ensure they are translated into effective rules that are binding on all countries in order to remedy the serious gaps identified, before any release of GDOs is even contemplated. The 2018 decision and previous related decisions of the Parties to the CBD on GDOs make a start in this direction. They establish precautionary obligations that Parties should comply with before considering any GDO release, and to which the United States – a non-Party – and any GDO developer should also adhere in good faith.

To allow for the space and time to put in place legally binding governance arrangements at the international level, which should include the establishment and operationalisation of the elements identified above, the following are critical steps forward in the interim:

- There should be no intentional releases into the environment, including field trials, of any GDO.

- There should be strict contained use standards applied to existing research and development in the laboratory, as well as strict measures for any transport of GDOs, to prevent escape.

- Monitoring and detection for unintentional releases and unintentional transboundary movements of GDOs have to be conducted during this period, with emergency response plans in place.

- International rules for this period of constraint, including for their enforcement and for liability and redress should there nevertheless be damage, must be effectively operational, including at national levels.

Conclusions and recommendations

- Engineered gene drives are a new form of genetic modification that provides the tools for permanently modifying or potentially even eradicating species or populations in the wild. This is done by modifications of genetic material that interfere with evolutionary mechanisms and inheritance patterns. This is the first time humans have been able to create this type of radical genetic change.

- Ethical governance of gene drives should not just openly and inclusively consider gene drives themselves but should also consider the range of alternative ways of formulating and framing the problems that the technology is claimed to address. These alternative framings of the problems (e.g. disease control, invasive species control) will encourage discussion of a range of alternative approaches to solving them. Many of these alternatives may carry fewer risks, may be more actionable in the short-term, more sensitive to local needs and resources and/or may better align with a diverse range of worldviews.

- Because spread and persistence in nature (in other words, invasiveness) are the raison d'être of gene drive organisms (GDOs), they carry an extra level of risk in addition to the one they already have as genetically modified organisms (GMOs). Despite all the new genetic knowledge gained, we can still say very little about what will happen with gene drives in actual real-life settings, with completely different surrounding conditions, high genetic variation in wild populations and myriad interactions with other species and complexities. The behaviour of gene drives and GDOs in the real world may be very different

from any laboratory experiments and modelled predictions.

- CRISPR/Cas-based homing drives, one of the most advanced gene drive systems and conceived as global gene drives, are not fit for application due to important uncertainties at the scientific, technical and practical levels and due to serious limitations with their functioning.

- Most of these uncertainties and limitations of CRISPR/Cas-based homing drives have only been addressed in theoretical models and designs so far, such as the various daisy drive designs, or the "anti-gene drive"-drives. This new layer of 'solutions' will also carry, and needs to be assessed for, their own risks and limitations, such as their potential for crossing over to non-target species.

- Gene drives should not be categorised on the basis of applications and desirable benefits, but on the basis of organisms and ecosystems. This is essential if one wants to focus on solving real problems in conservation, healthcare or agriculture and to avoid being blinded by alluring technological fixes.

- Given the high level of unpredictabilities, the lack of knowledge and the potentially severe negative impacts on biodiversity and ecosystems, including agroecosystems, this report recommends that any releases (including experimental) of GDOs be placed on hold until there is sufficient knowledge or alternative solutions to the problem are available.

- There is no solid scientific basis for performing an adequate and robust risk assessment that would cover all the points we have raised, and that we regard as essential to safeguard biodiversity as well as human health. The wisdom of applying the Precautionary Principle may be our best guide when facing this new and potent technology.

- Discussion about gene drives must not be restricted to the technical assessment of their feasibility and their risks, but in the first place must involve the knowledge and opinions of the inhabitants and farmers of the regions concerned, as well as of patients, consumers and/or workers in the field of the application concerned. The technology is being developed in their interest, so they are the most important rightsholders and stakeholders. Private interests should not control gene drive development.

- Public engagement has to take place at the very beginning of the process, when funders, innovation stakeholders and researchers define what a problem is and set R&D priorities. The public rights- and stakeholders must be involved in this problem-defining and priority-setting. Gene drives, at this stage, should not by definition be considered better solutions than the alternatives.

- Complete transparency and honesty regarding the underlying motivations for the technology's development and use are moral requirements.

- Military funding is one of the largest resources of gene drive research. This shows that offensive or defensive weapons are considered as potential applications. However, gene drive R&D for civilian use and for military use cannot be separated.

- Good governance demands that actors specifically reflect on how values and assumptions shape and inform their work. This is important if we are to understand and critically question how desirable futures are being imagined, and by whom, as well as how problems and solutions are framed. It will particularly allow for divergent worldviews to be brought into the open, rather than being obscured by an overly narrow debate about human and environmental risk.

- Failure to properly include alternatives and exaggeration of the effectiveness of gene drives can lead to significant opportunity costs (mis-spending of money), especially if large sums of money – and other resources, as well as time – are wasted on unrealistic future promises rather than implementing existing interventions effectively and

conducting more cost-effective, diverse, and appropriate R&D.

- Addressing the social issues around GDOs requires taking a properly precautionary approach, which acknowledges uncertainty and ignorance. This is the best guarantee for effective and efficient innovations that respect public health, the environment and biodiversity.

- Public debate about gene drives should be organised and should include the above points. The debate should not be framed by unsubstantiated and unrealistic claims about gene drives as compared to other problem approaches, nor even by the premise that gene drive technology will be accepted.

- There is an urgent need for effective international and legally binding regulation of GDOs. Existing biosafety rules, established for 'conventional' GMOs, are deficient and not fully equipped to manage the unique risks of GDOs.

- In our assessment, the Convention on Biological Diversity (CBD) and its Protocols, whose aims include the protection of biological diversity, whose scopes include GDOs and which have begun substantive work specific to GDOs, are currently the best home for their international governance.

- The necessary elements of a precautionary legal and regulatory regime for GDOs are not fully in place and urgent efforts need to be undertaken to ensure they are translated into effective rules that are binding on all countries, before any release of GDOs is even contemplated.

- To allow for the space and time to put in place legally binding governance arrangements at the international level, as well as genuine public engagement, the following are critical steps forward in the interim: there should be no intentional releases into the environment, including field trials, of any GDO; strict contained use standards need to be applied to existing laboratory research; monitoring and detection for unintentional releases and unintentional transboundary movements of GDOs have to be conducted during this period; and international rules for this period of constraint must be effectively operational, including at national levels .

- If gene drive advocates wish to obtain a clear social licence, it will be essential that they take all ecological and ethical concerns into account and follow the responsible practices of governance outlined above.

Introduction

From wiping out disease-carrying insects or invasive mammals to stopping weeds from evolving resistance to herbicides – even if some applications are still theoretical, gene drives are, without a doubt, the most intriguing and at the same time the most controversial offshoot of genetic engineering. This goes for engineered gene drives. We need to distinguish these from certain natural genetic systems that show a particular similarity to them. Some scientists call these systems 'natural gene drives'. Justified or not, this is reminiscent of the beginnings of the genetic engineering debate in the 1980s, when the argument was used that genetic engineering occurs in nature too, e.g. by viruses transferring their DNA to animals, plants and humans, or by the soil bacterium Agrobacterium tumefaciens injecting a few genes into fruit trees to make them produce rare nutrients, which only this bacterium can live on (Pitzschke et al. 2010, Setubal et al. 2009). The point, however, is: what nature does automatically and what humans do through engineering is, in spite of superficial similarities, quite different – both in execution and in effects. One of the goals of this report is to show the differences.

So what do we mean by gene drives – and what do we do when we make them? The comparison with nature turns out to be quite informative. Gene drives enforce their own propagation with time, down the generations and throughout a population – this is the main feature of what we mean by the concept 'gene drive'. They bias their own inheritance, they 'drive' themselves into a population. At first glance, we do find something similar happening in nature, in what are often called 'selfish genes', meaning genes that ensure their own survival – though not all selfish genes do this purely by means of their DNA; many owe their favoured propagation to the observable characteristic (phenotypic trait) to which they are linked.

If selfish genes show a tendency to copy themselves to their home location ('locus') on the other chromosome of a pair (which only some types of selfish genes do), we say they 'home in' on this spot. Hence the term 'homing endonuclease gene', one example of this. 'Homing' is another property that is favoured for engineered gene drives – though it is human engineers now deciding what the genes' 'home' shall be, what place on the chromosome they should go to (and what genes should be propagated). Indeed, for some engineered gene drives (the so-called 'suppression drives', the type that eradicate a population), homing is the only thing we want them to do – but homing in to a locus where they have never been before, with the effect of killing the organism. Furthermore, it is important to be aware that many of the natural propagation mechanisms of selfish genes are not yet fully understood, and that these mechanisms are certainly not simply copied one-to-one into engineered gene drives. Just consider the currently most popular engineered gene drives, the ones based on CRISPR/Cas. These are quite different from anything natural, since they transfer a bacterial defence system to animals, something never found in nature. CRISPR/Cas plays its natural role in bacteria and does not appear in other realms of nature.

An essential aspect of all this is the context in which it happens: the organism and its ecosystem. If we say, as above, that a gene drive 'enforces its own propagation' or 'biases its own inheritance', we suggest that a gene does something with itself. Can it? Will it do this outside of the organism to which it belongs? What actually makes it do what it does? A reasonable answer seems to be: the organism makes the gene do what it does – in the natural case. Here is one of the major differences between natural and engineered gene drives: with natural gene drives (if we can speak of such), it is the organism that makes them do what they do; with engineered gene drives, it is humans who make them do what they do – inside the organism. As obvious as this may seem, it has far-reaching consequences. It also

highlights that those who engineer gene drives are responsible for what they do.

This shows us that we need to be careful that our arguments are quite correct. But it should also teach us that it is crucially important to form ideas and conceptions that reflect physical reality. This starts with choosing words that reflect that reality. What happens in the DNA of a living organism when a fragment of it is propagated to the offspring more effectively than the rest? Why does nature do this? We need to consider if words like 'selfish' are adequate vehicles to express one of these phenomena, and what phenomenon exactly they express. Similarly: how do we, human engineers, achieve the favoured propagation of a DNA fragment to the offspring of an animal or plant? Why do we do this? To find correct words to express the reality of what we do and why we do it, is essential to the fate of our endeavours.

Why are engineered gene drives suddenly the focus of attention, when the concept is rather old, first coming up in the 1940s? What is the game changer today? This is the rise of CRISPR/Cas, the most popular of the newer genetic engineering techniques, in the past seven years. It was quickly demonstrated that this technique could be used to realise the concept of engineered gene drives, which up to then had, to a large extent, remained theoretical. A steadily growing number of experiments followed, investments soared – and so did the debate. The proof of principle for CRISPR/Cas gene drives came partly in 2015 for fruit flies (Gantz et al. 2015) and more completely in 2018, when a population of caged mosquitoes was wiped out after seven to eleven generations, by a gene drive that destroyed a sex determination gene essential to the survival of the mosquito (Kyrou et al. 2018).

The advent of the CRISPR tool has meant a sudden and radical change for gene drives, from a hypothesis with no means of verification and no practical consequences, into a factual and very rapidly developing technology with a distinct possibility of being applied. The high speed of this innovation brings with it a correspondingly high responsibility for avoiding and minimising risks. The reason usually given for developing an engineered gene drive is the promised benefit of the application: eradicating disease-carrying insects or invasive mammals; protecting vulnerable populations of plants or animals from disease; or adding diversity to species experiencing genetic bottlenecks. The temptation is to go for these laudable goals and just make them happen. A striking aspect of gene drives, however – and of genetic engineering at large and indeed of many other recent technologies – is that the goals or benefits are thus depicted as unquestionable; while the risks are often played down as questionable, not having been 'proven' or demonstrated. Reality is different. As this report shows, the ability of engineered gene drives to perform according to plan and to deliver the envisaged benefits is still largely hypothetical; the associated risks to biodiversity, human health and agroecosystems, on the other hand, are very real.

The ethical questions relevant to gene drives are not all about risks and benefits. The essential starting question that must be asked for every application of a gene drive, of course, is: is this the best way to solve this problem? What exactly is the problem, what options exist to solve it and how does a gene drive compare with the other solutions? To take one example: are we using all existing tools and opportunities for fighting malaria? What can a gene drive add to the actual state of this effort? Such questions should also play a role in the various gene drive applications for conservation purposes, such as eradicating invasive animals or plants or protecting vulnerable populations from disease. Do conservation biology and biotechnology mix well? Conservation biology aims to preserve species and protect them from extinction. Biotechnology, in this case gene drives, aims to do the opposite: to modify, sometimes even exterminate, entire populations of species. Again, the debate needs to be carefully developed and include a broad range of critical arguments which reflect reality.

Attached to this is our responsibility to avoid opportunity costs. Money spent on gene drives cannot be used for implementing existing tools and opportunities to fight the problem in question. Again, ma-

laria is a case in point where this question should definitely be addressed.

There is one notable exception to the rule that the first question should always be "is a gene drive the best way to solve this problem?" This is the military use of gene drives. It is obvious that the power to modify or to eradicate populations of plants or animals (or even humans) can also be used as a weapon, to spread disease, to eradicate or poison food crops, etc. Significantly, the US military is one of the largest funders of gene drive research. Some of their projects take place at universities and other civilian research institutions and have no overtly military goals. However, the technology developed in this way can be used for both civilian and military applications. The term "dual use" for such technology indicates that research and development for civilian use and for military use cannot be separated. Significantly, though, some of these projects with military funding aim to develop ways to counter or reverse the effects of gene drives.

Technological solutions have all too often in history been applied too quickly and caused more problems than they solved; the term 'technofixes' has been coined for this phenomenon. Technology has brought us great benefits, but also immense problems that threaten all natural life support systems on earth (Harremoës et al. 2001, Gee et al. 2013). Avoiding the problems while reaping the benefits requires asking the right questions and taking the time to answer them carefully. Many times quick answers have been given to questions that were never asked, while the relevant questions were not asked either, let alone answered. We ought to think twice before repeating this mistake with the technology of gene drives, which introduces deep, unprecendented changes in nature.

An important feature of many technofixes, and one that certainly holds for gene drives, is that they only 'fix' one variable within a complex system. This means that technofixes often create new problems at other points in the system. These problems are often addressed with a new technofix which can have a similar fate, and so on. Thus technofixes may easily lead into a series of bottlenecks or treadmills. Gene drives are quite likely to be examples of this, with their risk of spreading into populations where they are not meant to be; the resistance against gene drives that the targeted organisms may develop; and many other unknown variables. These problems are often approached with further refinements of the genetic technology, including concepts called 'local gene drives', 'reversal drives' and 'self-limiting drives'. The reversal drives, for instance, although not operational yet, are claimed to be able to reverse or 'overwrite' the genomic change brought about by the original gene drive, with yet another genomic change (DiCarlo et al. 2015). (The concept of reversal drives, incidentally, contradicts the old claim of controllability of genetic modifications, which is being being repeated for gene drives by some scientists.)

When it comes to CRISPR/Cas, the question of regulation becomes vital. This technique and its 'sisters', the other genome editing techniques (some of which may also be used for gene drives), have been the subject of long-drawn political controversy, mostly centred in Europe. From a scientific point of view, there is a strong case for stringent regulation of genome editing techniques, and gene drives only strengthen this case further (ENSSER 2017). In 2018, the European Court of Justice ruled that the genome editing techniques are genetic modification in the sense of the existing EU regulations. In global and other regulatory frameworks (notably the Convention on Biological Diversity and its Cartagena Protocol on Biosafety) there are also good starting points for regulating gene drives. This report provides an overview of all of these regulatory frameworks and their connections with gene drives.

It is all of society's responsibility to make sure that the high speed of development of gene drives does not prevent *time* being taken in order to: critically compare them to alternative measures; investigate the risks of gene drives; and inform and consult all people affected by a proposed deployment. (A peculiar aspect of gene drives compounding this challenge is the fact that any field trial or outdoor test is virtually equivalent to deployment.) We must be aware that we currently still have the chance to do this; if it is ignored, and the technology

passes a certain developmental point, this opportunity will be gone. This critical point may not be far away. Christine von Weizsäcker has defined the "critical relative speed of innovation" as "the speed beyond which it is difficult or impossible, in terms of regulation [of] technology and theory of learning, to steer the direction of innovation in a reasonable way." She adds: "This happens when the speed of technical innovations outruns the speed in which the environment can show its impacts …. Beyond the critical speed of innovation there is "novelty without compass". And you cannot learn from errors" (Weizsäcker 1998). In these terms, our task is to keep the speed of development of gene drives below this critical relative speed of innovation.

Another one of the many serious questions that we need to face and that are asked in this report, is: what is the role of private interests in driving gene drive development? For many of the technological developments which have already reached the marketplace, private interests seeking profits have proven to be the main drivers. Looking at the laudable goals of gene drives mentioned above, in most of these cases (like malaria) it is quite clear that public interest, not private interest, ought to be the main driver of gene drive development; this is why they are laudable. Making sure that public interest is at the steering wheel and private interest does not take over, requires a very high moral standard from developers. This moral call is embodied in the Precautionary Principle. This principle emphasises the avoidance of harm, based on serious signs that such harm may happen. This is an important link to what was said above: it is crucially important to form ideas and conceptions that reflect reality. Reality 'on the ground', in society, in nature and in scientific research, shows whether or not harm is imminent. Objections to precautionary measures are usually, if not always, based on expectations of economic gain or loss. The reality of such expectations, in the case of gene drives, will have to be weighed against that of the potential harms. This is a moral exercise, which can only be carried out if the ideas and conceptions involved reflect the reality of life. We humans have many examples from our recent history that should teach us how to proceed (Harremoës et al. 2001, Gee et al. 2013).

Informing and consulting all the people affected by a proposed deployment of gene drives is one moral requirement that can help guarantee that public interest drives gene drive development. The Conference of the Parties to the Convention on Biological Diversity, in its recent meeting in Egypt, has called on governments to seek the prior and informed consent of indigenous peoples and local communities potentially affected by the introduction of organisms containing engineered gene drives into the environment (COP14 CBD 2018). This is a political step forward, but it will be hard to achieve if consultation and participation do not start right at the beginning of the research and innovation chain, as opposed to current practices, only seeking such social approval at the end.

The speed of innovation in gene drives is high. The uncertainty about their functioning and their consequences is also high, as this full report demonstrates. The appearance of these consequences may be slow, with the result that no coherent learning process will be possible. This combination of factors is the main argument for the necessity of an organised public debate.

In this context, we should be aware of the effect of both hype and 'anti-hype' (counter-hype, the suppression of hype) on the public discourse. The role of hype in gene drive research and development is considerable, as this report points out. However, anti-hype also plays a big role. Many proponents of gene drives actively try to play down the concerns of their critics in order to divert attention away from the subject. One way of doing this, as already mentioned above, is by suggesting that the risks are questionable, whereas the benefits are unquestionable. This does not reflect reality, which is often closer to the opposite – but the aim of such anti-hyping is to silence the discussion. While hype heats the public discourse, anti-hyping mutes it. Both should be avoided.

The same factors that demand a public debate (high speed of innovation, high uncertainty and potentially slow emergence of consequences) raise the question if, for the duration of the public debate, releases of gene drive organisms into the environ-

ment should not be halted. Several gene drives are already reaching the stage where the developers wish to seriously test them, preferably by a release into the environment. Such a case brings us to the verge of exceeding the "critical speed of innovation" (see above) and passing a point of no return. It will then be too late for a public debate. We should not allow facts to be created that make the whole discussion obsolete. This study's goal is to lay a solid foundation for a public debate.

When realisation of a technology becomes possible, as in the case of gene drives, we should re-evaluate our wishes about it. Why did we think we wanted it in the first place? Was this a valid reason? Here we can learn from the old story of the sorcerer's apprentice (Goethe –). In this cautionary tale, an old sorcerer leaves his workshop to the care of his apprentice. The latter then uses magic to clean the workshop, but since he has not sufficiently been trained, he overestimates his skills and consequently causes trouble which he cannot control. At the start of the story, he had wished for something which, at the end, he wished he had not wished.

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Chapter 1

What are Gene Drives? The science, the biology, the techniques

Ricarda A. Steinbrecher and Mark Wells

1 What are Gene Drive Organisms and how do Gene Drives work?

Synthetic gene drives are a new form of genetic engineering that provide the tools for permanently modifying or potentially even eradicating species in the wild. Unlike the previous GMOs, Gene Drive Organisms (GDOs) are not meant to stay where they are released, but instead are designed and purpose-built to spread and to *drive* their modified genes far and wide. One idea for example is to push wild populations back and replace them with specially designed populations that additionally will cause offspring to die if neighbouring populations interbreed with each other. The intention for synthetic gene drives is to rapidly alter the genetic make-up of wild populations, with the aim of either changing certain of their characteristics or eliminating them. An example would be using gene drive technology to genetically prevent mice from having any daughters, then releasing such gene drive mice into an island ecosystem so that they breed with the wild population. Producing only male offspring the whole population eventually collapses and eradicates all the mice on that island. The list of targets is manifold - fruit flies, mosquitoes, snails, rats, mice, plants, feral cats, possums – and new proposals appear frequently.

Whilst primarily aimed at organisms that are perceived as a problem by some parts of human society, whether or not they have been classified as agricultural pests, disease-spreading insects or invasive alien species, the fact is that the technology could be applied much more widely, and indeed could be weaponised or used for industrial sabotage.

A gene drive target may be any organism that sexually reproduces and that does so with reasonable frequency. Thus, gene drives are specific to organisms that reproduce through a process called meiosis, and only work as intended in such organisms. Meiosis is a dedicated and particular form of cell division that ultimately generates non-identical sex cells. It is common in eukaryotes (higher organisms) but absent from prokaryotes, which thus discounts all bacteria and archaea. Moreover, the genes that are subject to alteration by engineered drives are those situated in the nucleus[1], and not genes elsewhere, such as in mitochondria. As noted above, they will only work when the organism reproduces via meiosis and not if for example it does so instead via vegetative reproduction, of which many kinds of organisms are capable, including some plants and probably all fungi.

Looking specifically at organisms that are diploid, i.e. whose nucleic DNA is made up of two sets of genetic material with one set from each parent, this information will be mixed and halved before it is passed on through sex cells e.g. sperm or egg cells.

1 The nucleus is only found in eukaryotic organisms. It is a compartment within a eukaryotic cell that holds the chromosomal DNA and is surrounded by a porous membrane. Other compartments holding DNA are for example mitochondria or chloroplasts.

In that process, the DNA of the parents gets redistributed randomly with the only proviso being that it will have to result in a complete set again.

Whilst normal genes have this 50% chance of inheritance, gene drive elements have changed the odds in their own favour. Some call this "super-Mendelian" inheritance (Chevalier and Stoddard 2001; Hammond et al. 2016; Grunwald et al. 2019). When genetically engineering an organism with special or specifically designed gene drives, these may force their own inheritance to a level of 80% or nearly 100% (see Figure 1). This is particularly the case with CRISPR/Cas9-based gene drives, which have been reported to resemble a "mutagenic chain reaction" (Gantz and Bier 2015). Depending on whether they have been designed as a population *suppression drive* (to reduce or eliminate a target species), or as some kind of *modification drive* (to spread a specifically designed or desired trait), the release of GDOs with such gene drives may - and is generally intended to - either lead to the collapse of a population or to a change of traits and characteristics throughout the entire population.

For example, a population suppression drive could be a gene drive that will spread female sterility. In theory, when passed on to each and every offspring, and also carried and thus spread by each of the males, the wild populations would be quickly reduced and eventually collapse. However, in reality - and depending on gene drive type and species - there might be significant practical difficulties, as well as significant unintended and unpredicted consequences.

There are various genetic mechanisms that have evolved in nature that will result in an increased inheritance rate of specific genetic elements, genes or even whole chromosomes, irrespective of whether their presence negatively impacts the fitness of the organism. Whilst initially not referred to as 'gene drives' or even 'drives', the term has now come to mean a whole broad spectrum of mechanisms, many of which are being investigated, proposed or developed for application as *synthetic* (or *engineered*) gene drives.

Gene drives are currently defined as systems where genetic elements have a biased inheritance trait, irrespective of a benefit or lack of benefit for the organism. They can be used to carry additional genes often referred to as "payload genes[2]" and spread these and their traits throughout a population.

There is a further aspect to synthetic gene drives that is of crucial importance. Deploying GDOs is also a form of *ecosystem engineering*, either as an intentional aim, or an accidental and unintentional consequence of suppressing or eradicating one or more species, or of the intentional modification of biological functions and characteristics of one or more species. The risks and potential serious negative consequences of such ecosystem engineering cannot be addressed in this chapter, yet this aspect needs to be born in mind when discussing the science and technologies.

2 Short historical background

The idea behind using gene drives to suppress or modify whole populations, especially those regarded as pests, by genetic control methods and strategies is not new; it is only the technical capabilities scientists have very recently developed that are. As early as the 1940s, scientists such as Serebrovskii (1940) and Vanderplank (1944) proposed redirecting an insect's own genetic system (against itself), in order to either destroy insect populations or to make them less destructive to human endeavours

2 Different names are being used for such genes that are being linked to and transported by the engineered gene drives: e.g. payload genes (Champer, Buchman, and Akbari 2016), effector genes (Sinkins and Gould 2006; Marshall and Akbari 2018) or simply cargo (Hay et al. 2010).

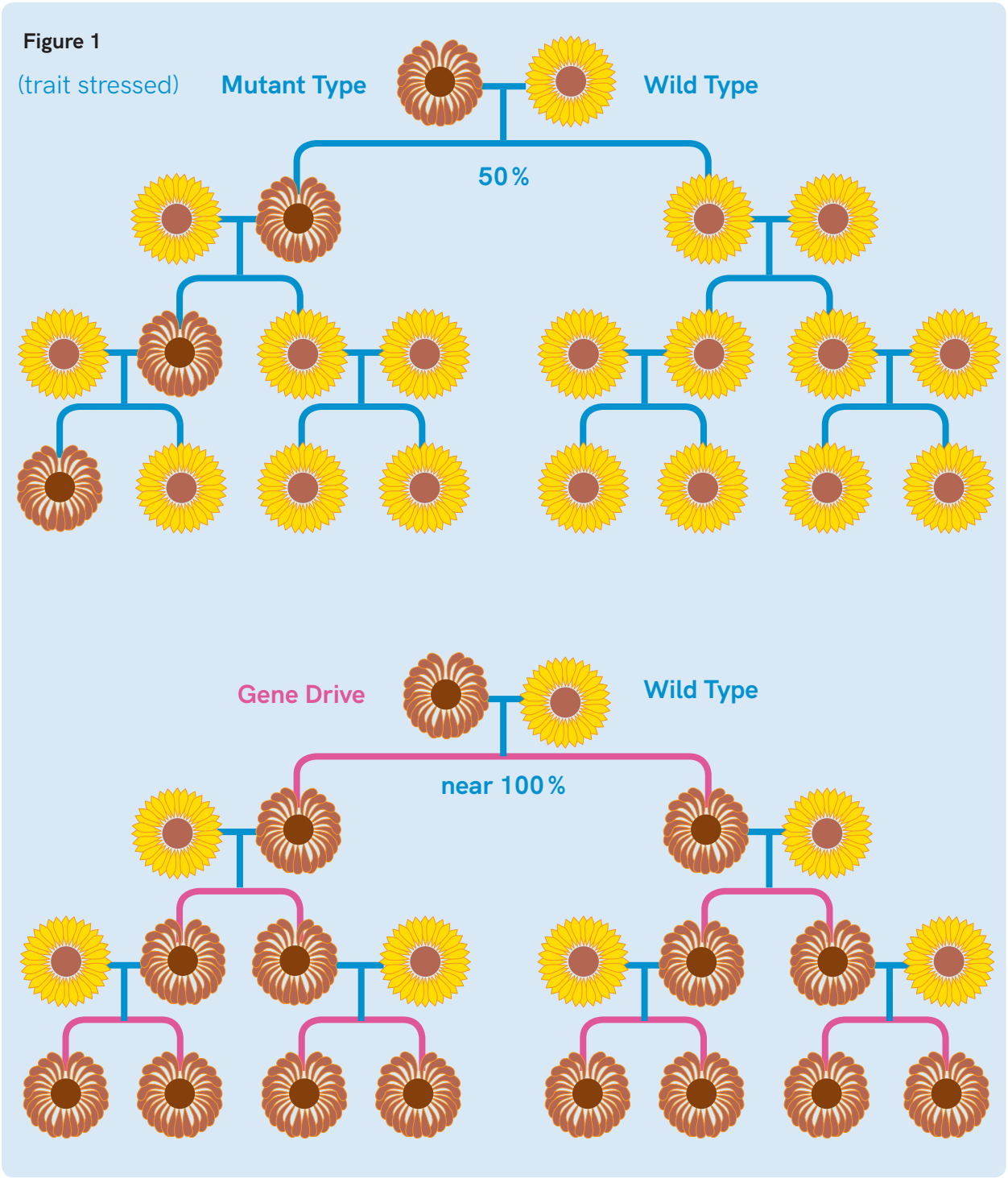

Figure 1: Synthetic gene drives & super-Mendelian inheritance: in a population, a mutation that has no fitness benefit will quickly disappear with the Mendelian inheritance rate of 50%. On the other hand, a synthetic gene drive system with a near 100% inheritance rate ensures the spread of a trait, even if that trait has a clear fitness cost.

such as growing crops (for review see Gould and Schliekelman 2004).

Serebrovskii's theory involved reducing the fitness of insect populations or causing sterile offspring by releasing large numbers of mutated strains, in particular strains with *chromosomal translocations* (the exchange of whole segments between different chromosomes). This concept was revived by Curtis in the late 1960s (Curtis 1968). Vanderplank's work was different in that he suggested and later demonstrated for tsetse flies in Tanzania, that releasing a closely related species or subspecies that will mate with the target species would lead to reduced viability or sterility in the resulting hybrids (Vanderplank 1947; 1948). This approach is now referred to as 'hybrid sterility'.

In a separate approach, Knipling spearheaded the sterile insect technique (SIT), which works by releasing vast quantities of sterile males, with sterility caused by chromosomal abnormalities induced by radiation (Knipling 1955). A massive and successful screwworm fly SIT-eradication program was carried out in the US, starting in Florida in 1957, succeeding in 1966, and begun in Mexico in 1972 and succeeding in 1991 (Gould and Schliekelman 2004).

Other research projects also got under way, seeking to affect at least 31 insect species in specific regions, with particular focus on agricultural pests (e.g. fruit flies, bollworms, boll weevils) and vectors of diseases (e.g. different species of mosquitoes and tsetse flies) (LaChance 1979 in Gould and Schliekelman 2004).

By the early 1980s, the 'golden era' of research on 'autocidal control and strain replacement' had come to an end (Gould and Schliekelman 2004), and funding was drying up, partly due to the lack of further such 'loud' and 'easy' successes. Theoretical population genetics intended to design genetic control programs were equally put back. There were a variety of reasons for this, including lack of function outside laboratories[3] (see also Box 1), funders losing interest, and the need for large governmental infrastructure.

In short, they couldn't quite make it work, although as so often happens with new genetic and technology approaches, there was a great deal of talk and publicity, optimistic claims that brought a great deal of funding and prestige, but then calmed down when results were less than had been expected.

Box 1: Density-dependence: Problems not just for SIT (sterile insect techniques)

Applying SIT to mosquitoes is complicated by what scientists call "density-dependent" effects on mosquito populations. The size of a population of mosquitoes does not depend only on how well the mosquitoes reproduce, but also on other factors, such as competition for food between larvae and for breeding sites. Reducing reproductive fitness may have little effect if the size of the mosquito population is limited mainly by these factors, rather than by its ability to reproduce. Density-dependent effects mean that reducing the numbers of mosquitoes that breed successfully can sometimes have little effect on total numbers of adult mosquitoes, and paradoxically might sometimes even increase populations: for example, because reducing breeding success also reduces competition between larvae for resources, resulting in increased survival rates or a rebound in numbers. Density-dependent effects can influence the current generation of mosquitoes or only affect future generations (delayed density-dependent effects) (Gould and Schliekelman 2004; Juliano 2007; Walsh et al. 2011; 2012).

Excerpt taken from p.2 (GeneWatch_UK 2012)

These early efforts, often referred to as 'classical genetic pest manipulation,' (Gould and Schliekelman 2004), basically showcase the history of the broad concept of using genetics to exert control over or destroy undesired insect populations. Whilst linked to the same aim of suppression or replacement of wild populations, there had been no 'drive' element, no notion of altering the evolution of entire species in any of the examples or strategies mentioned above. These relatively recent strategies required repeated releases of such altered organisms

3 These include issues of mass rearing, sterilisation methods, release methods (e.g. the unintended release of females alongside, who are often not as easily sterilised as males; or greatly reduced male fitness, or loss of fitness over time); but also issues of density dependent populations in the context of SIT.

on a large scale; but none of them were capable of being 'run-away' or true 'gene-drive' technologies, nor were they intended or designed to actively and aggressively spread into all future generations and neighbouring populations.

However, by the early 1990s, with the advent of genetic engineering and the ability to construct artificial genes, recombining different DNA sequences and inserting novel gene sequences into an organism became more commonplace. The possibility of using various 'drive elements' and 'drive mechanisms' to actively spread genetic traits in a population seemed to open up. One idea was, for example, to use parasite resistance genes in mosquitoes in order to stop the spread of pathogens, like the malaria-causing pathogen *Plasmodium*. Drive elements, like the 'piggy-back transposon,' a mobile and highly active genetic element with the ability to carry extra DNA and insert it into host DNA, were also utilised and developed for producing transgenic insects, as well as for modelling the spread of infertility (Ribeiro and Kidwell 1994).

Research intensified around drive elements, that is to say genetic sequences that had an increased inheritance ratio above the standard 50%. Sometimes referred to as 'selfish genes', these drive elements include transposable elements (TEs), first discovered in maize, as well as homing endonuclease genes (HEGs). As transposable elements had also been found in *Drosophila* and other insects, they were the first to be proposed as drive elements in the early 1990s (Curtis 1992; Kidwell and Ribeiro 1992). Burt, however, advocated the use of site-specific selfish genes as drive elements (such as the homing endonuclease genes), to be able to target and knock out essential host genes, and in this way to eradicate entire populations (Burt 2003).

There are a number of genetic elements, as well as specific genetic mechanisms, that can give rise to 'drive', that is, to increase the rate of inheritance of a specific trait. Some of these elements and mechanisms have been investigated or are being developed as gene drive systems, such as for example MEDEA (Maternal Effect Dominant Embryonic Arrest), underdominance, meiotic drive, *t*-complex in mice, and X-shredder. They will be introduced and addressed in Section 4 of this chapter.

3 The breakthrough: the CRISPR/Cas9 or RNA guided Gene Drive system

Whilst development of Gene Drives and GDOs was moving relatively slowly, the advent of CRISPR/Cas9[4] in 2012 (Jinek et al. 2012) radically changed the pace of developments and advances, igniting a fevered push for application.

CRISPR/Cas9 has its origin in bacteria, where it was found to act as a natural defence system[5] against viruses. Utilising this bacterial ability to recognise and cut up the DNA of its invaders, it was eventually developed as an easy-to-use 'genome editing' tool, designed to cleave (or break) a double-strand of DNA at a specific recognition site (Jinek et al. 2012). As such it is made up of two components: the CRISPR part is a single strand of RNA termed 'single guide' RNA (sgRNA), able to recognise a specific DNA sequence and to 'guide' the Cas9 protein to this location. The 'CRISPR-associated' protein 9 (Cas9) is an endonuclease, and is thus the part of CRISPR/Cas that will cause the DNA 'double strand break' (DSB) at the target site. In order for the sgRNA to recognise and bind to a DNA target site, the nucleotide sequence of both the RNA and the target DNA need to be near mirror images of each other.

4 CRISPR/Cas9 stands for: 'clustered regularly interspaced short palindromic repeats' / 'CRISPR-associated' protein 9

5 It is not tested or known whether this is the cause of CRISPR evolution in bacteria or indeed if there is another cause.

It is easy to make Cas9 cleave the DNA at a different site by altering the nucleotide sequence of the guide RNA. This is sometimes referred to as 'programming' a site-specific nuclease and requires detailed knowledge of the DNA sequence of an organism, since a target sequence should be unique so as to avoid cleaving the DNA unintentionally at multiple places. Different endonucleases have been identified and developed, like Cas12a (formerly Cpf1) which creates staggered ends of DNA strands rather than the blunt ends of Cas9. Others are also tested, to work under different conditions, though to do the same task, namely the cleavage (or 'breakage') of a DNA double-strand.

3.0.1 DNA repair mechanisms after double-strand breaks (DSBs)

In genome editing the major role, if not the only role, for site-directed nucleases (SDNs) is to create a DNA double strand break (DSB) at a specific location within the genome. A breakage will in turn induce the cell's own native DNA repair, which has two main repair mechanisms available: the error-prone, non-homologous end joining (NHEJ), and the more specific homology-directed repair (HDR[6]), which requires a template (see Figure 2).

DSBs are preferentially repaired through **non-homologous end joining (NHEJ)**, whereby the ends of the broken DNA molecule will often be further processed, and sequence information can be lost or altered upon rejoining, making this an error-prone repair process (Wyman and Kanaar 2006). NHEJ thus often results in small *in*sertions or *dele*tions (*indels*), or in the substitution of a few nucleotides at or near the cutting site. Because the mechanisms behind this type of DNA repair are not yet fully understood, it cannot be controlled or predicted what exact type of DNA modification will occur when no external DNA template is supplied. The nature and detail of these small mutations are thus regarded as *random*.

Homology-directed repair (HDR) requires a repair template with extensive regions of homology to the DNA sequences neighbouring the breakage site. If such a template is present and if the HDR pathway is triggered, the DSB will be 'repaired' according to the sequence provided in the template, which might be small alterations or the insertion of longer DNA sequences, including whole genes. CRISPR/Cas-based gene drives rely on the actions of this pathway.

Which DNA repair mechanism will be triggered depends largely on the species and taxonomic groups, developmental stage of the organism, cell type, and presence of environmental factors. The predominant repair mechanism is the NHEJ pathway.

3.0.2 CRISPR/Cas variants

Other variants have been developed that will perform other tasks than the initial double strand break of Cas9 and Cas12a. Modifying the Cas9 endonuclease to cut only a single strand of DNA, such nickases (nCas9) are also used to initiate mutations or to create double strand breaks when used as a pair. A highly versatile variant is the deactivated dCas9, which can be fused with other enzymes such as deaminases, able to alter individual nucleotides, such as cytidine, and are now termed 'base editors'. It can also be linked with gene activators or deactivators, which are in fact used in specific synthetic gene drive systems described in Section 4.1.2, underdominance, referred to as CRISPRa.

6 This repair system is given different names by different authors, e.g. homologous recombination (HR), homologous repair (HR), homologous recombination repair (HRR), and homology dependent repair (HDR).

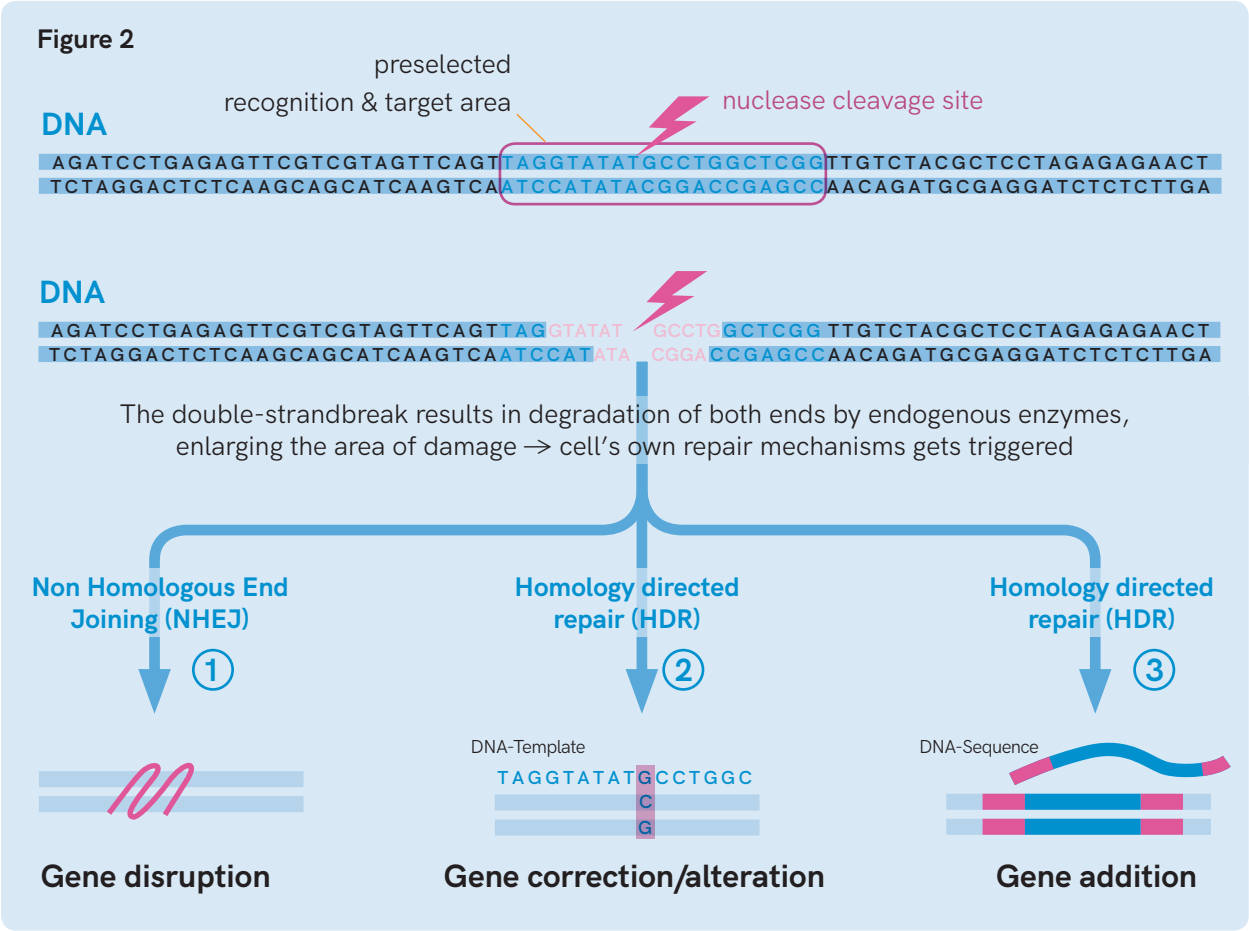

Figure 2: Genome editing and the DNA repair pathways: Top row: After having constructed a site-specific nuclease (SDN)[7] that will recognise a chosen DNA sequence, this SDN will create a DNA double-strand break at its target site. Second row: degradation of both DNA ends by endogenous enzymes may occur, enlarging the area of damage (pink letters above) before the cells own repair mechanism will step in. Bottom half: Depending on circumstances, one of the following three actions may occur. (1) The error-prone 'non-homologous end joining' (NHEJ) repair pathway is triggered, resulting in smaller random mutations near or at the cleavage site. This is predominantly used to create gene knock-outs. (2) & (3): If repair templates are added, the homology directed repair (HDR) pathway may be triggered. For (2) this is a short template with a few mismatches intended to achieve small specific sequence alterations, either to 'correct' a gene or to 'set' specific mutations. (3) resembles the insertion of a longer DNA sequence at a pre-determined site, by supplying a template framed by DNA sections of high sequence homology with the site for insertion. Such inserts could be regulatory sequences or a gene coding for a protein.

Whilst NHEJ (1) is regarded as a routine application for many plant species, HDR (2 & 3) remains challenging, in particular for plants.

In the EU, for regulatory purposes, a classification has been suggested according to the intended outcomes of the actions of site-directed nucleases (SDN), i.e. gene disruption (1) gene correction with template (2) and gene addition (3). In the EU classification these are termed SDN1, SDN2 and SDN3 respectively (Lusser et al. 2012).

7 Site directed endonucleases used in genome editing include: Zinc Finger Nucleases (ZFNs), Transcription Activator-Like Effector Nucleases (TALENs), meganucleases and CRISPR/Cas9. They have different modes of action and of sequence recognition.

3.1 Limitations and uncertainties of CRISPR/Cas

It is well established that CRISPR/Cas9 works by inducing a double strand breakage at a (genomic) DNA target site, with sufficient sequence homology to its own guide RNA[8]. After the repair there will commonly be the intended on-target effects, but additionally there is also evidence of unintended on-target effects, as well as unintended off-target effects.

Unintended on-target effects: Working with both mouse and human cell lines, researchers from the Sanger Institute, UK, for example, reported evidence of significant on-target mutations, such as large deletions -- of up to 9.5 kb -- and complex rearrangements around the DNA breakage site (Kosicki, Tomberg, and Bradley 2018). Additionally, they found mutations (deletions, rearrangements and even insertions) away from the target site, i.e. not physically linked to or running on from it. Whilst the implications of these specific and complex rearrangements have not been investigated, such rearrangements constitute a clear risk, as they can alter gene expression, give rise to further mutations during reproduction, as well as disable or alter the sequence of genes at the site of rearrangement. However, the same situation may also arise for unintended off-target sites, as the action of CRISPR/Cas9 would work under the same rules for both. Off-target sites though have not yet been investigated for complex rearrangements, a fact that needs urgent attention, given that the risks are likely to be the same.

Furthermore, a recent pre-publication is indicating that intended on-target indel mutations – set by the error-prone NHEJ repair mechanism – may have very unexpected and problematic consequences. Tuladhar investigated the consequences of intended knock-out mutations, in particular of frameshift mutations induced by indel mutations. The researchers looked at the processing of the resulting RNAs, their translation into proteins as well as the impact on gene regulation (Tuladhar et al. 2019). Pre-publishing in a not yet peer-reviewed form they reported: "By tracking DNA-mRNA-protein relationships in a collection of CRISPR/Cas9-edited cell lines that harbor frameshift-inducing INDELs in various targeted genes, we detected the production of foreign mRNAs or proteins in ~50% of the cell lines." (Tuladhar et al. 2019, 1). The news here is the generation of new internal ribosomal entry sites (IRES) leading to the production of truncated proteins and the alteration of pseudo-mRNAs resulting in protein coding RNAs. Were these findings found to be common in CRISPR/Cas induced indel mutations, this would have serious implications for safety as well as predictability. These findings are however a reminder that CRISPR/Cas9 is a new technology that due to its ease of use, has found wide-spread application without the necessary time to establish all the consequences and risks of that use.

Unintended off-target effects: A problem that has already been long recognised is that of off-target effects. At the DNA level, off-target effects are those where the RNA-guided nuclease cuts at a site that is not the intended target site. This is thought to primarily happen at sites that are not identical but that have high sequence similarities to the guide-RNA. Experiments have shown CRISPR/Cas9 may cut DNA even with 2-3 nucleotide mismatches between the DNA sequence and the guide-RNA, albeit with lowered efficiency. There does not seem to be a hard rule as to how many nucleotide mismatches are tolerated by the HD repair mechanism, as this also depends on the species, cell type, the actual nuclease variant and the experimental conditions.

Whilst there is an increasing reliance on the use of algorithms to calculate and predict the potential off-target sites, according to the degree of homology (based on the number and position of mismatches), there is also increasing concern about this. In fact, the sole reliance on algorithms to accurately predict the potential off-target sites or regions for off- or on-target effects has come into question repeatedly, as only whole genome sequencing, an increasingly affordable technology, would be able to pick up some of the mutational effects observed. This does not only refer to extensive mutations delinked from the actual cutting site (Kosicki, Tomb-

8 And in the presence of a PAM site.

erg, and Bradley 2018), but also to the integration of vector backbone DNA derived from the plasmid used in the original transgene construct, and for example observed in genome editing experiments with oilseed rape (Braatz et al. 2017).

(Akcakaya et al. 2018) find that many studies reporting no or few off-target effects (mutations) will have failed to identify actual off-target effects due to the limitations of the "*in silico*" (i.e. computer modelling) predictions of potential off-target sites[9].

Since CRISPR/Cas has been found to cut sites with even seven mismatches, or to bind to sequences with as many as 9 consecutive mismatches, Chakraborty argues that restricting searches for potential off-target sites to 3 or 4 mismatches is failing to investigate properly (Chakraborty 2018, 226). He states: "In conclusion, the off-target problems associated with CRISPR-Cas have not been addressed conclusively, which does not bode well, since non-specificity is an intrinsic feature of CRISPR-Cas, evolved over billions of years—otherwise hyper-variable viruses would evade this microbial immune-system with ease and render it ineffective."

It is important to bear in mind that any predictions of potential off-target sites require extremely good and accurate knowledge of the DNA sequence of an organism. This will be a real difficulty when dealing with wild and diverse populations, and the degree of variation present within a whole species (see Section 3.3, Limitations). Thus far, only laboratory data has been generated, and it can be anticipated from the findings, that unintended on-target effects as well as off-target effects will take place. This is a serious concern, as it adds additional risks to the release of GDOs into wild populations.

3.2 How does a CRISPR/Cas Gene Drive work?

When CRISPR/Cas is used as a homing endonuclease, it becomes a 'drive element'. In this scenario, the whole CRISPR/Cas construct will need to be copied across into its own target site (see Figure 3). This can only work properly when the construct contains sequences at its outer borders that are homologous to those present next to the specific CRISPR/Cas target site. Once the construct is present on one chromosome it will produce the CRISPR/Cas molecule, i.e. the RNA-guided endonuclease, which will cleave the DNA at its target site in the parallel (homologous) chromosome. Once the target site is cut, the repair mechanism kicks in and uses the homologous chromosome as a repair template, in this case containing the CRIPSR gene drive construct. With the homology-directed repair (HDR) mechanism activated, the construct gets copied into the target site, and thus ensures the 'inheritance' and spread of the construct.

The construct may or may not contain a 'payload gene' (Champer, Buchman, and Akbari 2016), opening up the possibility of introducing new genes and traits into the target organism (see Figure 3). One category of payload genes aimed for are so-called *refractory genes*, that will stop a disease from spreading or being transmitted, such as genes for malaria resistance (Gantz et al. 2015).

The adaptation of CRISPR/Cas9 as a drive element was suggested in 2014 (Esvelt et al. 2014), and is based on Burt's proposal of using site-specific homing endonuclease genes (Burt 2003). CRISPR/Cas9 gene drive systems were quickly put to test by different research teams, offering proof of principle in four different species. Gantz and Bier were the first with drosophila, entitling their finding aptly as a 'Mutagenic Chain Reaction' (Gantz and Bier 2015), followed by yeast (DiCarlo et al. 2015), *Anopheles stephensi* mosquitoes (Gantz et al. 2015), and *Anopheles gambiae* mosquitoes (Hammond et al. 2016). More recently mice were added to this list of proof of principle, though conversion rates were low (Grunwald et al. 2019). See also Table 1.

9 "To our knowledge, our report provides the first demonstration that CRISPR–Cas nucleases can robustly induce off-target mutations in vivo. Previous in vivo studies have reported no or very few off-target mutations, but used the cell-based 'genome-wide unbiased identification of double-strand breaks enabled by sequencing' (GUIDE-seq) method12–14 or other in silico approaches that have not been validated to effectively identify these sites *in vivo* (see Supplementary Discussion)." (Akcakaya et al. 2018, 419)

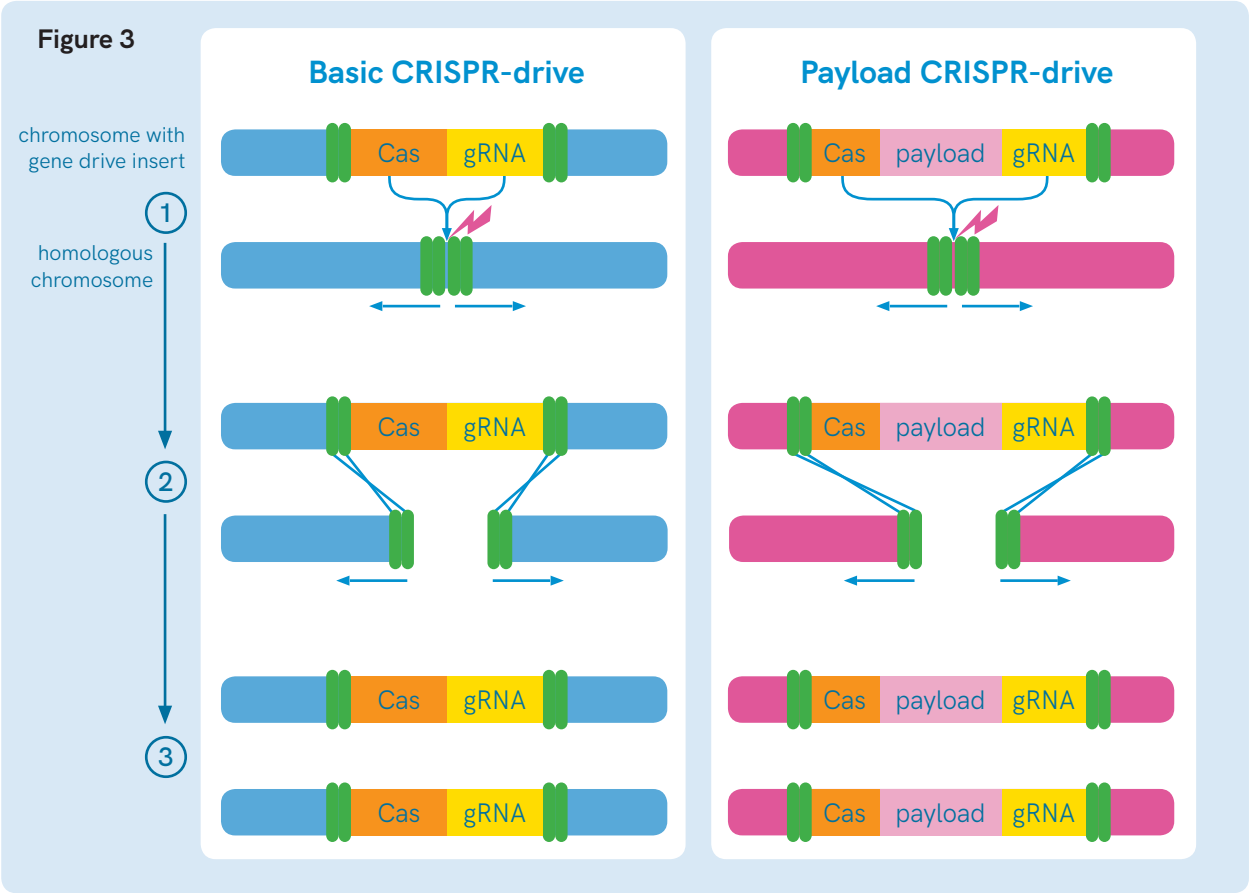

Figure 3: The homing of a CRISPR/Cas gene drive: The CRISPR/Cas construct is composed of the gene sequence for the Cas protein and the sequence for the guide RNA (gRNA). Additionally there are flanking sequences that are identical to the sequences found on either side of the DNA cleavage site, and which are required for the homology-directed repair. (1) Once activated (depending on the promoter used) CRISPR/Cas molecules will be assembled, find the recognition site on the homologous chromosome and sever the DNA. (2) The areas of sequence homology align: i.e. the areas bordering the cleavage site align with the flanking sequences of the CRISPR/Cas construct. (3) In the process of homology-directed repair the CRISPR/Cas construct is copied across to the homologous chromosome. Left panel: Here the drive is meant to disrupt a gene, e.g. for female fertility or pesticide tolerance. Right panel: Here the construct carries an additional payload gene, e.g. for pathogen resistance.

3.3 Limitations, shortcomings and uncertainties of CRISPR/Cas Gene Drives

Here we summarise the limitations encountered, such as emergence and build-up of resistance, inefficiency, off-target effects, lack of specificity and inability to be recalled once released. These shortcomings are being clearly recognised not just by researchers, but also by funders like DARPA, which has developed a 'Safe Genes Project', not simply to get gene drives to work, but to find ways to counter or undo them. This will be detailed below.

3.3.1 Resistance

Resistance to CRISPR/Cas almost inevitably happens. Endonucleases recognise specific DNA sequences as their target sites. If the sequence of a target site changes for whatever reason, the nuclease will not recognise the target and thus will not or cannot cut. In the case of a CRISPR/Cas-based gene drive, this means the drive will be stopped. The organism with such an altered target site has become resistant to the gene drive. There are two sources for such altered target sites to occur: First, there is

natural variation of the target site sequence within a population; and second, new mutations arise due to the activity of the CRISPR/Cas-based gene drive itself.

Natural variation is a common phenomenon, yet there are genes with more highly conserved sequences. Early advocates of endonuclease-based gene drives thus proposed using such *conserved genes* as the target of choice (Burt 2003). 'Highly conserved' means that the DNA sequence of a gene (or the corresponding amino acid sequence) has remained the same over time on an evolutionary scale, and that it has not been changed by random mutations. Such genes are commonly essential genes. This strategy has recently been picked up by Kyrou et al. for mosquitoes (Kyrou et al. 2018) (see also Section 4.1.2 on ZFNs, TALENs and CRISPR/Cas based homing systems).

The problem of new mutations arising is a consequence of the actions of the cell's own repair mechanisms. In fact, what makes CRISPR such a popular mechanism for genome editing for breeding or research purposes is also its biggest weakness for gene drives[10]. As detailed in Figure 2, a cell has two main pathways to deal with a double-strand break of the DNA: to either stick the ends roughly back together again with the non-homologous end joining pathway, (NHEJ) or to find and use a DNA template for the homology-directed repair (HDR). The NHEJ pathway commonly results in random mutations. The frequency by which the NHEJ is triggered will depend on species, cell type and developmental stage, but also on other factors not yet fully understood.

Looking at mutation rates of two different CRISPR/Cas9 gene drives in the fruitfly *Drosophila melanogaster*, Jackson Champer and colleagues reported: "We observed resistance allele formation at high rates both prior to fertilization in the germline and post-fertilization in the embryo due to maternally deposited Cas9. Assessment of drive activity in genetically diverse backgrounds further revealed substantial differences in conversion efficiency and resistance rates. *Our results demonstrate that the evolution of resistance will likely impose a severe limitation to the effectiveness of current CRISPR gene drive approaches, especially when applied to diverse natural populations."* (Champer et al. 2017, 1, emphasis added)

One suggested approach to dealing with this problem is "multiplexing", where a gene drive is equipped with multiple guide-RNAs capable of targeting different sequences. So far, no one has been able to experimentally advance the idea far enough to show a convincing avoidance of resistance. This will be discussed in Section 6.

3.3.2 Inefficiency in plants

In order for CRISPR/Cas gene drives to work, a major prerequisite is the triggering of the homology-directed repair (HDR) mechanism after the DNA double strand breakage (induced by CRISPR/Cas). Without this, the gene-drive element (or construct) cannot align next to the breakage point and be copied across into the target site (see Figure 3). However, the predominant repair mechanism in plants is the 'non-homologous end joining' (NHEJ) pathway, which simply sticks the loose ends of the broken/severed DNA strand back together in a haphazard way. Usually such a repair site will contain small mutations when compared to the original DNA sequence, and will in future be immune to being cut again by the same CRISPR/Cas. Researchers found that homology directed repair will rarely happen in plants, even in the presence of templates with high homologies. There are only a few examples in plants where CRISPR/Cas9 as a genome editing tool using a sequence insertion has been successful. The efficiency rate has been very low. Hahn for example reported, that even with specific frequency enhancing methods they only achieved a frequency of 0.12% HD-repair in the model plant *Arabidopsis* (Thale cress) (Hahn et al. 2018).

10 See also Grunwald et al.: "The alternative DSB repair pathway, non-homologous end joining (NHEJ), frequently generates small insertions and deletions (indels) that make CRISPR-Cas9 an effective means of mutating specific sites in the genome." (Grunwald et al. 2019, 105)

3.3.3 Inefficiency in mice

Experiments did show that whilst a CRISPR/Cas9 gene drive can work in mice, it does so with only very limited efficiency (Grunwald et al. 2019)[11]. In this case the gene drive was designed to spread a mutation, which, instead of trying to cause infertility, attempts to change coat colour from grey to white. When inherited through the female germline, the gene was transmitted to 73% of offspring, exceeding the 50% expected from Mendelian inheritance. However super-Mendelian inheritance was not observed when the CRISPR/Cas9 construct was passed through the male germline, for reasons that are not yet understood. The researchers state that levels of transmission efficiency fall short of what is needed to rapidly drive a gene through a wild population without resistance arising, and comment that, "…both the optimism and concern that gene drives may soon be used to reduce invasive rodent populations in the wild is likely premature." (Grunwald et al. 2019, 108)[12]

3.3.4 Issues with p53

A further complexity has emerged for CRISPR genome editing from experiments on cultured human (and mouse) cells. This showed that genome editing is often counteracted by the cell's natural defences against DNA damage, and that such editing is most likely to be successful in cells in which such a protective defence is somehow not active. These protective mechanisms, which are mediated through a tumour-suppressor protein known as p53, may represent an unanticipated hurdle in designing gene-drives in some organisms, in particular mammalians, as explored in Box 2

3.3.5 CRISPR/Cas off-target effects

There are a number of issues regarding off-target effects, in particular in relation to the behaviour of CRISPR/Cas9 in wild populations. Firstly, and as detailed above, there have been cases where substantial mutations have occurred either at the target site or at a distance from the target site. Whilst the mechanisms and reasons behind this are not understood, there is even less knowledge concerning how CRISPR/Cas may behave under 'natural' conditions, outside laboratory settings and in wild and diverse populations. Secondly, the same is true for off-target effects, where DNA breakage occurs at non-target sites and where repair occurs via the error-prone NHEJ pathway. Will the rate of such off-target breakages change once released into the wild, where the conditions may be significantly different from any settings previously tested? Furthermore, the genomic DNA sequence of wild populations will entail substantial variations as compared to any laboratory reared strain. CRISPR/Cas may thus find accidental target sites that were not intended as target sites and which once cut may be repaired with mistakes.

In fact, releasing CRISPR-Cas9 gene drives into the wild is placing the laboratory and genetic modification procedures into wild populations, with no means of any control at hand. Unintentional mutations arising may be harmless or may be highly problematic, such as disrupting genes, altering gene regulation or producing new proteins or RNAs, clearly adding significant risk to any release.

3.3.6 Invasiveness and potential global reach

The majority of gene drives designed or modelled to date, including the CRISPR-Cas9 based homing drives, have the potential to be highly invasive (see Section 5). Because populations of species breed with other neighbouring groups, over the course of many generations genetic material can spread throughout a whole species. Therefore, a drive released in one country or region could spread to other neighbouring areas, and eventually

11 first published online in 2018 without peer review on https://www.biorxiv.org/content/early/2018/07/07/362558

12 The same authors state: "Although HDR of CRISPR-Cas9-induced DSBs does occur in vitro and in vivo in mammalian cells and embryos, usually from a plasmid or single-stranded DNA template, NHEJ is the predominant mechanism of DSB repair in somatic cells[8,9]." (Grunwald et al. 2019, 105)

could reach all reproductively linked populations of a species around the globe. This means that there are considerable technical difficulties in designing a gene drive that can be confined to a particular geographic area. This has been recognised widely as a serious problem. Invasiveness, combined with a lack of recallability and reversibility (see Table 2), and also combined with the potentially increased rate of mutations and modifications within a wild gene drive population, is likely to make the risks incalculable and potentially very high.

3.3.7 Irreversibility

Almost all of the gene-drive designs constructed so far, and especially the homing CRISPR-Cas9 technology, make effectively irreversible changes to the genome. One possible exception may be very low release rates of underdominance based drives, which however are not CRISPR-based homing drives. This leads to difficult questions about what steps could be taken if a CRISPR gene drive behaves in an unpredicted or harmful way, and what can be done in order to prevent this. Some suggest that a way to reverse the effects of a drive would be to release *another* gene drive to 'overwrite' the changes induced by the first drive. However, alongside the obvious potential for further unpredicted effects, this approach could not completely restore the genomes of affected species to the baseline states, because now both the sequence, as well as the CRISPR/Cas activity of the second gene drive, would be present in the natural population as well, gradually spreading throughout. This is such a thorny technical question, the irreversibility of CRISPR/Cas based homing drives has now become a major funding focus of DARPA's 'Safe Gene' program, a circumstance which underlines the degree and urgency of this problem.

Box 2: p53 and CRISPR
Introducing p53, the 'Guardian of the Genome'

Since its discovery in cultured mouse cells in 1979 (Lane and Crawford 1979), the tumour suppressor p53 has become one of the most intensively studied proteins in the mammalian cell[13].

Biologists' fascination with p53 arises from its role in protecting organisms from cancer. In response to signals triggered by events such as DNA damage (Kastan et al. 1991) or uncontrolled cellular replication, p53 activates protective responses which include halting cellular replication (cell-cycle arrest), DNA repair or programmed cell death (apoptosis) (reviewed by Kastenhuber and Lowe 2017). This role has earned p53 the title 'guardian of the genome' (Lane 1992). Inactivation of p53 through mutation of its gene, *TP53*, allows a potentially cancerous cell to avoid these defence mechanisms, and hence this is the most commonly mutated gene in human cancers (Kandoth et al. 2013).

p53 versus CRISPR

Following its invention only a few years ago, in 2012, CRISPR-Cas9 genome editing of mammalian cells has become a routine laboratory experimental procedure, generating great interest in its potential to treat human disease (Adli 2018). However, it was only in 2018 that evidence emerged from studies of cultured human cells showing that the cell's natural defence mechanisms, centred on p53, counteract the genome editing process by inducing a DNA damage response and cell cycle arrest (Ihry et al. 2018, Haapaniemi et al. 2018). Equally, when p53 is inactivated, CRISPR/Cas9 becomes more effective. In human stem cells gene editing was observed to be 17 times more efficient in the absence of p53 (Ihry et al. 2018). This means that cells which have been successfully edited are likely to lack this vital protective mechanism, posing a significant cancer risk if they are re-implanted in a patient without appropriate screening. This discovery has led to calls for caution in applying the technology in the clinic.

How widespread are p53 type protective mechanisms?

Given the intention for widespread application of CRISPR/Cas9, the question arises: in which organisms and in which cell types might we expect similar interference in genome editing? Answering this question requires a little more background. In humans and most mammals, p53 has two additional and similar 'sister' proteins, p63 and p73, which perform a variety of functions, some of which are related to controlling development, and some of which resemble or even overlap with those of p53 (Belyi and Levine 2009). All three have some role in protecting genomic integrity by responding to

13 More than 90,000 publications on this protein can be found on Pubmed

DNA damage and inducing apoptosis (Lin et al. 2009; Zaika et al. 2011). The protective activity of each form appears to vary in different cell types: p63, for example, has been shown to protect female germline cells (i.e. reproductive cells) (Suh et al. 2006), whereas the core function of p53 is protecting somatic (non-reproductive) cells (El Husseini and Hales 2018), with an apparently less prominent role in protecting the germline (Muller, Teresky, and Levine 2000).

The p53/p63/p73 family can be found in all bony fish, mammals and birds, whilst related proteins are found in other vertebrates, mollusks, insects and nematodes, but not yeast (Belyi et al. 2010). The common ancestor of the p53 family is believed to have been present in very early animals: a descendant of this ancestral p53 is found in modern day sea anemones, which diverged from other animals around a billion years ago, and has been shown to protect the genome by inducing apoptosis in response to DNA damage (Pankow and Bamberger 2007) in germline cells, but not somatic ones. This implies that the *ancestral p53 evolved to protect germline genomic integrity and that this function has been retained within the p53 family throughout the animal kingdom.*

What does this mean for gene drive research?

The complexity of the many processes involved make it difficult to fully predict the consequences of the interplay between a CRISPR/Cas9 homing gene drive and the protective mechanisms mediated by the p53 family. It might be expected that if CRISPR/Cas9 genome editing is activated in germline cells to propagate a gene drive, members of the p53 family could promote repair of the DNA breaks (without integration of the gene drive) or activation of programmed cell death, both of which could interfere with propagation of the drive. Whilst gene drives have been shown to work in insects (Kyrou et al. 2018) which possess p53 family proteins, this does not rule out that the p53 type responses could be activated in other cases, either due to a higher sensitivity to DNA damage, or to differences in gene drive design. This may account for the observed low efficiency of CRISPR/Cas9 gene drives in mice (Grunwald et al. 2019), which possess a p53/p63/p73 family similar to that found in humans with obvious potential to counter-act CRISPR/Cas9. Indeed, the presence of this powerful set of defence mechanisms may present a significant obstacle to efforts to apply gene drives in many animal taxa beyond insects.

3.4 CRISPR/Cas as enabler for many Gene Drive systems

CRISPR/Cas9 has become a key element in the development and feasibility of gene drives. This is not exclusively but is particularly true for homing drive systems, as just mentioned above, where CRISPR/Cas9 has become the prime agent in the role of an RNA-guided homing endonuclease (CRISPR/Cas-based homing drive).

However, there are other gene drive systems that have received little attention, but because of the utilisation of CRISPR/Cas (as a site-directed endonuclease and genome editing tool), are now experiencing accelerated development (Marshall and Akbari 2018), for example the X-shredder and toxin-antidote systems, discussed in the following section.

4 Mechanisms and techniques used

Engineered gene drives have two main goals for practical and/or commercial use in the fields of human health, industry or agriculture: to either **alter (modify) and replace** a population; or to **suppress and eliminate** a population or a species. In this, some applications depend on the ability to transport or carry a 'payload' or 'cargo' gene, together with or linked to, the drive element. *Payload or cargo genes* envisaged for altered characteristics may include, for example: toxin genes, disease resistance genes or disease-*refractory* genes. The latter are genes coding for compounds that will stop vectors (e.g. mosquitoes or flies) from transmitting diseases (e.g. Zika or Malaria), by blocking the pathogen from developing or spreading in the host-vector. Whether a particular drive mechanism has the ability to relia-

bly transport such extra cargo is a criterion indicated in the sections below and summarised in Table 2.

Most *drive mechanisms* are based on so-called 'selfish genetic elements', also referred to as 'active genetic elements' by some (e.g. Gantz and Bier 2016, Grunwald et al. 2019). As detailed below, these drive mechanisms can be categorised as two main types, which attempt to achieve inheritance bias through: 1.) over-replication of the genetic element, thus also referred to as 'replication distorter'; 2.) preferential segregation or transmission of the genetic element, also referred to as 'transmission distorter'.

The utilisation of CRISPR-endonucleases features strongly in both types, enabling the development of synthetic gene drives for different mechanisms and modes of action. In fact, there is an overlap between the use of different genetic elements, the mechanisms, and the modes of action, that is detailed below.

4.1 Selfish genetic elements:

Genes within a genome are commonly seen as working together collaboratively to produce a viable organism (Runge and Lindholm 2018). As part of this collaboration, all genes get an equal chance of transmission during sexual reproduction, which, according to Mendel's Law of Inheritance, gives each gene from each of the two parents a 50:50 chance of being passed on to the next generation (i.e. from 'child' to 'grandchild'). Most multicellular organisms are (at least) **diploid**, meaning they have two complete sets of genetic material in the form of chromosomes, one set from each parent. This means that each gene is present in two copies, occupying the same position or 'locus' on the parallel (or homologous) chromosome, often with slight variation. The different variations of a gene are termed **'alleles'**, coding for example for yellow or green seed colour. If the two copies or alleles of a gene are identical within an organism, this organism is termed to be **'homozygous'** for that gene or allele (or sometimes trait) (see Figure 4).

If there are two different versions or alleles within the organism, the organism is termed '**heterozygous**' for that allele (or trait). These alleles will be passed on (transmitted) in a 50% ratio to the offspring.

There are, however, specific genetic elements that do not play according to the same rules. This is why they are termed 'selfish genes' or 'selfish genetic elements'[14] (Werren, Nur, and Wu 1988), they seem to solely look after their own interests rather than the new offspring's. They are not part of the collaborative effort of upholding or enhancing the viability and fitness of an organism, and do not follow the 50:50 rule of inheritance. Instead, they have gained control over their own transmission. They are also capable of altering the odds of inheritance in their own favour, and thus are able to rapidly propagate through populations (Manser et al. 2017). They can even do so at a high fitness cost to the organism. This in turn leads to "counter-adaptations" by the rest of the organism's genome "that generate unique selection pressures on the selfish genetic element. This arms race is similar to host–parasite co-evolution …" (Runge and Lindholm 2018, 1). In this sense, genes can be seen as a type of society, in which most members behave in a certain way, but there are occasionally outlaws or other aberrant members. As in society, the outlaws sometimes confer an advantage or disadvantage to the group, but unpredictably. Yet the story does not stop there.

Rather than casting the selfish genetic elements (SGEs) in a negative light, and focusing on the aspect of 'selfish', it is precisely this co-evolution and co-adaptation that is becoming a focus of research. Instead, some of the elements or mechanisms, for example the over-replication ability of transposable elements, are increasingly regarded as vital components for genome evolution and even speciation (Biemont 2010). John H. Werren importantly noted: "The story that is emerging increasingly supports a central role of SGEs [selfish genetic elements] in shaping structure and function of genomes and in playing an important role in such fundamental biological processes as gene regulation, development,

14 or sometimes parasitic genetic elements or selfish DNA.

Figure 4

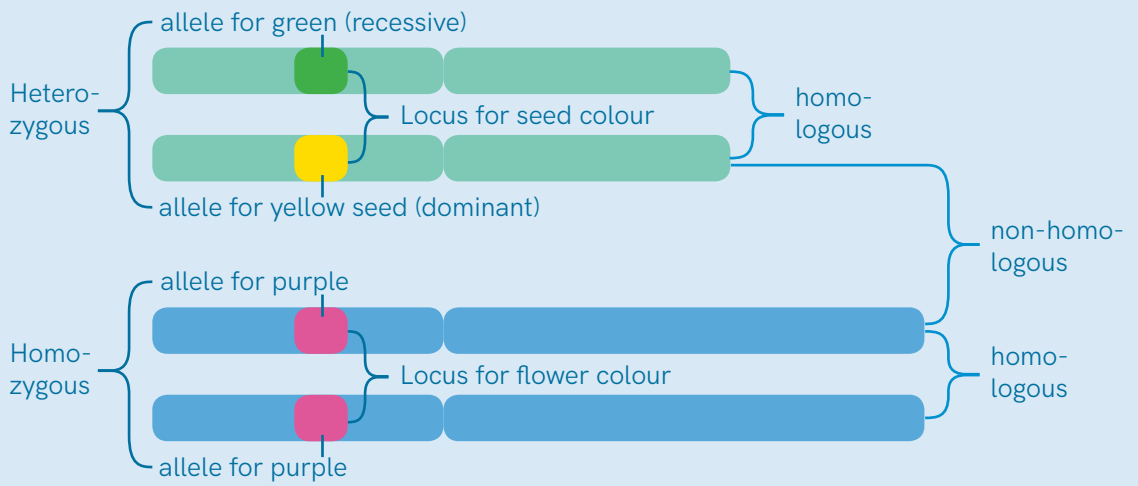

Figure 4: Diploid chromosomes, alleles and their terminology. Depicted are two pairs of chromosomes, with one chromosome of each pair (here a short and a long one) derived from each parent. The chromosomes within a pair are termed *homologous* chromosomes and are basically the same in that the position (locus) of the genes are the same, though they may be different alleles. If the alleles are identical then the organism is *homozygous* for that gene or trait (e.g. purple flower colour). Otherwise the organism is *heterozygous* for a gene or a trait (e.g. seed colour).

evolution of genetic novelty, and evolution of new species." (Werren 2011, 10863). In fact, the study of these elements and the processes involved are now contributing to an emerging re-think of what a genome is and how it interacts with its environment. (Werren 2011; Lindholm et al. 2016).

Consequently, when talking about engineered gene drives, which are all based on and are exploiting the mechanism of these SGEs, there is a level that we cannot comprehend at this point in time. SGEs are vital evolutionary players, deeply embedded in a long evolved and complex regulatory structure. What therefore does it mean to take SGEs out of their own context, reshape and alter them, and place them back into this interactive system? What might the consequences be at that specific level?

This is an important discussion that needs to take place now. It would be wrong to inadvertently assume that SGEs are only a "tool" that can be readily adapted and utilised for the purpose of modifying organisms and whole populations in the wild. They are much more than that and it could be most unwise to disregard this.

Setting aside their important role in evolutionary dynamics and focusing on the aspect of gene drive, there are many different ways by which 'selfish' genetic elements enhance their own presence in a population or species. Such genetic elements may for example be genes, sections of chromosomes or even whole chromosomes. There are the **'over-replicators'** (McLaughlin and Malik 2017) that flourish by copying or moving themselves to other parts of the genome, which are termed 'transposable elements', or into their own (allelic) locus in the parallel chromosome, termed 'homing endonuclease genes'. The other group are the **'transmission-distorters'**, which ensure they are the genes transmitted to the next generation, not "the other" ones. This is often done by actively destroying "the other", whether that is at the DNA level (e.g. X-shredders) or at the level of cells or embryos that will die (e.g. Medusa).

A number of these selfish genetic elements, their multiplication or transmission mechanisms, and their mode of action, are being or have been considered for the construction and use of engineered gene drives. The following briefly describes these selfish genetic elements and/or drive mechanisms by which these elements multiply or change the odds of their inheritance and transmission. Also indicated is the extent to which these may potentially lend themselves as gene drive systems for population eradication or modification, the latter also depending on the ability and reliability of carrying and spreading payload genes. This section also lists limitations and risk factors, such as inactivation of or build-up of resistance to gene drive mechanisms, the lack of reversibility, and vertical gene transfer to neighbouring populations or closely related species. A summary is given in Section 5 (Table 2).

The elements and drive mechanisms described in this section work at very different levels and cannot easily be compared. Some focus on the intentional outcome (e.g. sex-ratio distorters) or the mode of action (e.g. toxin-antidote based drives), whilst others refer to the mobile element itself (e.g. 'transposable' element). An overview is given in Figure 5, which is based on discussions in (McLaughlin and Malik 2017; Lindholm et al. 2016; Simoni et al. 2014).[15]

4.2 Over-replicators / replication-distorters

As outlined above, over-replicators achieve an inheritance bias in their favour by creating extra copies of themselves in the genome. There are two members in this group, the transposable elements

Figure 5

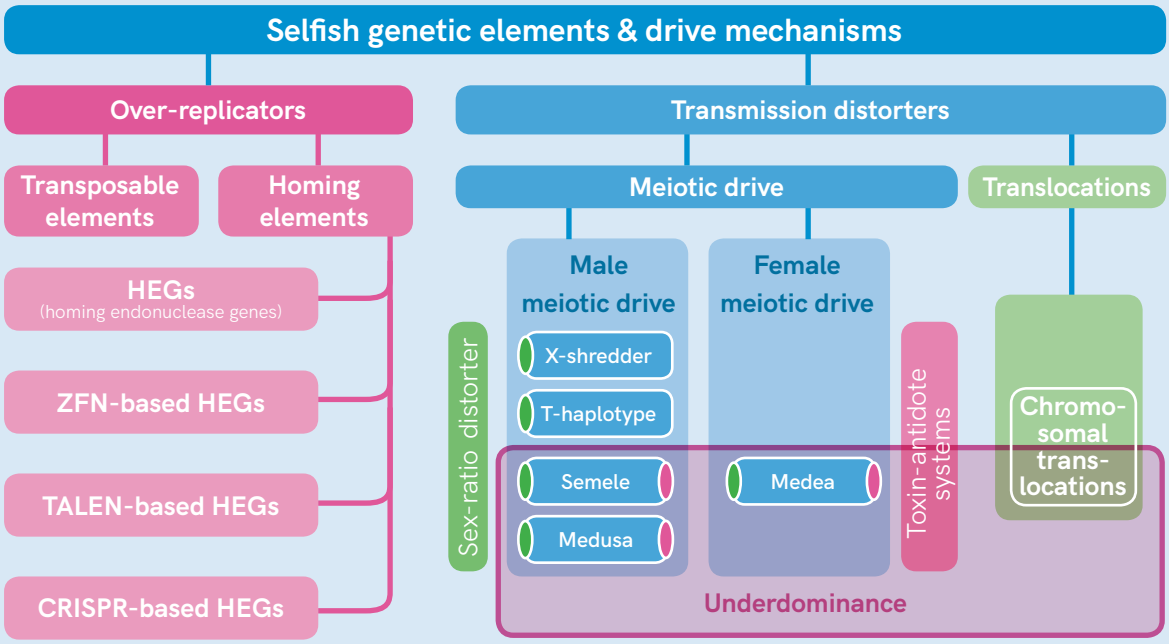

Figure 5: Overview of selfish genetic elements and gene drive mechanisms: Schematic representation with over-replicators on the left and transmission-distorters on the right. It shows that underdominance is not a defined category in itself, but that various mechanisms can be used to create an underdominance system, including chromosomal translocations. Equally it shows that toxin-antidote mechanism can be used for sex-ratio distortion and underdominance.

15 Simoni for example states: "Naturally occurring selfish elements include transposable elements, meiotic drive chromosomes, sex ratio distorting elements and homing endonuclease genes (HEGs). HEGs are highly specific endonucleases that generate double-strand breaks (DSB) at specific loci in the host genome (2)." (Simoni et al. 2014)

(TEs) and homing endonuclease genes (HEGs). TEs do not have a mechanism to guide the insertion of a new copy to a particular site in the genome, although the insertions do not occur randomly either; whilst the HEGs have the means to guide their insertion to a precise location on the genome, namely at the exact same position where they are, but on the parallel chromosome.

4.2.1 Transposable elements (TEs)

Transposable elements[16] (TEs) are a type of 'mobile genetic elements' that are found in almost all species. Discovered by Barbara McClintock in maize in the late 1940s (McClintock 1950) and later described as 'jumping genes', a TE is a segment of DNA that can change its position within the genome of an organism on its own accord. This process is commonly referred to as *transposition*. During transposition, TEs will often increase their copy number within the host genome, thus leading to a higher inheritance rate in subsequent generations.

Whilst there are many different families of TEs, they can all be grouped into two classes: (I) those that move by copy & paste mechanisms (via an RNA intermediate); and (II) those that move by cut & paste mechanisms, often referred to as 'DNA transposons'. Transposition of class-I TEs will automatically result in multiplication, as the original TE remains in its place whilst a copy inserts itself at a different location in the genome. This is not the case with class II TEs, although replication may occur through a number of mechanisms (summarised in Marshall and Akbari 2016), thus still leading to their enhanced rate of inheritance.

If, for example, a DNA transposon moves position during the stage of DNA replication of the cell cycle, it could jump from a location that has already been replicated and land in a location that has not yet been replicated, resulting in a net gain of one TE. Additionally, once the TE is excised for transposition, there will be a gap in the DNA where it had been. The cell's repair mechanism may simply rejoin the loose ends by non-homologous end joining (NHEJ) or it may fill the gap via homology-directed repair (HDR), using the duplicated DNA strand containing the TE as a template.

Whilst TEs are commonly referred to as selfish genetic elements, (Munoz-Lopez and Garcia-Perez 2010), this view is not shared by all. Biemont for example states: "TEs are no longer seen as ''junk'' and ''selfish'' pieces of DNA—the predominant view from the 1960s through the 1990s—but as major components of genomes that have played a significant role in evolution, an idea also first proposed by McClintock (1984: her Nobel Prize lecture)." (Biemont 2010, 1085). Whilst high TE activity outbursts can at times be associated with speciation, such outbursts are usually very time limited, as the host organism will soon generate counter-measures to shut down the activity of the TEs and have them back in order. Measures like gene-silencing will for example disable the production of compounds that TEs need in order to multiply or jump.

TEs of class II are known to be able to spread widely throughout populations. The *'P* element' is a good example of this. Now commonly found throughout populations of the fruit fly *Drosophila melanogaster*, the *P* element seems to have only arrived in this species in the 1930s, rapidly spreading throughout all its populations within 50 years (Anxolabehere, Kidwell, and Periquet 1988). They are thought to have horizontally transferred from *Drosophila willistoni,* possibly via the semiparasitic mite *Proctolaelaps regalis* (Houck et al. 1991).

Due to their ability to spread widely and to enhance their presence in a genome, TEs can make up a substantial portion of the genome of a species. However, most of these TEs will have been inactivated over time through acquired mutations and various host defense mechanisms, including gene-silencing mechanisms such as DNA methylation and RNA interference (Munoz-Lopez and Garcia-Perez 2010)[17]. For example, the genome of silk-

16 Though a selfish element, TEs are not considered by everyone to be a gene drive.

17 "On the other hand, host organisms have developed different mechanisms of defense against high rates of transposon activity, including DNA-methylation to reduce TE expression […], several RNA interference mediated mechanisms […] mainly in the germ line […], or through the inactivation of

worms *(Bombyx mori)* is comprised of around 45% TEs, that of honeybees *(Apis mellifera)* only of 1%, in (Biemont 2010) and that of the main malaria-carrying mosquito *(Anopheles gambiae)* about 15% (Holt et al. 2002). Whilst some plants, especially maize, have a genome with more than 70-80% TE sequences, humans have around 45%, mice about 37% and some fish 10%, see (Munoz-Lopez and Garcia-Perez 2010 and Biemont 2010).

TEs as gene drive mechanisms:

The rapid spread of the *P* element initially raised hopes that class II TEs could be used as gene drive systems, transporting engineered 'payload' genes throughout populations of intentionally modified/engineered organisms. It is these TEs of class II that are regarded as having the potential for gene drive applications. They basically consist of a transposase gene framed by terminal inverted repeats (TIRs). A payload gene placed adjacent to the transposase gene would thus – at least in theory - move together with the TE construct and spread above the 50:50 odds of inheritance.

Genetically engineered TEs have been used to transform and genetically modify insects, first achieved in *Drosophila melanogaster*, utilising the *P*-element (Spradling and Rubin 1982). The *P*-element, however, only works in drosopholid insects. The *Hermes*, mos1/mariner, Minos and *piggyBac* elements were identified to work in some mosquito species (listed in Macia et al. 2017B and reviewed in O'Brochta et al. 2003).

Attempts have been made to harness TEs as gene drives in mosquitoes, yet when engineered into an organism the integrated engineered TEs have very low remobilisation rates, meaning they stay where they are and do not jump. Macias et al. commented recently: "It was imagined that transposons would also be useful as a gene drive system, but transposons that could mediate insertion into a mosquito's genome were not so easily remobilized […]. Only recently has a synthetic construct based on the piggyBac transposon been demonstrated to mobilize itself once inserted into a mosquito genome, but rarely […]" (Macias, Ohm, and Rasgon 2017, 3). Even special attempts to improve the post-integration mobility of artificial *Hermes* and *piggyBac* elements have only resulted in mobilisation rates less than 1% (Smith and Atkinson 2011; Macias, Ohm, and Rasgon 2017) and 6% (O'Brochta et al. 2011). This is much too low for gene drive requirements.

Draw backs & limitations:

- TEs do not integrate at specific recognition sites – and therefore cannot be used to disrupt or knock out a specific target gene, such as a gene crucial for development, fertility or gender. TE-based gene drives could thus only be used in replacement strategies for – in theory at least – spreading particular trait or effector genes.

- Low efficiency: As pointed out, experiments have shown that the post-integration mobilisation of engineered TEs has so far been extremely low and insufficient for gene drive purposes.

- Insert size (payload gene or cargo) can be a problem – size matters. Frequently, TEs with large cargo sizes don't jump or spread easily, e.g. *Sleeping Beauty* element (Izsvak, Ivics, and Plasterk 2000). Lampe et al., for example, found for the *Himar1 mariner* element (in horn fly) that "transposition frequency decreased exponentially with increasing transposon size" (Lampe, Grant, and Robertson 1998).

- Stability and integrity of the construct and insert: It has been observed that engineered TEs can lose (or throw out) the added cargo DNA sequences, for example those found with the *P* element (Carareto et al. 1997), or that the sequence of the insert is being mutated. The consequence would be the spread of the element, but not the additional effector gene sequences (Marshall 2008), which would not be desirable.

- Furthermore, cells or organisms are able to develop defence mechanisms against the mobilisa-

transposon activity by the action of specific proteins […]." (Munoz-Lopez and Garcia-Perez 2010, 116)

tion, jumping and spread of TEs. Proof lies in the large quantities of stationary and mostly deactivated, mutated or silenced TEs that often make up substantial portions of the genome.

- The specificity of particular and well-adapted TEs for particular species would make the use of TEs a new challenge for each new species.

- A serious drawback is that of horizontal gene transfer, where the TE (and a linked payload gene) is transferred to another species by mechanisms that are not fully understood. Transfer via sexual reproduction will keep a TE within the same species, yet TEs specific to one species have been found to appear in other species. Bourque et al. have summarised this recently: "There is now a large body of evidence supporting the idea that horizontal transposon transfer is a common phenomenon that affects virtually every major type of TE and all branches of the tree of life […]. While the cellular mechanisms underlying horizontal transposon transfer remain murky, it is increasingly apparent that the intrinsic mobility of TEs and ecological interactions between their host species, including those with pathogens and parasites, facilitate the transmission of elements between widely diverged taxa […]." (Bourque et al. 2018, 4).

A number of papers have drawn the conclusion that if TEs were to be used as gene drive systems, they would require a lot more experimentation, knowledge and research (Sinkins and Gould 2006) – and are in that sense regarded as either too costly (Marshall and Akbari 2016) or superseded by other gene drive methods.

A key question is also if genetically engineered gene-drive TEs will keep to the same pattern of semi-random integration, e.g. avoid inserting itself into the actual coding sequence of a gene. If it were to insert into coding sequences the outcomes would be highly unpredictable and could be problematic, even if the TE were blocked by the organism from further movements.

4.2.2 Homing endonuclease genes (HEGs)

Homing endonuclease genes (HEGs) are another type of 'mobile genetic element', originally discovered in budding yeast in the 1970s and early 1980s by researchers in the Pasteur Institute (Dujon 1980, Jacquier and Dujon 1985). HEGs have since been found in many bacteria, bacteriophages, fungi, and plant chloroplasts.

The principles underlying how HEGs are constructed and how they achieve drive are at the centre of current gene drive development, with the CRISPR/Cas-based homing gene drive being the best known category of engineered HEGs.

In general, HEGs are genes that code for an enzyme (endonuclease) that is able to recognise and cut a specific DNA sequence of 14-40 base pairs (Stoddard 2005), and to then have themselves copied into the middle of that sequence via homology repair. This overall process is called '*homing*' (Stoddard 2005[18]). The homing gene thus resides within the recognition sequence cut by the endonuclease.

If one chromosome contains a HEG and the equivalent homologous chromosome does not, the endonuclease will detect the recognition site on that chromosome and induce a site-specific double strand break. The HEG will be copied across via homology-directed repair (see Section 3 and Figure 2). The severed recognition sequence now becomes the flanking sequences (see Figure 3). If, however, the cleaved ends get rejoined by the NHEJ repair, mutations will occur in the recognition/cleavage site, making this chromosomal site unrecognisable to, and 'resistant' to, the specific endonuclease. Equally, natural sequence variation at the recognition site could protect the site from HEG insertion.

Homing gene drives

Austin Burt was the first to suggest utilising HEGs and their ability to spread by inserting themselves into the parallel chromosome, with the aim of either altering or eradicating natural populations of target

18 "Homing is the transfer of an intervening sequence (either an intron or intein) to a homologous allele that lacks the sequence (Dujon 1989; Dujon et al. 1989; Belfort & Perlman 1995), leading to gene conversion and dominant transmission and inheritance of the mobile element." (Stoddard 2005, 50)

species. As naturally occurring HEGs are limited in the DNA sequences they may recognise, Burt envisaged that through genetic engineering it would be possible to alter the site-specificity of the endonuclease in order to make it target essential genes (Burt 2003). With an appropriate promoter (e.g. for meiosis), and ensuring that the resulting knock-out was recessive, Burt suggested a population could – in theory – be eradicated in 20 generations. Another possible action suggested was to engineer the HEG construct to contain an extra gene, a so-called payload or cargo gene (Champer, Buchman, and Akbari 2016), which would get copied across together with the HEG and thus also spread in a super-Mendelian fashion.

The potential use of homing endonucleases as gene drive systems in animals was first tested in the fruit fly *Drosophila melanogaster* (Chan et al. 2011, Chan, Huen, et al. 2013) and the mosquito *Anopheles gambiae* (Windbichler et al. 2011). Using HEGs derived from yeast and inserting artificial target sequences into the respective genomes, the experiments provided a proof of principle for homing processes to work in these species, although drive conversion levels were low.

These experiments also indicated the importance of the proper timing for when an HE gene is activated and for the resulting homing endonuclease to find and sever its target sequence. Depending on which point during gametogenesis and meiosis a DNA double-strand break occurs, different repair mechanisms dominate the process (see Section 3 and Figure 2 for repair pathways). Increased frequency of NHEJ-induced repair will result in increased frequency of target site mutations, thus enhancing the rise of resistance. This means that choosing the right promoter element in an HEG construct is crucial to the outcome (see Chan et al. 2011, Table 1).

If HEGs were to be used as gene drive systems, their target specificity would need to be adaptable for different sequences. Researchers from Cambridge, UK and Seattle in the US redesigned and engineered HEGs based on yeast HEGs with altered specificity, and also used artificial target sites. Working with *Drosophila*, they found that the redesigned homing endonucleases had a *reduced* conversion frequency, as compared to the original yeast HEG (Chan, Takeuchi, et al. 2013). The authors suggested that site specificity alone is not sufficient for successful homing.

ZFNs, TALENs and CRISPR/Cas based homing systems

To test if site-specific nucleases could be used as homing endonucleases, researchers turned to zinc finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs). Using the same experimental system and design as Chan in 2011 and 2013, researchers at Imperial College, London, tested ZFN-based and TALEN-based HEGs. They found these site-specific nucleases triggered a much higher rate of NHEJ repair than the actual/original HEGs (Simoni et al. 2014). As a consequence, there was an increased level of target-site mutations, which in turn creates resistance to the gene drive, because the enzyme is no longer able to recognise or cut the target site.

However, with the arrival of RNA-guided site-specific nucleases such as CRISPR/Cas9, the picture drastically changed. As already detailed in Section 3 of this chapter, the recent uptake of CRISPR/Cas as a homing gene-drive system has resulted, most of the time, in high conversion rates (rates of homing) in laboratory studies, although these also demonstrated the occurrence and build-up of resistance[19] (see Table 1). Whilst demonstrating proof of principle for the fruit fly *Drosophila melanogaster*, the yeast *Saccharomyces cerevisiae* and the mosquitoes *Anopheles stephensi* and *A. gambiae*, the issue of gene drive resistance remained an insurmountable hurdle.

This changed suddenly in 2018, when researchers from Imperial College London, UK, succeeded

19 Researchers at the University of California, San Diego, changed the body colour of Drosophila (Gantz and Bier 2015) and drove an anti-parasite gene through a laboratory population of the malaria mosquito Anopheles stephensi (Gantz et al. 2015). Researchers from Harvard Medical School demonstrated proof of concept for yeast, by adding a gene, disrupting another and correcting a third one. Conversion rates were very high, though reporting was only for a few generations (DiCarlo et al. 2015).

in completely crashing a laboratory population of caged *Anopheles gambiae* mosquitoes (Kyrou et al. 2018). Strictly following Burt's original strategy (Burt 2003), they did so after 7-11 cage generations without any emergence of resistance. This was a first, and has brought this technology to a further step of proof of principle, at least in enclosed, caged, artificial systems.

The strategy was to choose a target gene that was both highly conserved and essential in gender determination, the *doublesex* gene. Disrupting this gene at a particular site with a CRISPR-Cas9 gene drive results in sterility in females carrying the drive. 'Highly conserved' means that the DNA sequence of a gene has remained the same over time on an evolutionary scale, and that it has not been changed by random mutations. A 'highly conserved sequence' implies a conserved and highly protected gene, where any alteration to that gene sequence would result in a non-viable life form. Choosing a highly conserved gene sequence, in particular the sex determination '*doublesex*' gene, as the gene drive target site, means that no viable resistance alleles (gene variants) arise and spread to save the caged (or potentially, the wild) population. This is a new strategy on the path towards overcoming this type of gene drive resistance and so far has resulted in the above-mentioned crash of a population of caged mosquitoes.

Because of its vital role, the doublesex gene has very little scope for mutation and therefore the minor mutations which normally allow resistance to evolve do not appear; this is likely to be the mechanism allowing this drive to completely eradicate laboratory populations. Significantly, the gene sequence is completely conserved across the *Anopheles gambiae* species complex, meaning the drive would function just as effectively in these sibling species. Given the capacity of members of this complex to hybridise, if this drive were released in the wild it could potentially affect the entire species complex alongside *gambiae* – along with the ecosystems linked to them.

The strategy of targeting highly conserved genes to avoid the build-up of target site resistance thus adds an extra layer of risks and concerns to what is already perceived to be a very high-risk technology.

Experiments have also been carried out in mammals, in this case mice. When both gene copies (alleles) of a targeted gene controlling coat colour are disrupted, in order to change grey coat to white, the researchers found that the gene drive did not work readily. Drive activity in early embryo or male germlines resulted in mutations, rather than drive conversion, as the predominant repair mechanism was NHEJ. Of the various strategies, limiting the gene drive activity to the female germline gave an efficiency or conversion rate of 73%, but also showed NHEJ-induced mutations. Whilst providing a proof of concept, the authors noted that the "precise timing of the Cas9 expression may present a greater challenge in rodents than in insects" in terms of efforts to prevent resistance to the gene drive (Grunwald et al. 2019). (see also Chapter 2, case study on mice).

4.3 Segregation & transmission distorters

One mechanism for genetic elements to achieve drive or super-Mendelian inheritance is by their own duplication (over-replication) and insertion into other chromosomal loci. This is the mechanism used for TEs and HEGs.

The drive mechanisms of transmission distortions described in this section result in an inheritance bias by means of eliminating, outmanoeuvering or outracing the competition. The term 'distortion of transmission' was first coined by L.C. Dunn in the late 1930s[20], working with mice that were showing a very biased inheritance pattern, due to a selfish genetic element now known as the *t-complex* (see below) (Dunn and Bennett 1971).

20 Bennet 1977, referenced in Herrmann and Bauer 2012.

Table 1: CRISPR/Cas9 based drives: Relevant proof of concept work published on RNA-guided gene drives. This table compares the proof of concept drives both for the conversion rate as well as for the degree of resistance to the drive observed. Whilst not directly comparable due to differing experimental procedures, including numbers of generations observed, the development of resistance is common to all except for Kyrou et al. (2018).

Species	Trait	Kind	Conversion rate (homing rate)	Resistance	Institute	REF
Drosophila melanogaster **(fruitfly)**	Yellow body colour	Loss of function (X-linked gene)	97%	Not tested [3% ?]	University of California, San Diego, US	(Gantz and Bier 2015)
Saccharomyces cerevisiae **(yeast)**	Colour change	Gene addition, Gene correction, Gene disruption	>99%	Not found	Harvard Medical School, Boston, US (+)	(DiCarlo et al. 2015)
Anopheles stephensi **(mosquito)**	anti-Plasmodium falciparum effector genes (refractory)	Introgression (population modification)	99.5% (in germline) ~50% in egg	Yes. In particular, if homing action leaked to egg from females with drive. (>70%)	University of California, San Diego & Irvine, US	(Gantz et al. 2015)
Anopheles gambiae **(mosquito)**	Female sterility	Loss of function, suppression & payload gene	91.4 to 99.6% initially. 69–98% at later generations	Yes, including in-frame mutations (6 bp deletion)	Imperial College London, UK, University of Cambridge, UK, University of Perugia, Italy (+)	(Hammond et al. 2016)
Mus **(mouse)**	White coats	Loss of function	Minimal in early embryo and male germline. Up to 72% in best case.	Yes	Univesity of California, US	(Grunwald et al. 2019)
Anopheles gambiae **(mosquito)**	Female sterility	Loss of function, suppression	100%	unlikely	Imperial College London, UK	(Kyrou et al. 2018)
D.melanogaster	Sex-conversion to males	Loss of function, suppression		30% (third of which in-frame mutations)	University of Göttingen, Germany	(KaramiNejadRanjbar et al. 2018)

Meiotic drive(r)

Meiosis is the key phase for sexual reproduction in a higher organism where the sexual reproductive cells (gametes - e.g. egg cells or sperm) are being produced and the genetic material is divided up in a random fashion in line with Mendel's Law. During meiosis, diploid cells are divided into haploid cells, in which only one copy of a gene or a chromosome will be present, originating from either of the parents.

'Meiotic drive' is an overarching term referring to any selfish genetic element or drive mechanism that manipulates the processes of meiosis[21] and the "production of gametes[22] to increase their own rate of transmission, often to the detriment of the rest of the genome and the individual that carries them." (Lindholm et al. 2016, 315).

In the meiotic drive system, the determining tasks are 'who' will succeed in getting a ride in the gametes, eliminating or outmanoeuvering the competitors. And which embryo will survive, which may depend on the presence of an antidote to counter the toxin produced at an earlier stage by part of a selfish genetic element team. This for example would be the tactic pursued by the 'toxin-antidote' based drives.

The forces present in this dynamic between genetic elements, mode of action and responses and protective efforts by the individual organism and species, are tremendous. The review "The Ecology and Evolutionary Dynamics of Meiotic Drive" by Anna Lindholm et al. (2016) offers an insight that reminds us that synthetic gene drives based on the mechanisms of naturally-occurring meiotic drives will not only be exposed to (and have to withstand) the same counter-forces, but synthetic drives will also shape responses in their turn and thus influence ecology and evolution.

There are many types of meiotic drive systems, the main ones of which are explained below.

4.3.1 Sex-ratio distorters

Sex ratio distorters are drive systems that skew the gender ratio, resulting in either predominantly male or female offspring. Also referred to as 'sex-linked meiotic drive' (Champer, Buchman, and Akbari 2016), they are the main drive systems under development for synthetic gene drives. If the key factor for determining population size is the number and productivity of females, then eradicating females becomes the action of choice for gene drive systems. There are two options: to place the modified selfish element either on the male sex chromosome (the Y-chromosome), or on an autosome (a chromosome other than a sex chromosome). The highest and swiftest suppression rate can be achieved if the drive is linked to the Y-chromosome (Champer, Buchman, and Akbari 2016; Marshall and Akbari 2018).

Sex ratio distorters achieve an inheritance advantage by destroying 'the other'. If, for example, the X-chromosomes gets destroyed during spermatogenesis, there can be no female offspring of that organism, if the determinant for female is XX. A mechanism ensuring that only the Y chromosome gets through spermatogenesis would change the sex ratio drastically towards male. Such a strategy would – in theory - cause a population to collapse over time.

Male bias (sex-ratio distortion) is found in nature, for example in *Aedes* and *Culex* mosquitoes (Craig, Hickey, and Vandehey 1960; Newton, Wood, and Southern 1976; Sweeny and Barr 1978). Although the actual molecular mechanism behind this is not understood, there is a specific type of Y chromosome that will result in 90% male offspring. Somehow the presence of this driving Y chromosome during spermatogenesis leads to breakages in the X chromosome, disabling or preventing female progeny (Burt and Crisanti 2018).

However, it is obvious that those natural occurring sex-distortion mechanisms have not resulted in the elimination of those populations or species, as

21 This action and timing require meiosis-specific regulatory elements (promoters).

22 Gametes are mature sexual reproductive cells, with female gametes being egg cells (ovules) and male gametes sperm (pollen).

they can still be found. This was already being discussed in the 1960s when the use of organisms with naturally occurring drives were suggested as a form of biocontrol. Hamilton (1967) argued that there would be a response, a counter mutation or counter elements, to contain and 'mask' any sex distortion factor, especially a strong Y-linked male bias factor. In this way, a co-evolutionary process would bring the sex-ratio back to equilibrium[23] (Hamilton 1967).

The question remains open as to what extent such 'counter-measures' would arise in response to engineered sex-ratio distortion drives. And if so, would they be quick enough to save the population or species? Or can gene drives be developed in such a way that such counter-measures can be blocked? There are currently three types of engineered sex-ratio distorters under consideration and being investigated as synthetic gene drives.

As already detailed above: A CRISPR/Cas9-based **homing drive** developed at Imperial College London was engineered to target the highly conserved *doublesex* gene in the mosquito *Anopheles gambiae* and resulted in male only offspring (Kyrou et al. 2018). Already presented in Section 4.1.2 under HEGs, this gene drive has been highly effective in the artificial environment of caged trials.

The second sex-ratio distorter drive is a mouse specific ***t*-haplotype**-based gene drive, being developed at Texas A&M University intended to produce 'daugtherless' mice, to eradicate mouse populations. There is no proof of concept so far. See below under Section 4.1.2 (a), t-complex or t-haplotype.

The third drive is the synthetic **X-shredder** gene drive, developed at Imperial College London.

a. *t*-complex or *t*-haplotype

The *t*-haplotype or *t*-complex is a meiotic drive and sex-ratio distorter located on chromosome 17 that naturally occurs in mice. Its discovery goes back to 1927, when Nadine Dobrovolskaia-Zavadskaia, evaluating X-ray experiments in mice, first thought this to be the gene for short tails or taillessness (gene symbol T), hence the name (Herrmann and Bauer 2012). However, further evaluations with crosses showed that "tailless mice produced only tailless litters upon intercrossing, but neither short-tailed nor normal-tailed pups. Inspection of the embryos from such crosses showed that about half of the embryos died *in utero*." (Herrmann and Bauer 2012)

It was much later that it became evident that this region of chromosome 17 was what would later be called a selfish genetic element, containing not only genes for transmission distortion, but also for male infertility and embryonic lethality. Mice that are homozygous for the *t*-complex (i.e. where both parallel chromosomes contain the gene for embryonic lethality), will die before birth. And males with a copy of the *t*-complex will pass this on to 90% of offspring (Lyon 2003; Lindholm et al. 2013). This lethality is based on a toxin-antidote system, where a toxin will be released into the cells during spermatogenesis (sperm development) and only those sperm will survive or be able to fertilise an egg cell that carry the gene for the antidote, which is located on the t-complex.

This meiotic drive system is specific to mice. Where mice are perceived as a problem, e.g. on islands, plans are underway to try to alter and convert this system into a synthetic gene drive to turn against the mice. The idea here is to create 'daughterless' mice by modifying the *t*-complex with a mouse gene called *Sry*.[24] This gene will act during embryo development and trigger the development of male characteristics irrespective of the actual gender of the mouse. Released into the wild, any offspring should have male characteristics. With no females left to breed, the idea is that the population would collapse.

23 Such a sex-ratio equilibrium is also known as the 'Fisher's principle'.

24 The *Sry* gene is a mammalian sex-determining gene located on the the Y-chromosome. It determines maleness and its name is short for 'sex-determining region (of the) Y'. Here, as payload gene of the drive system, it would be on an 'autosome', i.e. not on a sex chromosome, and thus present and active also in genetically female offspring. These would thus develop male characteristics but be infertile.

It is highly uncertain, however, whether this genetically engineered gene drive would or could perform as envisaged, and also what actual outcomes would be. This is conveyed by the fact that the underlying drive system (the *t*-complex) has been part of the mouse population and its evolution dynamics, but is still not present at a higher level than it is. This brings up the question of how mice manage to handle this species-specific selfish genetic element. It is a co-evolved system, so wouldn't the mouse genome evolve a response? There are also reports that mating or fertilisation rates are lower with *t*-complex males than with wild type males (Manser et al. 2017). Altogether this may well mean that the system cannot deliver what researchers hoped for. However, the second question of course is whether this engineered gene drive is more aggressive and invasive than the natural mechanism it is based on, and what would happen to all and related species of mice if it found its way to other locations? As no experimental data are available, the performance of this gene drive remains speculative.

b. X-shredder

As indicated by its name, this type of transmission distorter will shred the X-chromosome during spermatogenesis (male meiosis), i.e. cleaving the chromosome at multiple sites by using a site-directed nuclease. Homology directed repair would not be possible at this stage, as there would be no second X chromosome that could serve as a template for such repair. First suggested by Austin Burt in 2003 (Burt 2003), it was in 2014 that Galizi reported on experiments with the malaria mosquito *Anopheles gambiae*, providing a proof of principle for this approach. Using a homing endonuclease (*I-PpoI* nuclease from a slime mold) to cleave the X-chromosome at multiple sites led to a sex ratio of up to 95% males (Galizi et al. 2014). He repeated the same experiments with a CRISPR/Cas-based site directed nuclease, giving rise to the same degree of transmission distortion and resulting in 86-95 % male offspring (Galizi et al. 2016). The authors suggest that higher gender distortion could be achieved by placing the gene drive on the Y-chromosome rather than on a normal chromosome, an 'autosome'. This would mean that all offspring (which in this case are always male) would automatically carry the X-shredder mechanism, rather than leaving its distribution to Mendelian inheritance rates.

4.3.2 Underdominance / Heterozygous disadvantage

This gene drive approach is envisaged to function as a tool for population replacement, that is, to spread a payload gene with its trait throughout a population and bring it to fixation, meaning that every individual will carry it.

Underdominance - also called 'heterozygous disadvantage' or 'heterozygous inferiority' - is a phenomenon where the heterozygous offspring is less fit than either of its homozygous parents. Where a gene has two variants (alleles - see Figure 4) and where it is an advantage to be homozygous for either one of these alleles (i.e., to have a set of either one variant or the other), a cross of the two differently homozygous parents will result in a heterozygous offspring with one of each allele. Under these circumstances, such a heterozygous offspring will have a lower fitness level than either parent and will over time be selected against. Ultimately, either one of the alleles will become firmly established (fixed) in a population, usually the one with the higher initial frequency (Davis, Bax, and Grewe 2001; Champer, Buchman, and Akbari 2016). There is also the chance that two distinct populations may arise, each occupying different or neighbouring territories. See footnote[25] for different definition. Examples of underdominance in nature are mentioned in (Champer, Buchman, and Akbari 2016).

Although resulting in transmission distortion, naturally occurring underdominance does not lend itself as a gene drive system for spreading payload genes (Sinkins and Gould 2006). However, an idea arose to create and use genetically engineered un-

25 "UD is a genetic property classically defined as the condition where, at a single locus, the fitness of heterozygotes is lower than that of either corresponding homozygote; generating this effect has been proposed as achievable through either chromosomal translocations or mutually suppressing transgenic toxin-antidote elements (though none have as yet been developed in exactly the latter format)." (Leftwich et al. 2018, 1204)

derdominance systems instead, utilising either reciprocal translocations or toxin-antidote systems, and increasingly also employing CRISPR/Cas, albeit not as a gene drive system, but rather to act as a 'toxin'. However, there are multiple hurdles remaining.

Davis et al. (2001) were the first to suggest using a double toxin-antidote system for this purpose (including modelling for it). This system would employ two separate constructs (see Figure 6), each consisting of a copy of the desired payload gene, a suppressor gene and a lethal gene, with a promoter that can be suppressed by the suppressor present on the other construct (Davis, Bax, and Grewe 2001). As long as both constructs are present within an organism or an embryo, nothing will happen, as the lethal gene is suppressed. But if the offspring ends up with one construct only, no matter which one, it will die – an approach the authors called 'extreme underdominance'. If sufficient numbers of individuals harbouring both constructs were repeatedly released, the expectation is that the engineered trait (and construct) would become established in the wider population.

Other teams developed these ideas and systems further, either keeping Davis's idea of a 'one locus' drive (where both constructs will be at the same chromosomal location but on the opposite homologous chromosome), or suggesting a 'two-locus' drive system, where the second construct would be on a separate chromosome all together. For example, Akbari & Matzen, then at the California Institute of Technology, designed and built a synthetic 'two-locus' gene drive system they termed 'maternal-effect lethal underdominance' (UD^{MEL}). Here the toxins are expressed maternally during egg-production, and it is the embryos that will die as a consequence unless they have the genes for the corresponding antidotes (Akbari et al. 2013). Males carrying the toxin genes will not express them. Tested in the model organism *Drosophia melanogaster,* UD^{MEL} was the first engineered threshold dependent gene drive system, and modelling suggesting a required release frequency of above 24%. Most papers published on underdominance drives however are solely theoretical papers, modelling both the thresholds and the multi-

Figure 6

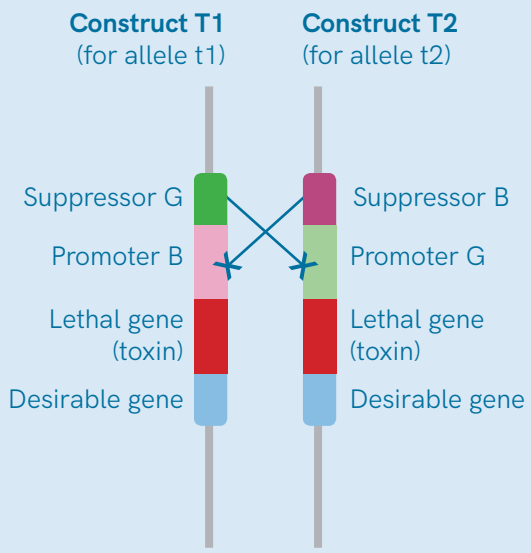

Figure 6: Underdominance with toxin-antidote system. A set of two constructs where each construct needs to be present to block (suppress) the production of a lethal toxin by the other. Combined they constitute an underdominance system, as, if only one is present, the carrier will die. The desired trait gene is here physically linked to the lethal gene and is thus part of the underdominance system and will become established in the population if released in sufficient quantities.

temporarily. These models also attempt to predict whether reversals might be possible, what variables need to be taken into account, etc. These models look at different theoretical gene drive constructs with different genes (toxins, suppressors, antidotes or replacement genes) as well as combinations with different promoters that will make drive components active either in females, males, adults or during embryogenesis or other stages of development or in different cell types.

Whilst the theoretical behaviour of underdominance has been run through various models and simulations, data from actual laboratory experiments is limited. Reeves et al. genetically engineered the fruit fly *Drosophila melanogaster* with a 'one-locus' system, using an RNAi transgene for blocking a vital ribosomal protein gene, but also adding an RNAi-resistant version of the ribosomal protein gene as the

'antidote' (rescue). In this system, offspring will not die but be weakened if they have only one underdominance construct. This experiment is viewed as a laboratory proof of concept for this particular type of drive, with potential for application in other species. However, it would "require releases to exceed an allele frequency of 61% in a given wild population", making this approach impractical for large populations (Reeves et al. 2014, 6).

A recent review on threshold-dependent gene drives divides underdominance into 4 subcategories, which includes **CRISPRa** (Leftwich et al. 2018). This mechanism does not use CRISPR/Cas9 as an RNA-guided homing-endonuclease gene drive mechanism, but rather uses a deactivated form of Cas9 (dCas9) that has been modified into a 'transactivator'. The transactivator is capable of triggering the overexpression or the untimely (ectopic) expression of chosen genes, which results in the death of the organism (Waters et al. 2018). It is devised as a toxin-antidote gene drive system, currently under development. First experiments in *D. melanogaster* however evidenced that much more research and understanding is required (Waters et al. 2018).

Reciprocal chromosomal translocations

Reciprocal chromosomal translocations arise when a segment of one chromosome is exchanged with a segment of another, non-homologous, chromosome.

Already suggested by Serebrovskii in the 1940s, and put forward again by Curtis in 1968 (Curtis 1968), translocations are considered a means to create, amongst others, underdominance systems that could replace current populations with modified ones that could for example carry refractory payload genes. It is only recently, that this approach has been taken up again, using genetic engineering methods and achieving translocation via chromosomal breakage and homologous recombination. Working with *Drosophila melanogaster* Buchman et al. reported the construction a high threshold drive, though also finding that further work is required (Buchman, Ivy, et al. 2018).

4.3.3 Toxin-antidote based drives

These systems use combinations of toxins and antidotes to achieve an inheritance bias. If we use these terms 'toxins' and 'antidotes' in the broadest sense, such combinations could, for example, consist of mechanisms to silence a vital gene (e.g. via RNAi), and then provide a replacement gene as an antidote that will not be silenced by the mechanism; or it could use a toxic protein neutralised by an enzyme, or by an RNA-based silencing mechanism, that will stop the production of the toxin.

In order for such gene drives to work, the presence of the 'toxin' needs to create a serious disadvantage (e.g. death) that can only be remedied if the 'antidote' is available. If the antidote is not present, the cell or organism will die. There are two main ways to achieve this: either by physically separating the genes for the toxin and the antidote so they will not automatically be inherited together; or by a time separation of the activities of the respective genes, combined with using a long durability toxin product. A payload gene could be tightly linked to the antidote gene and thus achieve drive.

In the first case, if the toxin and antidote genes were placed on different chromosomes, it would be easy for an organism to just de-select the toxin gene and make it disappear from a population, thus halting the drive mechanism, something that could happen rather quickly. This theoretical model was put forward by Gould et al. in 2008 as the *'killer-rescue'* system, regarding its weakness as a benefit (Gould et al. 2008). Suggested as a 'self-limiting' system, it would place a time limit to the lifespan of the drive, although the organisms genetically modified with both the rescue antidote and the payload gene would not necessarily vanish but possibly remain in the population.

In a different form, the toxin-antidote system could also be utilised to achieve *Underdominance* (see above), in situations where the toxin is tightly linked to an advantage, for example, carrying an antidote for a different toxin. In that case, a toxin could be produced in females during oogenesis, i.e. during egg production. If this substance is toxic

only at a later stage, such as during embryonic development, and if it is able to remain present into that stage of development, then only those offspring with the antidote gene will survive. In this scenario, the antidote gene would become active only in early embryogenesis, counteracting the toxin and thus rescuing the embryo. Examples of this are the UD^{MEL} underdominance design mentioned above and especially the *Medea* system detailed below, together with other variations, such as inverse Medea, Merea, Semele and Medusa.

Toxin-antidote components are found as part of other gene drive designs and systems, in particular underdominance and sex-ratio distortion. Increasingly, CRISPR-based nucleases are incorporated as toxins in these theoretical designs, with modified resistant genes added as the antidote.

a. Medea, Merea, inverse Medea and Semele

The following are all single-construct designs, meaning all genetic elements involved are tightly linked and transfer as a unit. All, with the exception of Medea, are theoretical designs.

Medea stands for 'maternal effect dominant embryonic arrest'. It is a selfish genetic element, in which the female will make a toxin during egg-production (oogenesis) that will lead to the death of the embryos--unless any of them has inherited a copy of the Medea element from its mother or father--as this also holds the antidote within the same element.

This phenomenon was first discovered in the flour beetle *Tribolium castaneum* (Beeman, Friesen, and Denell 1992) and takes its name from Greek mythology, where Medea is said to have killed her own children (with ancient sources differing as to whether by intent or accident).

In 2007, researchers from the California Institute of Technology, Pasadena, genetically engineered the first gene drive system, based on the principles of Medea, which is basically a toxin-antidote system (Chen et al. 2007). They did so in the model fruit fly *Drosophila melanogaster*. Using microRNA as the toxin to silence an essential embryonic gene (here *Myd88*), the antidote was the same embryonic gene, but modified with an altered sequence so it could not be silenced by the microRNA.

At least according to the models, Medea is regarded as a strong drive system that could spread payload genes rapidly, so long as it is released at high frequencies and the fitness cost is kept low (Sinkins and Gould 2006; Akbari et al. 2014). Recent laboratory experiments carried out with the spotted wing drosophila (*D. suzukii*), an agricultural pest in soft fruit production in California, confirmed the need for high release frequencies, and also showed in long term cage trials that selection for resistance to the microRNA-based toxin being used is a concern (Buchman, Marshall, et al. 2018).

Different possible Medea variations have been suggested and modelled, e.g. (Akbari et al. 2014). In fact, there is a multitude of different systems inspired by these Medea principles, the closest of which are *Merea*, where the gene for the antidote is recessive, and *inverse Medea*, where the toxin is produced during early embryonic development, that is, unless the antidote was produced maternally during egg production (Marshall and Hay 2012b, 2011). These are all *theoretical designs* used for modelling of engineered gene drives in order to see if, for example, payload genes would easily find fixation in a population, gene drives would be less invasive, or suppression could lead to population collapse.

Semele is yet another design variant of Medea, except that in its case the toxin is produced during sperm development, so it is the father killing the offspring (Marshall et al. 2011).

b. Medusa

Medusa is a two-construct design within the toxin-antidote system. It has not gone past the model stage and again is simply a theoretical design intended for population suppression, in which a population crash might be kept to geographical limits (Marshall and Hay 2014).

Medusa is made up of four components, two toxins and the two respective antidotes. One toxin and the antidote will be located on the X-chromosome, the second toxin with the antidote to the first will be located on the Y-chromosome. One without the presence of the other could therefore not survive. This system will thus select for individuals with both the transgenic X and Y chromosome, thus selecting against females (XX); and, if initially released at a sufficiently high frequency, could bring the population to collapse.

5 Gene Drive categories and attributes, their limitations and risks

There are many ways to categorise and compare these various potential or theoretical gene drive systems. Depending on the purpose of such an evaluation or comparison, different attributes and parameters will be of importance. Some of these will largely be of interest to the developers, such as the ability (or inability) of each system to stably carry payload genes, or its susceptibility to resistance and inactivation.

Naturally, a quite different selection or combination of attributes and parameters are considered when the main goal is to understand the risks to the environment, health or biodiversity, that are, or can be associated with, a particular (potential) gene drive system. Parameters of relevance here are such qualities as invasiveness, the potential for global spread, the speed of spread, the lack of reversibility or removability, horizontal gene transfer, and the potential for eradication (suppression) or alteration (replacement) of a population/species.

A fundamental difficulty presents itself when different gene drive systems are assessed within the various parameters. The main problem is that there is very little reliable data. Only a few gene drive systems currently have a proof of concept, and these are restricted to laboratory conditions and largely to laboratory strains (with the exception of *Drosophila suzukii*). Many gene drive systems are merely at the design stage or in an early state of development and assessments of them are thus also largely theoretical. Whilst a gene drive system may have a specific design, current evaluations are based on the assumption that the gene drive system, once engineered into a gene drive organism (GDO), will behave and *perform as designed*. Some will draw attention to this, like Champer et al. who state in their table 1: "The characteristics listed here are variable and depend on a range of factors (for example, ecology of the target species, population distribution, movement patterns, fitness costs, payload characteristics, and so on); therefore, *only ideal-case scenarios are compared to emphasize intrinsic differences of the various types of drives."* (Champer, Buchman, and Akbari 2016, emphasis added). This means that, overall, we are actually talking about "*potential* gene drive systems" (a term used by numerous authors when presenting their assessments).

A major question relevant to biosafety is whether a particular gene drive system can be confined, once it has been released or has escaped into the wild--or if its design will favour uncontrollable spread, with potential global eradication or permanent genetic modification of the entire species. In the following we will briefly introduce gene drive categories that are relevant to this question: a.) threshold-dependent drives; threshold-independent drives and temporally self-limiting drives; b.) suppression (eradication) vs. replacement or modification; and c.) recallability and reversibility.

As far as these drives rely on CRISPR/Cas for its ability to cause a DNA breakage at the site of a specific target sequence, the systems are vulnerable to the development of resistance.

5.1 Threshold-dependent, threshold-independent and temporally self-limiting drive systems

These categories have been given different names by different groups and authors. Min et al., for example, refer to these same categories as threshold, standard and self-exhausting drive systems (Min et al. 2018). We are using here the terminology chosen by Marshall & Akbari in their 2018 review entitled "Can CRISPR-based gene drive be confined in the wild? A question for molecular and population biology" (Marshall and Akbari 2018).

Predictions and statements made to date rely heavily on modelling, which again relies heavily on population biology, meaning that answers differ from species to species or even from population to population, as well as from ecosystem to ecosystem. In fact, many more factors will come into play. Looking at threshold-dependent drive systems, Gould's group found "that to determine the best method of spatial release, and the total number of engineered insects that must be released, it is important to take into account the age and sex of the released insects and spatial structure of the population." (Huang et al. 2011, 415).

Another major point is that of mating behaviour. Many models assume (implicitly) a deterministic representation of a randomly mating (panmictic) population (Edgington and Alphey 2018), which may well not reflect reality. Modelling outcomes will be different, if, for example, assortative mating (non-random) and polyandry strategies (female mating with multiple males) are taken into consideration eg. (Bull 2017). Leitschuh points out that wild rodents will "exhibit mating strategies such as polyandry and assortative mating, …and have seasonal population fluctuations…, while laboratory rodents have very controlled reproductive environments." (Leitschuh et al. 2018, S132). There is real concern that sexual selection might develop against drive-carrying individuals: "The costs associated with drive create a benefit to avoiding mating with individuals carrying a driver, and thus preferences against driver carriers are expected to evolve…" (Lindholm et al. 2016, 322) – as found for example in stalk-eyed flies (Johns, Wolfenbarger, and Wilkinson 2005, Cotton et al. 2014) or in mice carrying the t-complex (Manser, Konig, and Lindholm 2015). The mechanisms behind this are not understood.

It is important to remember that any predictions and assumptions made about gene drives and GDOs are most likely not realistic.

Threshold-dependent drive systems

Depending on its frequency[26] level when being released, this category of drive will spread into a population and achieve fixation, unless it is below the threshold frequency, in which case it will quickly vanish from the population (Davis, Bax, and Grewe 2001, Min et al. 2018). The determining factor here is quantity. Examples are engineered underdominance, Medea, or autosomal X-shredder (see Table 2).

According to some models, this drive category offers local confinement with local fixation. It is being argued that the dynamic assumed in simple population models may not hold true in the wild. Marshall and Akbari state, "…whether this holds true or not depends crucially on the dispersal patterns and population structure of the species being considered." (Marshall and Akbari 2018, 426). There may well be numerous other hurdles to this category functioning as intended, for instance selective mating behaviour.

'Dilution' has been suggested as a 'remedy' to counteract the drive and its effects, but that would necessitate a large-scale release of wild specimens (see 'reversibility' below).

Threshold-independent drive systems

This category of drive does not require a specific minimal frequency for its proliferation. Instead, it can spread from an initially very low occurrence. It is characterised by high invasiveness and high risk of spreading throughout populations, affecting a targeted species and its linked ecosystems globally. As mentioned above, this category is also referred

26 Frequency here means the proportion that the released GDOs constitute as compared to the whole of the existing population.

to as 'standard', with other researchers also calling it a 'self-sustaining drive, or a 'global drive' (Delborne et al. 2018) as well as 'global drive system' or 'global gene drive' (Noble et al. 2016).

For example, the engineered homing endonuclease drives, especially the CRISPR/Cas based homing drives, and the Y-linked X-shredder are all threshold independent gene drives (see Table 2).

Whilst there exist proof of concept from laboratory experiments for some of these, it is not clear at all whether or how this will perform in the wild. Success is debatable, but the risks of negative impacts are not; they are indisputably serious. It is in this context that a number of researchers are clearly indicating that *this category of drive should not be attempted or released into the wild unless it can be stopped from spreading and reversed.* One statement reads: "Before robust and efficient homing-based gene drive systems can be implemented in the wild, tools are required to remove the effector gene and possibly the entire drive system from the environment in the event of unwanted consequences." (Marshall and Akbari 2018, 427).

There are no such tools or countermeasures currently available, and none of the current conceptual models are capable of even hypothetically restoring the populations to a non-GM (and non-GD) population.

Temporarily self-limiting drives:

This category is highly theoretical, and conceptual models such as the so-called 'daisy chain drive' will be described in Section 6. To summarise, the idea behind this category is that a synthetic drive can be designed that will stop functioning after a given number of generations, for example by including elements with Mendelian inheritance. Whilst some suggest such drives will therefore be transient, others counter this optimism, stating, among other points, that this will largely depend on the fitness cost. For example:

"For payloads that incur relatively low fitness costs (up to 30%), a simple daisy-chain drive is practically incapable of remaining localized, even with migration rates as low as 0.5% per generation." (Dhole et al. 2018, 794)

Due to its theoretical time limitations and Mendelian non-drive component, there is a mistaken assumption that this means it will not be able to spread outside the target population. This result again is, entirely dependent on fitness costs (e.g. Dhole et al. 2018), as well as on biological and behavioural factors in a target population, such as dispersal rate.

5.2 Suppression (elimination/eradication) vs modification

Suppression drives are intended to reduce or eliminate a population. If combined with a threshold-independent drive, they may spread to a global scale and result in the eradication of an entire species. This may particularly become the case if the drive system itself has a low intrinsic fitness cost and no resistance develops to the drive (Champer, Buchman, and Akbari 2016).

Modification drives are intended to spread specific traits through a population, for example with the aid of payload genes. Again, if linked to threshold-independent global drives, and if it overcomes resistance problems, this may genetically modify an entire species. Modification drives are sometimes referred to as 'alteration drives', and occasionally as 'replacement drives'. The latter is problematic though, as it is not quite accurate here and it confuses the issue with population replacement seen for the underdominance system. Such replacement would strictly mean to replace one population with the other, without those populations mixing, or without relying on the spread of the modification via homing-CRISPR/Cas9 drives. Replacement would require a large scale release of a modified population reared in laboratories and cages.

5.3 Removability and reversibility

The inability to predict the behaviour and consequences of a gene drive once it is released has

Table 2: Comparison of potential gene drive systems. Please note, all table entries are not based on actual studies in the field, but are based on modelling in combination with laboratory findings or deductions. The entries thus largely reflect the potential if the specific gene drive system were to succeed in working as envisaged.

The table shows that hardly any gene drive system is confinable, with the potential exception of high-threshold lethal underdominance systems, which though whilst they may not mix with and spread into wild populations, would push them back and replace them.

(*1) large transposons will commonly not jump easily, and transposons are regarded as having a tendency to lose components and be mutated by host organism. PLG: payload gene.

	Threshold-dependent	Threshold-independent	Temporally self-limiting	Intended as Suppression drive (eradication)	Modification / replacement with payload gene (PLG)	Confineability
Transposable Elements	-	yes		-	Probably not (*1)	no
HEGs	-	yes		yes	Maybe (in theory - with tightly linked PLG	no
CRISPR-HEG	-	yes		yes	Maybe (in theory – with added PLG	no
autosomal X-shredder	yes	-		yes	-	medium-high (Mendalian inheritance)
Y-linked X-shredder	-	yes		yes	-	no
T-haplotype	-	yes		yes	yes	no
Medusa	yes	-		yes	-	
Medea	yes	-			yes, theoretically (esp. if PLG is placed between toxin & antidote genes)	
Engineered Translocations	yes	-			yes	yes (though can replace population)
Engineered Underdominance	yes	-			yes	depends on design & threshold
(toxin-antidote) killer-rescue	yes	-			yes	
Theoretical: (Daisy) Chain-Drive	(can in theory be engineered for that)		in theory		hypothetically	not necessarily

led many researchers and scientists to call for the requirement that gene drives be stoppable and reversible, e.g. (Marshall and Akbari 2016) – at the very least in initial testing phases.

Given their potential to modify entire ecosystems[27], the ability to stop and remove a gene drive system is seen by many as a necessary or at least highly desirable prerequisite for any release of a gene drive organism. This is particularly the case for any releases in the trial phase, where it is being highlighted as a 'must have'.

It is important to understand here that frequently a crucial distinction is being made between 'removability' and 'reversibility', which differentiates between sequence reversibility and trait reversibility (Min et al. 2018). '*Removal*' here means the ability to restore the population to its original wild-type state. In the case of high-threshold gene drives the suggested means to attain this is the large-scale release of wild-type organisms , which in itself is a serious challenge and may not be possible. '*Reversal*,' however, is to genetically counteract and to block, disable or neutralise a gene drive system once released or escaped into the wild, by releasing an additional second gene drive as a "reversal drive". This measure, however, does not mean that the original population will be reinstated. Crucially, Champer et al. point out: "Of note, despite their name, reversal gene drives do not restore the original modification to the wild type; rather, they induce further changes that may undo a phenotypic alteration caused by the initial gene drive." (Champer, Buchman, and Akbari 2016, 148). In short, this means there are additional biosafety concerns to be addressed for "reversibility".

It is important to note that some authors are not making this separation and may refer to both as 'removal' (Marshall and Akbari 2016).

6 Real problems and the search for safety

In July 2017, the U.S. Defense Advanced Research Projects Agency (DARPA) announced a significant programme of research, named 'Safe Genes', that gives insights into concerns in the wider research community about the potential for irreversible and global effects from the use of synthetic/engineered gene drives. The programme itself directs considerable funding towards proving methodologies that might address these risks, to achieve "spatial, temporal, and reversible control of genome editors [including gene drives] in living systems" and to "eliminate unwanted engineered genes from systems and restore them to genetic baseline states" (DARPA 2017).

Reading this not through the perspective of a goal, but as a clear reflection of the real safety problems involved, and in particular (although not only) for the CRISPR/Cas9-based homing drive, it makes clear (to paraphrase) that: We do not know, nor do we have the technical tools, to reliably stop gene drives from spreading and being active once in the wild. There is no spatial or temporal control system or mechanism that has any demonstration of proof of concept. It further states that once the (genetic) changes have occurred in the wild there are no tools or mechanisms for undoing this, i.e. for reversing it and restoring a living system back to its genetic baselines.

Synthetic gene drives, and not uniquely but in particular CRISPR/Cas9-based homing drives, are very potent instruments, with potentially serious and significantly negative, even devastating consequences for biodiversity and ecosystems. These issues of lack of control over an instrument and of its technical limitations have already come up in previous sections of this chapter and are of deep concern to many.

In the following we will give some examples of CRISPR gene drive concepts and designs that have

27 In Champer et al. 2016 its reference 40 & 41.

Figure 7

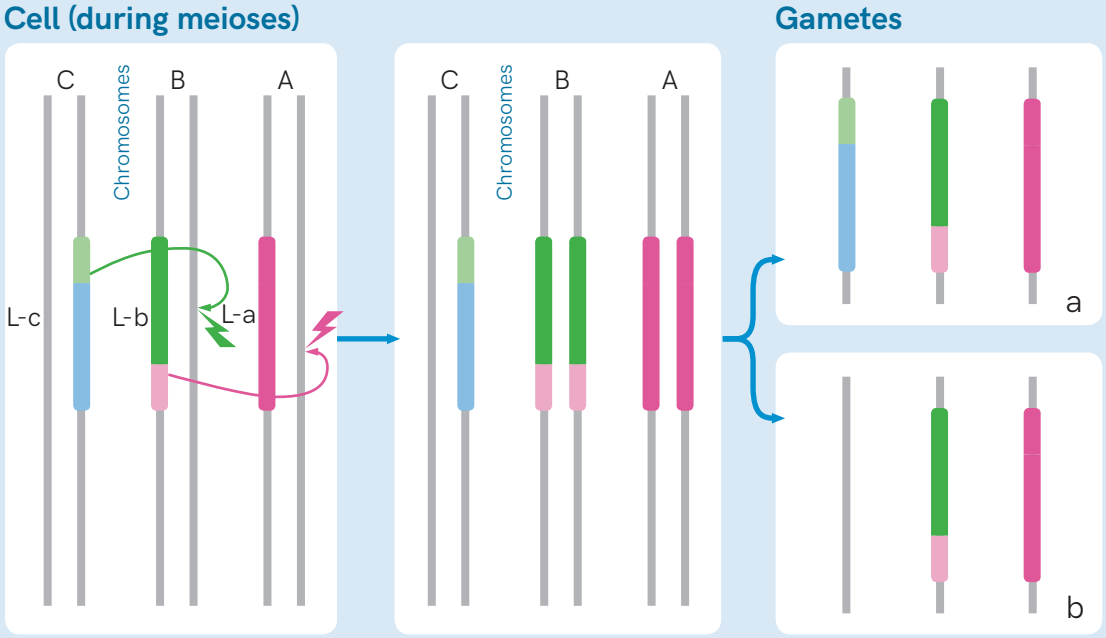

Figure 7: Design of Daisy Chain Drive. In a Daisy chain no drive element works on its own. It is a series of split drives; the guide-RNA for A is placed in construct B, and the guide RNA for B is placed in construct C. Thus, in a chain, A needs B, and B needs C. The last element in the chain, here C, does not have a drive and will thus not be copied across to the homologue chromosome. Instead it will be passed on in a 50:50 ratio. Thus gamete a (e.g. sperm) will have a full daisy-chain, whilst gamete b lacks construct C, and thus the ability to drive the next element.

been proposed as possibly providing some answers to the above concerns – should they themselves be made to work and be shown to work predictably. These examples are either DARPA-funded projects or related research.

6.1 Restrictive Gene Drives: (daisy) chain drives, split drives and global vs. local

The 'daisy drive' is a theoretical gene drive technology proposed by Kevin Esvelt, that theoretically would only 'drive' a gene into a population for a certain number of generations, and which is thus described as 'temporally self-limiting'.

It is a variation on a CRISPR/Cas homing drive described in detail by Noble et al., where the different elements have been split up and spread across different chromosomes (Noble et al. 2016). In fact, the principle is quite simple.

There are three separate elements: element A: a payload gene that is inserted into location (L-a); element B: a gene coding for a CRISPR-based endonuclease designed to cut the DNA at location (L-a) and itself inserted at location (L-b); finally element C: a gene coding for another CRISPR-based endonuclease, here designed to cut the DNA at location (L-b) and itself inserted at location (L-c). All these elements can function in a chain-like manner: element A (the payload gene) needs a helper to achieve drive and to get itself copied to its 'home' location on the homologous chromosome; element B will be that helper, in that it cuts the DNA at the spot element A needs to be copied into; yet element B also requires a helper to achieve drive, which will be element C. The only element that cannot obtain drive in this design is element C, which will be passed on

according to Mendelian Law. So, if a certain number of such gene drive organisms are released that are homozygous for all three elements, i.e. where all elements are present twice, then there will be drive for A and B but not for C. Once C gets thinned out in the following generations, then there will be reduced drive for element B, which will ultimately result in a loss of drive for element A.

If however recombination takes place between the gRNA of C with A, then this "could create a "daisy necklace" capable of self-sustaining global drive." (Noble et al. 2016)

'Daisy-chain drive' is one of the potential methodologies being proposed which can supposedly limit the geographical spread of a gene drive and its trait(s), and so is portrayed as a potential means of alleviating concerns about gene drives uncontrollably spreading through a whole global population. No proof of concept of this technology has yet been published, though Esvelt's team has secured significant funding to attempt to achieve their goal of such a local and reversible daisy-chain drive (DARPA 2017).

Whilst it is referred to as a 'local' drive by its designers, this may actually be somewhat misleading, as it is designed as a drive with temporal limited spread, a so-called 'self-exhausting' drive. Modelling studies carried out by researchers at North Carolina State University, Raleigh, suggest that there are flaws in this chain-drive concept once it is exposed to interbreeding with neighbouring populations. As mentioned previously, they concluded that daisy-chain will not be locally contained unless fitness costs are above 30% and migration rates are below 0.5% per generation (Dhole et al. 2018).

Furthermore, modelling studies also show that, should the drive perform as planned, a payload gene which has a 10% fitness cost may readily reach fixation in a population with an introduction frequency of as little as 3% (Dhole et al. 2018). There is also the potential for the genetic modifications, including payload gene, to spread more widely via normal Mendelian inheritance through the interbreeding of linked populations, depending on fitness costs.

A serious technical hurdle is the potential for rapid emergence of resistance, as two different CRISPR/Cas homing drives must be active for this drive design to work, and not just one, though the authors hope that the use of multiple sgRNAs may help the situation.

Split drives & synthetic target site drives

Concerns about accidental escape of GDOs from laboratories, transport or cage trials into the wild are shared by many, especially in terms of CRISPR-based homing drives. Given the possibility of human error or unforeseen natural events, Champer and his colleagues point out that relying on physical containment solely is insufficient and note: "Since very few escapees can establish an effective drive in a population (Unckless et al. 2015; Noble et al. 2018; Marshall and Hay 2012[a]; Marshall 2009), additional safety measures should be employed in any experiments with drives potentially capable of spreading indefinitely." (Champer et al. 2019, 3). Both split drives and synthetic target site drives have thus been designed for this particular purpose, namely to add an additional layer of safety to experimentation with GDOs in the laboratory (Akbari et al. 2015; Champer et al. 2019).

In a *split drive* the endonuclease (Cas9) is physically separated from the drive construct (the guide RNA and potentially a payload gene), and both need to be present for drive to occur. In this system, the endonuclease is inherited according to Mendelian Law. A *synthetic target site drive* is designed to recognise a DNA sequence that has previously been added to the laboratory strain through genetic engineering but that will be absent in wild populations. Both these designs have recently been tested in the model insect *Drosophila melanogaster* (Champer et al. 2019).

Whilst this is a good step for increasing the safety of laboratory experimentation, it should be a binding requirement, and not a voluntary approach taken by some.

6.2 Gene Drives targeting geographic sequence variants

An alternative proposed means of limiting the spatial range of a gene drive is to identify geographic variations in genome sequences, and target a gene drive to such particular variants. Also funded by DARPA (DARPA 2017), this strategy is being explored by teams developing gene drives in mosquitos (Wood 2017), mice and feral cats (AWC 2018), but again, no proof of concept in a laboratory has yet been published. Furthermore, unless the target gene is a highly conserved and essential gene (see Kyrou et al. 2018), resistance is bound to arise. Still, a highly conserved and essential gene would commonly have the same sequence across the whole species or even species group, thus being able to leak the gene drive quickly into the wider population. This leaves this approach clearly at the hypothetical stage.

6.3 Gene Drive 'catchers' – ideas and approaches for 'anti-gene drive'-drives

The question of how to counteract a gene drive, whether it is a drive which behaves in unforeseen ways, has unpredicted negative impacts, is an unintended release, or is used maliciously, is evidently a key concern in the research and development community. The theoretically most plausible method if it can't be countered with CRISPR inhibitors[28], which seems somewhat of an unlikely strategy at eco-system scale, then perhaps the only imaginable strategy for counteracting a gene drive is to release a second gene drive to 'catch' it, an 'anti-gene drive'. DARPA is clearly aware of this and is directing funding to developing "drives that can overwrite every copy of a 'rogue' gene drive" (Esvelt 2017) through their $65 million 'Safe Genes' research programme. Again, no proof of concept in a laboratory has yet been published.

6.4 'Immunising' drives

A yet different idea is that of target prevention. In the case of an unwanted or problematic CRISPR/Cas-based homing drive being 'on the move', the idea would be to release a separate synthetic gene drive that could over-write the target sequence of the first gene drive, thus 'immunising' the populations (Esvelt et al. 2014). This would be an approach that relied on genetically modifying a wild population with, once again, unforeseeable consequences. It is for example unclear what the implications are of leaving active Cas9 constructs/endonucleases in a population, and whether that might produce a background toxicity or give rise to off-target effects. Equally it is not understood what the chances are of accidentally arriving at an equilibrium between two counteractive gene drives and its possible consequences. (Vella et al. 2017). Again, no proof of concept in a laboratory has yet been published.

7 Summary and conclusions

As discussed in this chapter, gene drives are defined as a genetic element or mechanism that imposes a greater than 50% inheritance rate of itself or an associated trait, even if this inflicts a high fitness cost on the organism. Such elements and mechanisms have been found or observed in nature, and their roles are as yet not really understood. Termed 'selfish genetic elements' from early on, some of these, for example the over-replication ability of transposable elements, are increasingly regarded as vital components for genome evolution and even speciation (Biemont 2010). John H. Werren for example noted: "The story that is emerging increasingly supports a central role of SGEs [selfish genetic elements] in shaping structure and function of genomes and in playing an important role in such

28 A separate DARPA funding stream with in the 'safe genes' program

fundamental biological processes as gene regulation, development, evolution of genetic novelty, and evolution of new species." (Werren 2011, 10863). In fact, the study of these elements and the processes involved are now contributing to an emerging re-think of what a genome is and how it interacts with its environment. (Werren 2011; Lindholm et al. 2016).

The origin and design of synthetic - or engineered – gene drives is based on these genetic elements and mechanisms found in nature. There are basically two main categories of gene drives. The "over-replicators" actively pursue their own multiplication within a species by copying themselves directly across to the genomes of the next generation without passively awaiting their distribution during sexual reproduction according to Mendelian Law. These are the transposable elements and the homing endonuclease genes (homing drives). Then there are the 'transmission distorters', that will seriously disadvantage or eliminate 'competitors', such as sibling gametes or embryos that did not inherit the specific genetic element (e.g. some sex ratio-distorters), or that will weaken or kill the developing organism if an element is not inherited from both parents (underdominance drive). A major instrument with the genetic ability to kill rival cells is the toxin-antidote mechanism, which can be used in almost any transmission distorter system.

There are real complexities involved in the different mechanisms and systems described in this chapter. To imagine and build functional synthetic gene drives has long eluded the abilities of researchers. This changed completely with the arrival of the genome editing tool CRISPR/Cas9. This versatile endonuclease is currently being employed in almost all categories of gene drives. Whilst it can be used as a 'toxin' in the toxin-antidote mechanism, it is most prominent in the CRISPR/Cas-based homing drive (also known as the RNA-guided homing drive), and the CRISPR/Cas-based 'X-shredder', both of which quickly attained proof of concept in laboratory settings with model organisms.

The arrival of CRISPR/Cas thus seemed like a breakthrough, making gene drive construction appear simple and easy, and with this came many claims, hopes, dreams, promises and projections – and funding. At the same time, the discussion began to focus on the risks, complexities and limitations that were rapidly emerging from the research.

What follows is just a summary of concerns that voiced in the literature as well as at the CBD and other bodies. For example it was recognised from early on that the concept of the CRISPR/Cas-based homing drive, one of the most advanced and potent systems so far developed, poses major risks precisely because it is a global gene drive, because it is self-sustaining and thus threshold-independent. Its potential power to eliminate or modify means that there is no room for errors in the technology or for unintended effects on the target species or the ecosystem into which it is released. There is also no room for accidental escape from labs or cages, unintended spread, or crosses into closely related species, nor for a spreading payload gene to turn out to be problematic in the wild, or change a species such that it becomes invasive, a stronger or different pest or vector. There must also be no negative impacts on the resilience of ecosystems, or on biological diversity including agricultural biodiversity, food systems or human health, livelihoods, and cultural practices of indigenous peoples and local communities.

As pointed out, research is also revealing serious limitations and malfunctions to this technology, such as its inefficacy in many organisms, the rapid emergence of resistance, off-target effects, irreversibility and the impossibility of containment or recall once released. In view of both risks and limitations, this technology as it stands is not fit for application.

So are these issues being addressed? Major efforts are being undertaken to circumvent or overcome resistance. The other issues, so far, are stuck at the stage of theoretical models and designs, such as the various daisy drive designs, or the 'anti-gene drive'-drives, e.g. immunisation drive, reversal drive, drive catchers.

All these efforts are still lacking proof of concept and often merely exist in computer modelling,

which carries its own limitations. It is, however, important to recognise that, as the technology develops, so new problems and challenges emerge, requiring new layers of 'solutions', which in turn carry their own risks and limitations, and add to the overall complexities involved in assessing both performance and impacts of proposed applications.

It also applies to other gene drive systems with proof of principle that are being followed up, such as the CRISPR/Cas-based X-shredder (a potentially self-sustaining drive system), underdominance (Buchman, Ivy, et al. 2018) and Medea (Chen et al. 2007; Buchman, Marshall, et al. 2018), which will also have their own limitations and risks.

Whilst this, our report's first chapter, has looked at the technical and technological aspects of gene drives and related elements, it is still impossible to say very much about either the actual performance or the potential impacts of release under real life conditions, e.g.: on high genetic variation in wild populations, or on interactions with other species and response to the complexities of ecosystems. The behaviour of gene drives and gene drive organisms in such settings may be very different from laboratory experiments and modelled predictions, thus adding an extra layer of risk whose nature and gravity may be impossible to accurately predict in advance.

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Chapter 2

Potential applications and risks

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1 General introduction

Gene drives are genetic elements that are able to override the rules of inheritance. When genetically engineered and linked to a biological function, they are intended to be used to modify, and in some circumstances, eradicate, a whole population or even an entire species. This idea has largely remained just a theory until quite recently. With the arrival of the genome editing tool CRISPR/Cas9, the field of gene drives and the ability to eliminate undesired species and wild populations got a big boost. CRISPR/Cas-based gene drives were first proposed in 2014 (Esvelt et al. 2014) and the proofs of principle came swiftly, published in 2015 and 2016 for fruit flies (*Drosophila*), yeast and two species of mosquitoes (*Anopheles stephensi* & *Anopheles gambiae*) and in 2018 for mice. Gantz and Bier called it a "mutagenic chain reaction" when they delivered the first laboratory proof of principle (2015), showing that the genome editing tool CRISPR/Cas could in theory be turned into a self-spreading gene drive that might be capable of altering or eliminating wild populations or potentially whole species (Gantz and Bier 2015). Yet laboratory experiments picked up a flaw in this method – the emergence and build-up of 'resistance' to CRISPR/Cas, capable of stopping the functioning and spread of the gene drive, as discussed in Chapter 1. Crisanti's team applied a different strategy, which by targeting highly preserved (conserved) genes, proved capable for the first time of completely crashing caged populations of the mosquito *Anopheles gambiae* in laboratory settings (Kyrou et al. 2018a). This strategy, however, comes with heightened new risks of the gene drive mechanism spreading beyond the target species, as such genes are often highly conserved across a whole species group. Hybridisation (cross-breeding) within these groups would move the gene drive and its action into closely related species, a distinct possibility for the *Anopheles gambiae* complex. Whilst this strategy might have overcome the resistance problem in this particular instance, it has to be noted that caged experiments do not address the complexities of how species will actually respond in the real world.

Other strategies and designs of CRISPR/Cas-based homing gene drive strategies are being developed under DARPA (US Defense Advanced Research Projects Agency) funding, and different non-homing gene drive systems and applications are also under development, utilising for example MEDEA (e.g. for fruit flies), *t*-haplotype systems (mice) or X-shredder (e.g. mosquito) (see Chapter 1 for technical details).

Gene drive organisms and gene drives are clearly not just research interests and research projects on their own – they include the clear intention of application. This is revealed by significant factors: the large sums of funding being provided; the categorisation into fields of applications found in many reviews and reports, e.g. the report by the National Academy of Sciences, Engineering and Medicine (NAS 2016); the rationale presented in scientific papers published by research groups; the substantial budgets for public and policy engagement in DARPA-funded gene drive projects; and the general benefit-focused portrayal in the media.

With such a strong application and benefit mindset and focus on "deployment", there seems to be little room for crucial critical reflections, which should include: looking dispassionately at the real risks of this powerful technology; being clear about the fact that the claimed benefits are largely only

hypothetical and at best potential benefits, as none of them have undergone a scientific, and socio-economic, robust and transparent benefit analysis and assessment; taking note that there is no methodology in place for such needed assessments; taking time to investigate the spectrum of other solutions and approaches that might be cheaper or safer; trying to isolate and then address the underlying causes to the problems gene drives are supposed to address, which might actually require very different solutions; and finally, attempting to determine where the best answers to all these questions might lie - which may not always be with science and technology.

It would be problematic and inappropriate to view the use of engineered gene drives as some kind of a self-replicating, self-spreading, target-specific "pesticide", to be readily 'applied' or released to attack any pest, disease vector, invasive species, unwanted or disliked species or nuisance populations; and yet that tendency is already present in media coverage and in promotional claims. Such a view of usage demonstrates an unwarranted sense of familiarity with, as well as a misconception of, what engineered gene drives are. We are talking about living organisms, living and highly interactive systems. We are talking about completely new and unknown numbers and levels of risks and impacts.

Gene drives - in particular CRISPR/Cas-based homing drives - are a technology which gives humans the potential to intentionally (or unintentionally) re-engineer whole ecosystems, perhaps altering or wiping out wild populations of various species across vast regions. If they are deployed, that is, released into the environment, there is no doubt there will be impacts. These include impacts on biodiversity, which is already in unprecedented and rapid decline (Ceballos, Ehrlich, and Dirzo 2017; Sanchez-Bayo and Wyckhuys 2019; FAO. 2019); impacts on ecosystem functions and services, including agricultural systems, at a time when many are already at the point of collapse; there will be co-evolutionary responses of pests and associated pathogens and parasites; and the disruption, unbalancing and shifting of ecosystems in unpredictable ways, which may not only be triggered by the suppression or elimination of a population or species or by the alteration of their traits, biological functions and behaviour, but also from the engineered gene drive moving or crossing to other species. For example, the mosquito species *Anopheles gambiae* is known to cross with other closely related species, such as *A. quadriannulatus* or *A. arabiensis*, both in the laboratory and in the wild, resulting in hybrid offspring with fertile females and at times also fertile males (Coluzzi, Sabatini, Petrarca, and Dideco 1979).

There will also be consequences from the technology not working as expected, or from it working differently than expected. This has been discussed in Chapter 1 and will also be considered in Section 3 on risks and risk assessment at the end of this chapter.

Suggestions for proposed gene drive applications cover a wide range and extend across plants, animals and fungi. To date, they include mice, rats, fish, birds, insects (e.g. various mosquitoes, flies, beetles, hornets, etc.); also spiders, feral cats, snails, nematodes, plants such as pigweed (Amaranth) and horseweed; and finally the phylum of fungi.[1]

In order to understand the risks and identify the hazards of of gene drive organisms (GDOs), a categorisation into areas of application or envisaged potential benefits is of little help. Gene drive applications are frequently categorised into three areas: Public Health; Ecosystem Conservation (including combating alien invasive species); and Agriculture, mostly regarding pests, weeds, and diseases. Another category however, is military use; the potential weaponising of gene drives is commonly covered under the topic of "dual use", as the knowledge creation and technological capacities achieved in civil research and for civil application can equally be used or misused for intentionally harmful purposes, including military ones. When looking at potential dual use scenarios, the US National Academy of Sciences (NSA) argues in their 2016 report on gene drives: "Yet, with a better understanding of the basis of mosquito—pathogen interactions, it is not in-

1 See tables and special studies for references.

conceivable that rather than developing a resistant mosquito, one could develop a more susceptible mosquito capable of transmitting a specific pathogen more efficiently than wild-type mosquitoes. It might even be possible to develop mosquitoes that could transmit a pathogen that is not normally vector-borne, or that could even be able to deliver a toxin." (NASEM 2016, 161) There are in fact many scenarios one could conceive of, especially for insects, given the recent research advances in that field. Whilst spreading toxins and diseases to humans, livestock or plants is a serious prospect, it would be of equal concern to intentionally weaken or eliminate beneficial insects. The US National Academy of Sciences hence states in its conclusions: "Governance mechanisms need to be in place to address questions about the biosecurity implications of gene drive research and consider developing mitigation strategies that are not dependent on the underlying technology." (NASEM 2016, 171).

Such categorisations into fields of application does not only move the idea of benefit into the foreground, but also inadvertently raises sets of concerns and questions other than those necessary to identify hazards and understand risks. The former will look at questions related to doability, efficiency, reliability and simplification, that is, getting the gene drive to work despite or irrespective of environmental and ecosystem complexities; or to ideally creating a gene drive system that is easily transferrable to multiple species, e.g. to different insects that have become agricultural pests that could be new gene drive targets, (see for example criteria in (Marshall and Akbari 2016)).

Therefore, three points arise: Which categories are helpful to open up and reflect issues of hazards and risks? What questions need to be asked, and what kind of knowledge is required to answer them? Finally, is the experience we have with GMOs sufficient to deal with GDOs, or are there substantial differences?

Looking at the current experience with releases of approved GMOs (see Table 1), the vast majority are highly domesticated and uniform crop plants, as well as some trees and ornamental flowers. They are being released into simple, highly controlled (agricultural) and managed environments and are not intended to spread. Nonetheless, outcrossing and gene flow are regarded as serious problems and contamination incidents are frequently reported, such as for oilseed rape (Friesen, Nelson, and Van Acker 2003; Hecht et al. 2014), Maize in Mexico and South Africa (Pineyro-Nelson et al. 2009; Iversen et al. 2014) or for rice, alfalfa and creeping bentgrass in North America (Sharratt and Chopra 2019). With regard to GM animals, all are intended for rearing in enclosed systems, with strict containment requirements. The only open release of GM animals has been a few sterile GM insects, again not intended to spread, but instead incapacitated from doing so.

In contrast, GDOs will not be domesticated and uniform but genetically and behaviourly diverse. They will be released into open, wild, uncontrolled and highly complex environments. Unlike plants, most of them – especially insects - are highly mobile and are intended to spread and cross-bread, thus resulting in intentional contamination of wild populations and ecosystems.

Table 1: GM crops and GM animals that have gained approval in at least one country (source for plants: ISAAA 2019)

GM crops	GM trees	GM flowers & grasses	GM animals	GM insects
Predominantly: Cotton, Maize, Oilseed rape (canola), Soya bean **Also approved:** Alfalfa, Bean, Eggplant, Flax, Melon, Potato, Rice, Safflower, Sugar, beet, Sugar cane, Sweet pepper, Tobacco, Tomato, Wheat	Apple, Papaya, Plum, Eucalyptus, Poplar	Creeping Bentgrass, Carnation, Petunia, Rose	**In containment:** Pigs, Goats, Salmon, Mice (for research)	**For release:** Mosquitoes (sterile), Pink Bollworm (sterilised)

Suggestions about using regular GM risk assessment and risk management methodology with this new technology displays a misconception of what engineered gene drives and GDOs are. The most advanced engineered gene drives to date are CRISPR/Cas9-based gene drives (including homing drives). Being equipped with an active CRISPR/Cas9 machinery that genetically modifies each individual anew *in vivo* in the wild allows for multiple changes to occur that cannot be predicted or assessed in the laboratory. The release of such GDOs into complex interactive systems[2] is equivalent to introducing one complex system into another, even more complex system, the environment (Bar-Yam 2002). In systems theory, the result would by definition be unpredictable, or nearly impossible to compute; and assessing gene drive risks thus ascends to an unprecedented and potentially intractable level of complexity.[3] This is one reason that we are suggesting a different categorisation, namely one guided by taxa and ecological 'ranking', focussing both on the individual species, with all knowledge required (including its ecological role, linkages and interconnections), as well as on each of the complex ecosystem(s) that are the potential recipients of the GDOs or that are directly or indirectly impacted.

This chapter will look at the different envisaged applications, the status quo of research and development, as well as at the risks and associated negative impacts with a focus on biodiversity and ecosystems.

2 GDOs - applications under development

2.1 Introduction

This section consists of three main components. First, we provide a detailed overview of the various gene drive applications under development, indicating the stage of development, i.e. the readiness for application. This is illustrated in the form of detailed tables which cover insects (Table 2a), small mammals (Table 2b) and fish, birds, mollusks, nematodes, flatworms and fungi (Table 2c).

These tables are followed by three main case studies, namely mosquitoes, mice and Palmer amaranth (pigweed).

We will then look at two fields of potential application. The first explores the issue of agricultural insect pests, why they have become such a problem in modern agriculture, what the arguments are for targeting them with engineered gene drives, and what other possible actions, agricultural practices and solutions are also available to counter the increasing emergence of such pests. The second application field briefly covers the issue of dual use, i.e. of civil as well as military use of gene drive technology. This will be done in the context of specific research being funded under DARPA.

2.2 Overview of Gene Drive applications under development

To give an overview of which species are being targeted and why, Tables 2a, b and c describe the gene drive concepts that are being developed for each target and the stated intentions for their development. In many cases there is an intention to eventually employ the drive against the target species in the wild; however we have also included important proof of concept experiments in laboratory model organisms, for example the fruit fly (*Drosophila melanogaster*) or baker's yeast (*Saccharomyces cerevisiae*).

2 A system that can be analyzed into many components having relatively many relations among them, so that the behavior of each component depends on the behavior of others. [Herbert Simon]" https://www.informatics.indiana.edu/rocha/publications/complex/csm.html

3 "A central feature of a complex system is that attempting to understand it by breaking it down into smaller parts and studying those parts in isolation is likely to fail. Although any scientific endeavor must simplify a system in order to study it, the complex system itself cannot be simplified—it takes on its characteristics from the whole." (Vandermeer and Perfecto 2017, 698)

Scope of tables

We include:

- Representative published work on each drive concept from each research group. In this we combine into one group variations on a similar concept, for example the two insect X-shredder drives described by (Galizi et al. 2016) and (Galizi et al. 2014).

- Research proposals that have been funded, either for drive development or preliminary work.

- Representative examples of drives that have been proposed in the literature, but laboratory research has not yet begun.

We have not attempted to provide a comprehensive list of proposed gene drive concepts or applications as these are very numerous, especially those consisting mainly of the target idea without further reflections.

We have not included work aimed at:

(1.) Characterising the emergence of resistance (Hammond et al. 2017; Champer et al. 2017).

(2.) Improving existing drive concepts by

- multiplexing gRNAs in homing CRISPR/Cas9 drives (Champer et al. 2018; Oberhofer, Ivy, and Hay 2018);

- optimising expression of CRISPR/Cas9 (Champer et al. 2018; Hammond et al. 2018);

- improving biosafety by splitting drive components or targeting artificial sites (Champer et al. 2019).

(3.) Exploring feasibility of gene drives in the model organism *Drosophila melanogaster* using non-programmable Homing Endonuclease Genes (HEGs), which now appears to be superseded by CRISPR/Cas9 drives - (Chan et al. 2011; Chan et al. 2013).

2.2.1 Insects

Insects are increasingly becoming the main target for gene drive developments. On one hand there are the vectors of diseases such as the mosquitoes *Anopheles gambiae, Anopheles stephensi, Aedes aegyptii* and *Culex quinquefasciatus* (listed in Table 2a and in the Mosquito case study); on the other hand there is a long list of agricultural pests that are shifting more into focus as potential targets. Whilst research with *Dropsophila melanogaster* has no direct application, it nevertheless has been the main laboratory model insect organism for almost 100 years. Research carried out on *D. melanogaster* has therefore to be viewed as R&D research for developing the "right" gene drive system and understanding innate technical problems (see six entries in Table 2a). Additional to the 8 agricultural pests listed in the table, there are many others being suggested and proposed, such as: gene drives against the brown plant hopper (*Nilaparvata lugens*), the silverleaf whitefly (*Bemisia tabaci*), the diamondback moth (*Plutella xylostella*), and the New World screwworm fly (*Cochliomyia hominivorax*) (Scott et al. 2018). The question around agricultural pests is also explored in detail further on in 'Agricultural pests as gene drive targets'.

2.2.2 Small mammals

Whilst small mammals are definitely potential targets for gene drive applications, the work has not progressed as rapidly as for insects, due to technical obstacles that are not yet fully understood (see Chapter 1). At present, most of this development work is being carried out in mice, as mice are the laboratory model animal for mammals. Nevertheless, mice are also targets themselves for elimination gene drives (homing drive, X-shredder and t-haplotype), as illustrated both in the case study and in Table 2b. It is understood that once the system works in mice that many more small mammals will become targets for elimination gene drives, such as various rodent 'pests', feral cats, brushtail possums and stoats, which have been especially named already in scientific reports; work on feral cats and brushtail possums has received preliminary funding.

2.2.3 Fish, birds, mollusks, nematodes, flatworms & fungi

As can be seen in Table 2c, fish, birds, mollusks, flatworms and nematodes, are all on the radar as potential gene drive targets, whilst fungi and possibly nematodes are being employed as model organisms for developing gene drive technology. The table includes drives to target invasive species (lionfish and starlings) and organisms involved in disease, including the soil transmitted helminths commonly called hookworm (*Trichuris trichiura*), whipworm (*Necator americanus* and *Ancylostoma duodenale*) and threadworm[4] (*Strongyloides stercoralis*), as well as the parasites that cause Schistosomiasis and their intermediate snail host. These examples illustrates that if gene drives become established as a tool for controlling pests, invasive species or agents of human disease, they will likely be employed against other taxa beyond insects and mammals. It is also worth noting, that in contrast to the strategy of targeting disease vectors, which is the motivation behind many of the proposed gene drives in insects, the planned suppression drives against nematode (roundworm) and flatworm parasites directly target the parasite themselves. This becomes an option when the parasite reproduces sexually.

4 Note this is a different parasite to the one commonly known as threadworm in the U.K.

Table 2a: Insects

Species	Geographic range[1]	Problem it is aiming to address	Intended application	
Mosquitoes				
Anopheles gambiae African malaria mosquito	predicted distribution; red=present; blue=absent (MAP 2019, Wiebe et al. 2017)	Morbidity and mortality from malaria in sub-Saharan Africa	Population suppression	
Anopheles gambiae		Morbidity and mortality from malaria in sub-Saharan Africa	Population suppression 'collapsing …vector population to levels that cannot support malaria transmission'	
Anopheles stephensi Asian malaria mosquito	predicted distribution; red=present; blue=absent (MAP 2019)	Morbidity and mortality from malaria in India and surrounding regions	Population modification to 'interrupt parasite transmission'	

1 Please see separate bibliography for sources for maps and geographic range.

2 Principal investigator

The table also shows alongside *Drosophila melanogaster* and *Mus musculus*, the baker's and brewer's yeast *Saccharomyces cerevisiae* is increasingly becoming a model organism for developing the technology (and that the soil nematode *Caenorhabditis brenneri* will also perhaps become established in this capacity). *Saccharomyces cerevisiae* is a widespread organism, and this is likely why two of the studies include molecular safeguards to reduce the risk of the drive and the GDO spreading outside the laboratory. These studies and others (e.g. Champer et al. 2019) raise the additional and important question: should molecular safeguards be mandatory in the design of more gene drive experiments, in addition to high level containment?

Gene drives in agricultural weeds and other plants are speculative at this point in time, and we have not found examples that have been proven to work, even in the laboratory. Plants present several challenges for gene drive function. Their generally low rates of homologous recombination compared to other organisms makes it less likely that they will be suitable target organisms because of resulting mutations at target sites during NHEJ, or low rates of incorporation of genes used in drives. Seed buried in soil that may remain viable for many years could escape gene drive exposure, while many plant species are self-fertile or commonly reproduce vegetatively, also avoiding gene drive exposure.

	Type of gene drive	Global or 'local'	Phenotype	Readiness of technology 1 2 3 4 5 6 7 8	PI[2], institution and funder Source
	Autosomal 'X-shredder'	In theory local (may spread)	Male only (drive results in >95% male offspring)		A. Crisanti Imperial College Gates/DARPA/BBSRC (Galizi et al. 2016, Galizi et al. 2014, Facchinelli et al. 2019)
	Homing CRISPR-Cas9	Probably global (no localisation strategy clear)	Intersex and sterile females (Kyrou et al)		A. Crisanti Imperial College Gates/DARPA BBSRC (Kyrou et al. 2018, Hammond et al. 2015)
	Homing CRISPR-Cas9	Probably global (no localisation strategy clear)	Resistance to malaria parasite, *P. falciparum*		V. Gantz, E. Bier and A. James UCSD NIH/TATA/DARPA (Gantz et al. 2015)]

Species	Geographic range[1]	Problem it is aiming to address	Intended application	
Mosquitoes				
Aedes aegypti Yellow fever mosquito	'…predicted to occur primarily in the tropics and sub-tropics, with concentrations in northern Brazil and southeast Asia including all of India…'(Kraemer et al. 2015)	Transmission of Zika and Dengue in California	Probably population modification	
Aedes aegypti		Transmission of vector-borne diseases such as Zika and dengue	Population suppression	
Culex quinquefasciatus Southern house mosquito	blue=present (Samy et al. 2016)	Transmission of vector-borne diseases	Population suppression	
Culex quinquefasciatus Southern house mosquito		Transmission of avian malaria in Hawaii	Population replacement or suppression: 'engineered to be incapable either of transmitting the malaria parasite or of reproducing'	
Drosophila melanogaster				
Drosophila melanogaster Common fruit fly	cosmopolitan, present on all continents except Antractica (Miller 2000)	NA (Laboratory model)	Providing proof of concept for homing CRISPR-Cas9 gene drive	
Drosophila melanogaster		NA (Laboratory model)	To provide proof of concept for specific gene drive system	
Drosophila melanogaster		NA (Laboratory model)	To provide proof of concept for specific gene drive system(UD MEL)	
Drosophila melanogaster		NA (Laboratory model)	To provide proof of concept for specific gene drive system	

3 The particular underdominance system is not specified in the article, but is likely to be similar to Floyd Reeds RPM drive developed in Drosophila

4 Not clear if this work is funded or not

5 Not clear how much it would spread in the case of accidental release

6 Not clear if issues with resistance are present and need to be resolved

	Type of gene drive	Global or 'local'	Phenotype	Readiness of technology 1 2 3 4 5 6 7 8	PI[2], institution and funder Source
	probably Homing CRISPR-Cas9	Intention appears to be 'local'	Resistance to Zika Virus		O. Akbari UCSD NIH/DARPA (DARPA 2017)
	CRISPR-Cas9 Daisy chain drive	In theory 'local' (but no proof of concept for this method)	Sterile females		Esvelt and Alphey MIT/Pirbright DARPA (DARPA 2017, BBSRC 2018)
	CRISPR-Cas9 Daisy chain drive	In theory 'local' (but no proof of concept for this method)	Sterile females		K. Esvelt and L. Alphey MIT/Pirbright DARPA (BBSRC 2018, DARPA 2017)
	Under-dominance[3]	In theory 'local'	Resistance to avian malaria parasite *(Plasmodium gallinaceum)*	[4]	F. Reed University of Hawaii (Goldman 2016)
	Homing CRISPR-Cas9	Not intended for release.[5]	Yellow colour (due to lack of pigment)		V. Gantz and E. Bier UCSD NIH (Gantz and Bier 2015)
	Under-dominance by reciprocal chromosome translocations	Not intended for release: in theory local	Red fluorescence throughout body	[6]	B. Hay California Institute of Technology US Army, USDA, DARPA, NIH and others (Buchman, Ivy, et al. 2018)
	Underdominance: Maternal effect lethal under-dominance (UD MEL)	Not intended for release: in theory local	No detected phenotype (individuals not carrying drive do not hatch)		B. Hay California Institute of Technology NIH and others (Akbari et al. 2013)
	MEDEA (Maternal Effect Dominant Embryonic Arrest)	Not intended for release: in theory local	No detected phenotype (individuals not carrying drive do not hatch)		B. Hay California Institute of Technology NIH and others (Chen et al. 2007, Akbari et al. 2014)

Species	Geographic range[1]	Problem it is aiming to address	Intended application	
Drosophila melanogaster				
Drosophila melanogaster		NA (Laboratory model)	To provide proof of concept for specific gene drive variation (ClvR) using CRISPR/Cas9 as 'toxin'	
Drosophila melanogaster		NA (Laboratory model)	Aim is demonstrating underdominance system	
Others				
Drosophila suzukii Spotted wing drosophila	Brazil, United States, Canada, Europe and Japan (Polo et al. 2016)	Economic impacts of damage to soft fruit crops (e.g. cherries)	Here providing proof of concept for MEDEA in *D. suzukii* for population suppression or replacement	
Ceratitis capitata Mediterranean fruit fly	Africa, Mediterranean area Australasia, North and South America (FAO/IAEA 2017)	Economic impacts caused by damage to fruit crops	Population suppression	
Diaphorina citri Asian citrus psyllid	Central and South America, India, South East Asia and Saudi Arabia (Grafton-Cardwell et al. 2005)	Economic impacts of Citrus greening disease (caused by a bacterium which is transmitted by the psyllid)	Population modification or replacement	
Rhodnius prolixus Kissing bug	Venezuala, Columbia and parts of Central America (Sosa-Estani and Leonor Segura 2015)	Impacts of Chagas disease: *R. prolixus* is a vector for the causative parasite *Trypanosoma cruzi*	Population suppression	
Lucilia cuprina Australian sheep blowfly	Warmer regions worldwide, including areas of Australasia, North America and Sub-Saharan Africa.	Blowfly infection of sheep causes lesions which can cause death and/or welfare issues	Population suppression, (eradication in New Zealand)	

7 Not clear how much it would spread in the case of accidental release

8 Not clear if issues with resistance are present and need to be resolved

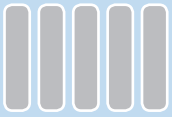
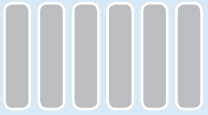
9 Reported to be stable for 200 generations

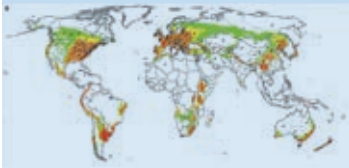
10 The funders acknowledged here are the German Academic Exchange Service, and the Excellence Foundation for the Promotion of the Max Planck Society

11 This project apparently encountered difficulties with developing molecular genetics tools in the target species. It was funded until 2017, but it is not clear if work is still ongoing.

12 Not clear if this work is funded or not

13 This investigator was recommended for funding but is a specialist in the parasite T. cruzi, so the gene drive itself would likely be constructed by a group specialising in insect molecular genetics

	Type of gene drive	Global or 'local'	Phenotype	Readiness of technology 1 2 3 4 5 6 7 8	PI[2], institution and funder Source
	Toxin-Antidote drive; Here via "Cleave and Rescue" (ClvR)	Not intended for release[7]	Red and green fluorescence markers	 8	B. Hay California Institute of Technology USDA (Oberhofer, Ivy, and Hay 2019)
	Under-dominance RPM-drive (Ribosomal Protein Minute Drive)	Not intended for release: in theory local	No detected phenotype except red fluorescent marker. Heterozygotes develop slower and have less viable offspring	 9	F. Reed University of Hawaii NSF and others (Reed et al. 2018, Reeves et al. 2014)
	MEDEA	In theory local but capable of spread	Here for testing: red fluorescence throughout body, weak green in eyes		O. Akbari UCSD California Cherry Board (Buchman, Marshall, et al. 2018)
	Homing CRISPR-Cas9	Potentially global with some discussion of theoretical potential for localisation	Either infertility or sex ratio distortion		E. Wimmer University of Göttingen[10] (KaramiNejadRanjbar et al. 2018)
	Possibly 'cleavage drive' (low threshold) or 'reciprocal chromosome translocations' (high threshold)	Both global and local are being considered	Various mechanisms under investigation to block transmission of the bacterium	11	B. Hay and others California Institute of Technology CitrusRDF (Turpen 2017)
	Probably homing CRISPR-Cas9	Need for localisation noted but no strategy as yet	Not clear: probably female sterility or sex ratio distortion	12	N. El-Sayed[13] University of Maryland PAF recommended for funding (Darrow et al. 2016)
	Probably homing CRISPR-Cas9	Intention is probably 'local' to New Zealand	All male offspring		NA (Dearden et al. 2018)

Species	Geographic range[1]	Problem it is aiming to address	Intended application	
Others				
Tribolium castaneum Red flour beetle	present on all continents except Antractica (IRAC 2019)	Economic impacts of consumption of stored grains	Population suppression	
Vespula vulgaris Common wasp	North America, Asia, Europe (Holartic species) and Australia and New Zealand	'Wasps attack native birds and insects and deplete critical food resources'	Population suppression, (Eradication in New Zealand)	
Vespula germanica German wasp	 predicted distribution; red/yellow = suitable; green= marginal (de Villiers, Kriticos, and Veldtman 2017)	'Wasps attack native birds and insects and deplete critical food resources'	Population suppression, (Eradication in New Zealand)	
Listronotus bonariensis Argentine stem weavil	South America (Argentina, Brazil, Chile, Bolivia, Uruguay), Australia and New Zealand	Economic impacts of damage to pasture grass	Population suppression, (Eradication in New Zealand)	

14 Not clear how localisation would be achieved

Table 2b: Small Mammals

Species	Geographic range[1]	Problem it is aiming to address	Application	
Mus musculus House mouse		Generating new lab mouse strains carrying multiple modifications is laborious	Proof of concept of CRISPR-Cas9 gene drive in mice as a mouse genetics tool	
Mus musculus		Impacts of invasive populations on islands – and potentially wider applications: see case study	Population suppression to eliminate invasive populations	
Mus musculus		Impacts of invasive populations on island biodiversity	Population suppression to eliminate invasive populations	
Mus musculus		Economic costs of rodent 'pest' populations in UK and elsewhere	Population suppression 'humane' and cost-effective control of rodent populations	

1 Please see separate bibliography for sources for maps and geographic range.

	Type of gene drive	Global or 'local'	Phenotype	Readiness of technology 1 2 3 4 5 6 7 8	PI[2], institution and funder Source
	Probably homing CRISPR-Cas9	Not clear (early stage)	Infertility or sex ratio distortion		M. Wade and G. Zentner Indiana University NIH and others (Drury et al. 2017, Scott et al. 2018)
	Probably homing CRISPR-Cas9	Intention is 'local' to New Zealand[14]	Infertility or sex ration distortion		NA (Dearden et al. 2018)
	Probably homing CRISPR-Cas9	Intention is 'local' to New Zealand[14]	Infertility or sex ratio distortion		NA (Dearden et al. 2018)
	Probably homing CRISPR-Cas9	Intention is 'local' to New Zealand[14]	Infertility or sex ratio distortion		NA (Dearden et al. 2018)

	Type of gene drive	Local or global	Phenotype propagated	Readiness of technology 1 2 3 4 5 6 7 8	PI, institution and funder
	Homing CRISPR-Cas9	Theoretically global but current efficiency likely too low to effectively spread in wild	all white coats		K. Cooper (with V. Gantz and E. Bier) UCSD NIH and others (Grunwald et al. 2019)
	T-haplotype	Not clear (but no localisation strategy given)	daughterless		D. Threadgill Texas A&M DARPA (Leitschuh et al. 2018)
	Homing CRISPR-Cas9	Not clear (but no localisation strategy given)	daughterless		P. Thomas University of Adelaide DARPA (GeneDriveFiles 2017)
	Homing CRISPR-Cas9 or CRISPR-Cas9 X-shredder	Not clear	sterile females		B. Whitelaw Roslin Institute, UK BBSRC (McFarlane, Whitelaw, and Lillico 2018)

Species	Geographic range[1]	Problem it is aiming to address	Application	
Peromyscus leucopus White footed mouse		Increasing incidence of Lyme's disease in humans	Population modification (to reduce tick borne transmission of Lyme disease to humans)	
Targeting rats in UK, probably ***Rattus norvegicus*** Brown rat		Economic costs of rodent 'pest' populations in UK and elsewhere	Population suppression	
Felis silvestris House cat, wild cat & feral cat	Wild cat range (excluding feral populations)	Feral cat populations in Australia preying on native wildlife	Population suppression (eradication of Australian feral cat population)	
Trichosurus vulpecula Brushtail possum	Native range	'Predator on native birds and invertebrates, eats native plants, carrier for bovine TB'	Population suppression (eradication in New Zealand)	
Rattus rattus Common rat		'Predator on native birds and invertebrates, eats native plants, carrier for diseases'	Population suppression (eradication in New Zealand)	
Mustela erminea Stoats		'Predator on native birds and invertebrates, eats native plants, carrier for diseases'	Population suppression (eradication in New Zealand)	

	Type of gene drive	Local or global	Phenotype propagated	Readiness of technology 1 2 3 4 5 6 7 8	PI, institution and funder
	Homing CRISPR-Cas9	Theoretically 'local' (daisy-chain drive) and potentially global	Intention: Resistance to tick bites or resistance to Lyme disease (Borrelia burgdorferi)		Esvelt MIT NIH/DoD Greenwall Foundation (Esvelt 2017)
	Homing CRISPR-Cas9 or CRISPR-Cas9 X-shredder	Not clear	Sterile females		B. Whitelaw Roslin Institute, UK BBSRC (McFarlane, Whitelaw, and Lillico 2018)
	Probably homing CRISPR-Cas9	Not clear	Sterile females or daughterless females		O. Edwards? CSIRO Australian Wildlife Conservancy (AustralianWildlifeConservancy 2017, 2018, Kachel 2018)
	Probably homing CRISPR-Cas9	Intention is 'local' to New Zealand, but not clear how this will be achieved	Not yet selected		NA (Dearden et al. 2018)
	Probably homing CRISPR-Cas9	Intention is 'local' to New Zealand, but not clear how this will be achieved	Not yet selected		NA (Dearden et al. 2018)
	probably homing CRISPR-Cas9	Intention is 'local' to New Zealand, but not clear how this will be achieved	Not yet selected		NA (Dearden et al. 2018)

Table 2c: Fish, Birds, Mollusks, Nematodes, Flatworms & Fungi

Species	Geographic range	Problem it is aiming to address	Application	
Fish				
Pterois volitans Lionfish	Indian Ocean, Red Sea, Invasive in Gulf of Mexico, Caribbean and Western Atlantic (FFWCC 2019)	'This invasive species has the potential to harm reef ecosystems... ...a top predator that competes with overfished native stocks'	Population suppression (eradication in Gulf of Mexico, Caribbean and Western Atlantic)	
Birds				
Sturnus vulgaris Common starling	Dark colours= native; Light colours = invasive	Not stated but probably impacts of invasive starlings on agriculture and competition with native species	Population suppression (eradication in Australia)	
Mollusks				
Biomphalaria glabrata Snail	Parts of Brazil, and Venezuela, the Lesser Antilles (Mavarez et al. 2002)	Human health impacts of infection with schistosome parasites for which the snail is an intermediate host	Populations modification	
Nematodes				
Caenorhabditis brenneri	Probably circum-tropical (Sudhaus and Kiontke 2007)	NA	Aim is development and testing of daisy chain drive and related concepts	
Necator americanus	Circum-tropical and some temperate regions (Palmer, Reeder, and Dunn 2000)	Human health impacts of soil transmitted helminth infection	Population suppression	
Nematodes				
Ancylostoma duodenale	Mainly South East Asia, and Mediterranean (Palmer, Reeder, and Dunn 2000)	Same project		
Trichuris trichuria	Circumtropical, Southern Europe and some other temperate regions (Palmer, Reeder, and Dunn 2000)	Same project		
Strongyloides stercoralis	Endemic in Central and South America, sub-Saharan Africa, India and South East Asia (Varatharajalu and Kakuturu 2016)	Same project		

1 It is not clear if this work has been funded or not

	Type of gene drive	Local or global	Phenotype to be propagated	Readiness of technology 1 2 3 4 5 6 7 8	PI, institution and funder
	Homing CRISPR-Cas9	Not clear if or how it would be localised	Not yet selected		P. Venturelli Ball State University Funder unknown (Vacura et al. 2018)
	Probably Homing CRISPR-Cas9	Not clear if or how it would be localised	Not yet selected		NA (Moro et al. 2018) (GISD 2019)
	Probably Homing CRISPR-Cas9	Proposal to localise with daisy drive technology	Resistance to infection with schistosome parasites		J. Teem ILSI Foundation Funder not clear (Teem 2016)
	CRISPR-Cas9 or CRISPR-Cpf1 Daisy chain drive (and variants)	Local (not intended for release)	Either a) change in fluorescence; or b) right hand coiled; or c) short (dumpy)		K. Esvelt MIT DARPA (Esvelt 2017)
	Probably homing CRISPR-Cas9	Not clear	Possibly biasing sex ratios	[1]	M. Berriman, Sanger Institute J. Lok Uni. of Pennsylvania Recommended for funding (Darrow et al. 2016)

Species	Geographic range	Problem it is aiming to address	Application	
Flatworms				
Schistosoma mansoni	Africa, the Middle East, South America and Carribean(Weerakoon et al. 2015)	Human health impacts of schistosomiasis (bilharzia) caused by infection with this parasite	Population suppression	
Schistosoma haematobium	Africa and the Middle East (Weerakoon et al. 2015)	Same project as above		
Fungi				
Saccharomyces cerevisiae Brewer's yeast	Found globally in domesticated, human and wild environments. (Can hybridize with closest relative S. paradoxus) (Peter et al. 2018)	NA	Aim is to study gene drives over 'hundreds of generations', to understand emergence of resistance	
Saccharomyces cerevisiae Brewer's yeast	Found globally in domesticated, human and wild environments (Peter et al. 2018)	NA	Validation of CRISPR-Cas 9 gene drive in S. Cerevisiae	
Saccharomyces cerevisiae Brewer's yeast	Found globally in domesticated, human and wild environments (Peter et al. 2018)	NA	Testing of various methods to modulate gene drive activity (e.g. Cas9 expression level) (Roggenkamp et al. 2018) and multiplexed gRNAs (Yan and Finnigan 2018)	
Candida albicans	A commensal organism in humans and animals (including mammals, and probably birds, reptiles, and fish)	NA	Aim is to easily create homozygous deletion mutants in diploid strains	

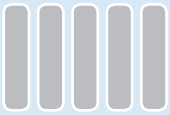
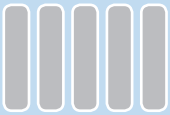
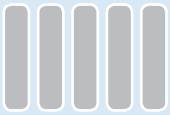
2 The sex of schistosomes is determined by Z and W rather than X and Y: females are ZW and males ZZ'. The proposed drive is conceptually similar to an X-Shredder design, the W-shredder would be encoded on the Z chromosome.

3 Not clear if issues with resistance are present and need to be resolved

Readiness of Technology. Categories are:

1 Gene drive proposed
2 Gene drive proposed with published preliminary research (but potentially not done with intention of creating gene drive)
3 Funded preliminary research (genome sequences, molecular genetics tools, etc)
4 Funded research on gene drive construction (with no results published yet)
5 Limited proof of concept for gene drive (i.e. there are outstanding technical issues such as resistance, low efficiency, too high fitness costs)
6 Laboratory proof of concept
7 Proof of concept in contained simulated natural environments
8 Releases in natural environment

Grey bars denotes gene drives that are not intended for release

	Type of gene drive	Local or global	Phenotype to be propagated	Readiness of technology 1 2 3 4 5 6 7 8	PI, institution and funder
	CRISPR-Cas9-based 'W-shredder'[2]	Population level "locally or globally" Drive is invasive	All male offspring		P. Brindley George Washington University (with K. Esvelt) Thomas Mather (Philanthropist) (Brindley and Esvelt 2019)
	Probably Homing CRISPR-Cas9 (as Gantz and Bier use this technology)	Not intended for release	Not public		S. Kryazhimskiy and J. Meyer (collaborating with O. Akbari, V. Gantz & E. Bier) UCSD DARPA (Aguilera 2017)
	Homing CRISPR-Cas9	Not intended for release (Contained: Cas9 expressed on episome separate from drive)	Pink colour	 3	G. Church Harvard Medical School DOE, NSF and others (DiCarlo et al. 2015)
	Homing CRISPR-Cas9	Not intended for release (Contained: Cas9 expressed on episome separate from drive and target sequence not in wild type)	Sensitivity to hygromycin	 3	G. Finnigan Kansas State University NIH and USDA (Roggenkamp et al. 2018, Yan and Finnigan 2018)
	CRISPR-Cas9	Not intended for release (containment strategy not described)	Various phenotypes relating to drug resistance and biofilm formation	 3	Collins MIT Various including NIH (Shapiro et al. 2018)

Abbreviations for funders and other organisations:
BBSRC – UK Biotechnology and Biological Sciences Research Council
Gates – The Bill and Melinda Gates Foundation
DARPA – US Defense Advanced Research Projects Agency
NIH – US National Institutes of Health
TATA – TATA trusts
USDA – US Department of Agriculture
PAF – Philanthropy Advisory Fellowship

2.3 Knowledge required to understand the risks of using a species as a GDO

In the following case studies, we tried to address some main points that we regard as essential for gaining an understanding of the complexities, uncertainties and possible hazards that are involved in gene drive organisms. For this we used in part the brief check list below, which is not intended to be exhaustive, but rather to illustrate the breath of elements and knowledge required. Some of these points will be picked up again in the final section on risk assessment.

A check list with important elements and questions for hazard identification

a) Ecological importance or "ranking" of gene drive target organism
   - Role within ecosystem; e.g. pollinators, place in food chain.
   - Knowledge of behaviour and interactions of GDO species
   - Listing of all predators, including their spectrum of prey and possible reliance on the GDO species.
   - Ability to spread; including speed of spread, distance of movement of individuals, ability to be carried by other organisms or by wind or water; dependence on particular ecological niche or ability to adapt easily to altered conditions.
   - Is it a "keystone species"?
   - Is it important for the survival of threatened or endangered species?

b) Global spread, ubiquity (only local, or everywhere)

c) Population genetics
   - Diversity of genetic background (within species)
   - Closely related species
   - Data on introgression (from hybridisation or in-crossing)

d) Are GDOs intended as a "solution approach", and if so, at which level?
   - The perceived problem
   - What underlies this perceived problem, including the causes, the root causes and what enhances or what reduces the problem. Is the perceived or addressed problem more a symptom of underlying causes and problems.
   - Which answers/solutions are already present, have been tried, suggested, or may be possible? e.g. push-pull systems, plants with semiochemicals, biological controls (release of predators or parasitoids), drying up water, crop diversity and enhanced pest enemy habitat, protection from pesticides, breeding crops for resistance.

e) The gene drive approach
   - Description of suggested gene drive approach: what is it? Who is suggesting it, developing it, funding it? (e.g. national weapons researchers, infectious disease agency, agribusiness, biotech venture companies, conservation researchers). Who is involved? How far has it gotten?
   - Is it the right approach (treatment of cause vs. symptom)?
   - Will gene drives actually be effective to solve the problem?
   - What negative implications, off-target effects and risks in general may this approach entail? (A central reference would be the CBD's AHTEG Guidance on LM mosquitoes)[5]
   - Does the gene drive approach provide important environmental co-benefits, and how does this compare to other approaches to solving the problem?
   - Has a similar approach to the problem been taken in the past (with other techniques)? What were the consequences? (e.g. SIT - sterile insect technique)
   - What would be a more sustainable approach or alternative solution?
   - Problems/solutions and other approaches (e.g. sterile insect technology SIT and GM RIDL mosquitoes; Wolbachia treatment for mosquitoes)

5 https://www.cbd.int/doc/meetings/bs/mop-08/official/bs-mop-08-08-add1-en.pdf

- Is the GDO acquiring an intended or accidental advantage as compared to the wild, non-modified population? (For example, endangered species might be given a resistance or advantage gene). What might those consequences be?

f) Social Implications
- Beyond the possible resolution of the immediate problem, who benefits from the gene drive approach compared to other possible solutions?
- Does the gene drive attract funding over other solutions because it benefits favoured segments of society?
- Does the gene drive have co-benefits for society broadly compared to other strategies?

All of the above considerations point to the complexity and challenges associated with the risk assessment of gene drives. Because of the intended or unintended spread of gene drives, their effects on the environment and society may be particularly complex compared to older technologies that are more contained and less likely to spread. Risk assessments for technologies like very widely used pesticides and GMOs in recent years have revealed many risks and harms several steps removed from direct impacts on target organisms. The scale of these technologies can be revealing for broad ecosystem of social effects. These effects have often been sub-lethal, on behaviour, fertility, the immune system, or other population level effects that have been difficult and time consuming for regulatory agencies to address. These have often not been effectively anticipated, and resulting harm only later detected. Similarly, social effects can be complex and favour some groups in society over others, prosing equity challenges. As the power of technologies like gene drives increases, their potential impacts can be much more complex.

2.4 Studies and specific applications

2.4.1 Case study 1: Mosquitoes

Introduction

Gene drives are actively being developed in at least four different mosquito species. Whilst technical issues remain, drives with the potential to suppress mosquito populations by biasing sex ratios or causing female infertility, or to modify populations with disease resistance genes, have been demonstrated in laboratories. In the light of these proof of concept studies, and the active pursuit by its developers for environmental release, focusing on the possible consequences of employing and releasing such technology has become paramount. Here we argue that, given the interwoven nature of ecosystems and the serious limitations in scientific understanding of these systems, and especially when combined with the unpredictability of the behaviour and actions of the engineered gene drives and GDOs, the attempted extinction or suppression of mosquito species would bring consequences that are difficult or impossible to fully or accurately predict, and which could be profoundly and irreversibly harmful.

Mosquitoes have existed at least since the beginning of the Jurassic, 200 million years ago (Reidenbach et al. 2009), co-evolving within a web of relationships to other species over this vast period of geological time (Tang et al. 2018). These relationships are not well explored; field studies usually only reveal single threads, or at best small parts of this web. Yet enough has been discovered to see these connections are likely to be significant. To consider some examples, one field study shows that for nesting house martens mosquitoes appear to be an important food source as they raise their young broods (Poulin, Lefebvre, and Paz 2010). Other studies reveal that for blunt-leaf orchids in the forests of North America, Scandinavia and Siberia, they are a major pollinator (Thien and Utech 1970; Gorham 1976). And in the tiny aquatic ecosystem inside the common pitcher plant, research shows their larvae are even a keystone predator, shaping

the diversity of the microscopic community within (Peterson et al. 2008).

Taking a broader view, the mosquito family has adapted to virtually all land habitats around the globe, from the arctic tundra to the tropical forests, resulting in a huge variety of species in many ecological niches. More than two centuries of dedicated work by entomologists has described over 3500 species (Harbach 2013), yet this number continues to grow each year; some tropical regions probably contain numerous species which are still unknown to science (Foley, Rueda, and Wilkerson 2007).

At least 160[6] species play some role in transmitting human pathogens and thus there is ongoing debate about the desirability of eliminating some or even all forms of the mosquito (Fang 2010), which has intensified with the arrival of CRISPR/Cas-based gene drives and suggestions that this technology could achieve such goals. To better understand the complexities, the potential hazards and the possible negative impacts of deploying such drives, we examine the various gene drive proposals, and briefly review the biology and ecological role of the mosquito, before moving on to consider the many uncertainties surrounding outcomes.

Gene drive proposals

Population suppression or eradication

At the time of writing, the most advanced gene drive technology targeting mosquitoes has been developed by a team at Imperial College London, UK, led by Andrea Crisanti, as part of the Gates Foundation's Target Malaria project. This group is conducting advanced trials (in simulated natural environments, according to news reports)[7] of at least two gene drive technologies theoretically capable of supressing or eradicating populations of the African malaria mosquito, *Anopheles gambiae*, which they plan to use against wild populations (Molteni 2018). One technology under development is the X-shredder, here making the mosquito produce endonucleases[8] to specifically target and sever sites on the X-chromosome during sperm production, resulting in the near absence of intact X-chromosomes in sperm and so producing almost entirely male offspring (Galizi et al. 2014; Galizi et al. 2016). If the gene for the endonuclease is engineered into an ordinary (autosomal) chromosome, the drive is not believed to spread rapidly, as it will be inherited in a Mendelian fashion. However, if the gene is engineered into the Y-chromosome (a sex-chromosome), the drive will be passed on to every male, making this drive theoretically highly invasive (Marshall and Akbari 2018). Whilst the first version has been tested in a laboratory (Galizi et al. 2016) the second version described by Marshall and Akbari 2018 has not yet been constructed. Following initial trials with conventional GM mosquitoes in Burkina Faso, the Imperial College group are proposing to release a theoretically self-limiting form of the X-shredder as a step towards gaining regulatory approval for more invasive and persistent drives (Molteni 2018).

Their second drive project is a CRISPR/Cas based homing drive (see Chapter 1). Resistance is a crucial issue in gene drive design (see Chapter 1): in the case of CRISPR/Cas9-based drives in particular, mutations frequently arise at the DNA target site as a result of erroneous repair after cutting, rendering individuals that inherit them resistant to the drive. Whilst it is unclear to what extent such resistance emerges to the X-shredder; the team has recently published details of a CRISPR/Cas-homing drive design which experimentally overcame this defence mechanism. They chose to disrupt a gene named doublesex, which results in sterility in females carrying the drive (Kyrou et al. 2018b). Because of its vital role, this gene has very little scope for mutation and therefore the minor mutations which normally allow resistance to evolve do not appear, allowing this drive to completely eradicate laboratory populations.

6 See Table 3

7 Results have very recently been published on the I-PpoI X-shredder in simulated natural environments see Facchinelli et al, 2019.

8 Two versions of this approach have been described one using CRISPR/Cas9 (Galizi et al. 2016) and another employing an altered homing endonuclease gene I-PpoI from the slime mold Physarum polycephalum (Galizi et al. 2014)

Population modification

In contrast to the goal of population suppression, a consortium of researchers in California including Valentino Gantz, Ethan Bier, Anthony James and Omar Akbari aim to use gene drives to modify populations to confer resistance to pathogens, an approach which they believe will reduce the pressure for resistance to the gene drive to evolve and to spread. A principal target is *Anopheles stephensi*, a major malaria vector in India, which has been modified in a proof of concept experiment with a homing CRISPR/Cas9 drive to spread genes conferring a level of immunity to the malaria pathogen in mosquitoes in laboratory populations (Gantz et al. 2015b). As observed with similar CRISPR/Cas9 designs however, mutations giving resistance to the drive appear rapidly, which the group are exploring methods to overcome. The consortium is also being funded to develop gene drives in *Aedes aegypti* (DARPA 2017), which may include drives to propagate genes that inhibit the capacity of this mosquito to transmit Zika virus (Buchman et al. 2019)[9].

'Self-limiting' gene drives

Because they wish to gain acceptance for the technology, the emerging view among gene drive researchers is that drives are required that will be self-limiting in their geographic reach or persistence, or indeed both. Theoretically, several designs of drive could achieve this goal (Marshall and Akbari 2018), including the autosomal X-shredder described above. Another gene drive technology, known as underdominance (see Chapter 1), has been successfully demonstrated in the laboratory in the fruit fly *Drosophila melanogaster*, a distant relative of the mosquito (Reeves et al. 2014), by a team led by Floyd Reed at the University of Hawaii. The same research team proposes to use this method to either modify or supress populations of *Culex quinquefasciatus* to control avian malaria in Hawaii (Goldman 2016). A variant of the CRISPR/Cas9 homing drive proposed by Kevin Esvelt, known as the 'daisy drive', has also gained much attention owing to its theoretical potential to provide a self-limiting drive. In other words, as it 'drives' through the species population, it slows down; and, depending on frequency, may stop altogether – although the genetic modifications would likely remain present in the population, especially the payload gene. Whilst the method remains a theory and has not been demonstrated in the laboratory, a consortium based at MIT in the US and the Pirbright Institute in the UK has been funded by DARPA to develop daisy drives in *Culex quinquefasciatus* and *Aedes aegypti*. Given these projects and the efforts by others, it seems likely that variants of the mosquito gene drive concept will continue to proliferate over the coming years.

Resources

Much of the massive investment in gene drive research has been directed at research in mosquitoes. More than $200 million from institutions, including the Gates foundation, the US Defense Advanced Research Projects Agency (DARPA) and the TATA trust, has been invested in gene drive research as a whole, and these driving resources are beginning to produce results, raising questions about who will decide which species are targeted and where. Although numerous technical difficulties remain, field trials of gene drives in *Anopheles gambiae* are planned by the research consortium Target Malaria, potentially in as little as 5 years, according to news reports (Molteni 2018). It is very possible that trials of systems targeting other mosquito species could follow in their wake.

Ecological importance

Scope

To help understand the risks and hazards of employing gene drives to suppress or modify mosquitoes in the wild, we here give an overview of ecological roles within the mosquito family as a whole, with reference to specific cases from the literature[10]. To consider the implications of any particular gene

9 This paper describes the modification of mosquitoes with genes encoding miRNAs that target Zika virus genes, which are reported to reduce the capacity of these mosquitoes to transmit Zika to mice.

10 A full literature review is beyond the scope of this report.

drive proposal, broad and detailed knowledge of the ecological roles of each potentially affected species would of course be required. This data is however lacking at the level of individual species, so taking a broader view is informative in identifying areas of concern. This bigger picture is also important because the numbers and identities of mosquito species that may eventually be suppressed or eliminated via gene drives, and the potential reductions in total mosquito biomass that would result, are both highly uncertain. As we later explore, gene drives may eventually be used against a wide range of mosquito species, and have potential to impact non-target mosquito species for example through hybridisation. It is also unclear what fraction of the total mosquito biomass, both locally and globally, would be represented by targeted species. It is beyond the scope to investigate this question in detail, but it is of ecological relevance that major vectors, which are likely to be among the initial targets, may be the more abundant species in at least some contexts[11].

Mosquitoes are an important food source

Across the global range of their habitats, the different phases of the mosquito life cycle support a wide variety of species. The aquatic larvae for example are predated upon by species of water bugs (aquatic *Hemiptera*), beetles (*Coleoptera*), flies (*Diptera*), spiders (*Arachnida*), flatworms (*Planaria*), tadpoles (*Amphibia*), fish (*Osteichthyes*) and crustaceans (reviewed by (Collins et al. 2019)). For the African malaria mosquito *Anopheles gambiae*, it is estimated that around 95% of larvae are con-

Figure 1

The life cycle of the mosquito

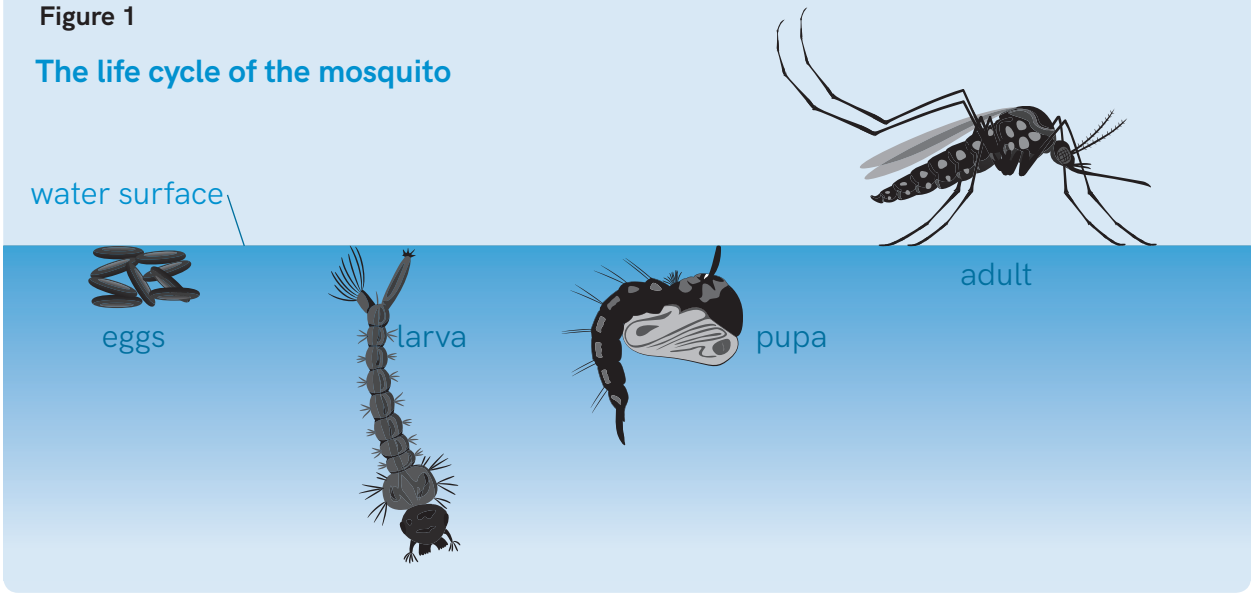


Figure 1: The life cycle of the mosquito The complex life cycle of the mosquito allows it to perform a wide variety of ecosystem roles. Its life cycle has four distinct stages: egg, larva, pupa and adult, the first three of which need standing water (for more detail see (Rozendaal 1997)). The eggs are generally laid in water, or in some cases just above the water line or in wet mud. Hatching requires water, and the larvae feed and develop in this aquatic environment. Eventually a larva forms a pupa, a non-feeding though mobile stage which undergoes metamorphosis before shedding its case to emerge as an adult, winged mosquito. Contrary to popular belief, the airborne adults feed mainly on nectar and other sugary plant juices (Foster 1995), and it is only the females (of most but not all species) that require a blood meal to produce eggs.

11 For example a study in a rice growing area of Kenya indicated that *Anopheles arabiensis, Culex quinquefasciatus,* both important disease vectors, together make up nearly 90% of the total mosquito population (Muturi et al. 2006).

sumed before reaching adulthood (Collins et al. 2019), implying that this stage makes the largest contribution to the food chain.

As adults, mosquitos are consumed by a different spectrum of predators, including species of dragonflies and damselflies (*Odonata*), spiders (*Arachnida*), bats (*Chiroptera*) and birds (*Aves*) (Collins et al. 2019). Insights into the possible effects of removing mosquitoes and larvae from ecosystems can be gained from studying the impacts of the use of *Bti* toxin[12], a selective biological control agent which is used to suppress or kill larvae. *Bti* is toxic to mosquitoes (Goldberg and Margalit 1977) and close relatives such as midges, but at the lower doses used in mosquito control is claimed to generally be non-toxic to other insects[13] (Lacey and Merritt 2004). Long term studies of the effects of *Bti* spraying in the Camargue wetlands, a nature reserve in Southern France, have shown harmful indirect effects. For nesting house martens, the average size of their clutches[14] and survival rate of fledglings were decreased (Poulin, Lefebvre, and Paz 2010)[15]; and for dragonflies and damselflies (Odonata) both species diversity and total numbers were roughly halved (Jakob and Poulin 2016). Since *Bti* affects both midges and mosquitoes, these impacts cannot be exclusively attributed to the loss of mosquitoes, however they do illustrate that reducing populations of even a small group of species can have significant and unintended effects.

Whilst many predators of larvae and adult mosquitoes consume a variety of other prey, there are species that specialise in hunting mosquitoes, such as *Evarcha culicivora*, an East African jumping spider (Salticidae) (Wesolowska and Jackson 2003). Whether many more such highly specialised predators exist remains an open question.

Some mosquitoes have over time spread into other regions and areas distant to their 'native' area, where they have then become established and often integrated into those ecosystems. Populations of *Aedes aegypti*, for example, have become established in many areas globally, and are also possible gene drive targets. This raises questions about the possible impacts of their suppression. The extent to which *Aedes aegypti* has become integrated into these new ecosystems has not been well investigated, but it would be expected that the species would be a food source for native predators in these new contexts, and there is some evidence that this is the case (Samanmali et al. 2018; Albeny et al. 2011).

Larvae are an important predator in aquatic ecosystems

Aquatic ecosystems contain a wealth of microorganisms, including photosynthetic primary producers, phytoplankton (algae), alongside various bacteria[16] and larger protozoa. At this microscopic scale, the protozoans are the predators feeding off the smaller microbes. Much of the diet of larval mosquitoes comes from this microbial community, including the protozoans, so the presence of larvae would be expected to have knock-on effects on this community. In the small pools of water inside common pitcher plants, the presence of larvae has indeed been shown to affect bacterial diversity, which is significantly higher when larvae are present (Peterson et al. 2008), presumably because they reduce numbers of protozoans.

In larger aquatic ecosystems, the effects of applying *Bti* toxin suggest that eliminating mosquito larvae could create complex changes within the aquatic microbial community, but again because both midges and mosquitoes are affected it is not possible to completely isolate the effects of mos-

12 The agent is derived from the bacterium *Bacillus thuringiensis* subspecies *israelensis (Bti)*, whose spores produce a variety of proteins which are endotoxins that are toxic/lethal to mosquito larvae. Note that the studies referred to use the natural form of the endotoxin as opposed to genetically modified forms.

13 Bti has some toxic activity against a range of insects (Palma et al. 2004), but these are dose dependent and non-equivalent, and Lacey and Merritt state that 'A multitude of studies conducted in lentic and lotic habitats reveal little or no direct effect of *Bti* on most nontarget organisms'.

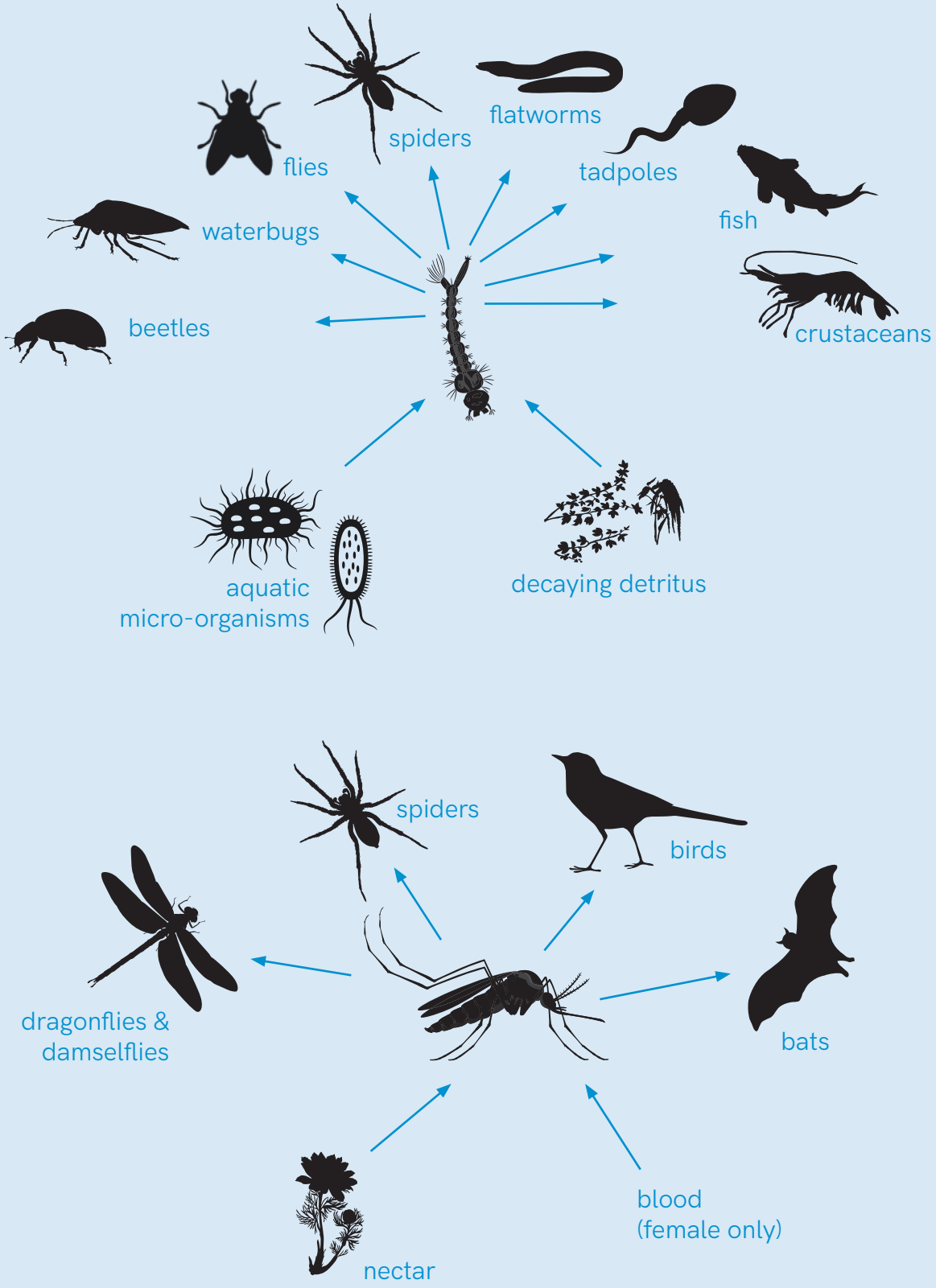
14 The average size of clutches was reduced from 3.2 to 2.3 chicks per nest.

15 This study shows that quantities of both *Nematocera* (mosquitoes and midges) and *Odonata* (dragonflies and damselfies), which prey on *Nematocera*, are significantly reduced in the diets of these birds in *Bti* targeted areas.

16 Some phytoplankton are forms of bacteria, whilst others are larger and more complex single celled organisms.

Figure 2

Trophic interactions of larval and adult mosquitoes



quito suppression given current data. In temporary wetlands in Sweden, a high dose of this toxin reduced the density of larvae by 97-100%, resulting in increases in the diversity and density of protozoans, as would be predicted when a predator is removed (Östman, Lundström, and Vinnersten 2008). The effects of removing larvae on other microbes appear complex. When samples of freshwater ecosystems are exposed to high doses of *Bti* toxin in a laboratory, thus reducing numbers of larvae, indirect effects are observed on microorganisms: phytoplankton densities are reduced, even though *Bti* is not toxic to these species; but bacterial diversity on the whole is increased (Duguma et al. 2015; Mulla and Su 1999). There is not always an immediate logic to such trophic chains and effects, which means that more detailed studies are required to more fully understand the processes involved. Long term studies of *Bti* mosquito control in the Camargue, for example, do not observe effects on phytoplankton (Fayolle et al. 2016), although there the doses of *Bti* were lower, reducing larval densities by around 80% rather than virtually eliminating them as in the Swedish experiment. Using these and similar studies to form a general understanding of the consequences of eliminating larvae is very difficult; the studies have observed different environments with different mosquito species, used different doses of toxin, and did not all observe the same groups of microbes. Thus, with current knowledge, the impacts on aquatic ecosystems of attempting to eliminate or suppress mosquitoes cannot be predicted with any confidence, and harmful knock-on effects, such as suppression of phytoplankton, cannot be excluded.

Mosquito larvae contribute to nutrient recycling

Because decaying organic detritus also forms part of the diet of larvae (Daugherty, Alto, and Juliano 2000; Daugherty and Juliano 2003), they contribute to recycling the nutrients in dead animal and plant matter into the food chain. As larvae represent a significant amount of biomass in some aquatic ecosystems (Yurchenko and Belevich 2016), their role in processing detritus in these contexts may be significant. Laboratory studies on the effects of using Bti toxin to suppress larvae have shown that both nitrogen and phosphorous in the water column are reduced when high doses of the toxin are used, although the mechanism for this effect is unclear (Duguma et al. 2015). Again, knowledge on this area is limited, but is sufficient to suggest that nutrient recycling could be disrupted by removing larvae.

Mosquitoes are important pollinators for certain plants

With the exception of females of certain species feeding on blood to support reproduction, adult mosquitos generally feed on nectar. This would imply possible roles in pollination, and whilst this question has not been well investigated, the mosquito's role as pollinator has been confirmed for some species. For example, six species of the genus *Aedes* have been shown to pollinate the orchid *Platanthera obtusata*, which has a large range covering the northerly regions of Europe, Asia and North America (Gorham 1976). Whilst it can be inferred statistically that the vast majority of the ca. 350,000 known flowering plant species rely on animal pollination the actual pollination of most wild flowering plants has not been studied (Ollerton, Winfree, and Tarrant 2011), so with current information it is not possible to know how significant the role of mosquitoes in pollination is. It is thus possible that mosquitoes are important pollinators for other flowering plants, giving potential for elimination programmes to impact these plant species and their related communities, particularly given that wild insect pollinators are already in decline in many areas (IPBES 2016).

Potential impacts of mosquito suppression

Whilst mosquitoes have been well studied compared to many insects, research has generally been driven by interest in identifying disease vectors and controlling numbers, and the ecosystem roles of the thousands of species within the family have only been investigated in individual and narrow circumstances. Nevertheless, the limited knowledge available is sufficient to show they are embedded in a wide network of relations to many other species. Where they are abundant they will be an important food source both as larvae and adults, will exert complex influences on the community of aquatic mi-

croorganisms, and will contribute to recycling nutrients into the eco-system. Knowledge of their roles in pollination remains limited, which means that the possibility of important pollinator relationships. Indeed other eco-system roles in certain circumstances cannot be excluded. Any proposals to eradicate mosquito species or groups of species, even in a localised setting, should therefore be viewed within this context of science's limited understanding of their complex system of relationships.

To summarise, at the ecosystem level, effects could occur in five broad areas, although their nature and extent is extremely difficult to anticipate:

- Decline in numbers and/or diversity of predators
- Reductions of other species that have become the new prey of predators
- Complex effects on aquatic microbial communities
- Reductions in nutrient availability in aquatic ecosystems
- Potential reduction in pollination and ensuing consequences

Whilst it is likely that empty ecological niches would be filled or that populations could rebound due to some form of resistance, even a temporary reduction in mosquito populations could have significant impacts on predator species and aquatic ecosystems, particularly if they were already under stress from other factors.

Role in human and animal disease

The requirement for blood feeding brings most mosquitoes into relationship with other sets of species, including humans. Recent genetic evidence suggests that mosquitoes have evolved rapidly to adapt to blood feeding on humans (Neafsey et al. 2015) and to live in anthropogenic environments (White, Collins, and Besansky 2011), seizing the opportunity created by the large fraction of biomass represented by humans (Bar-On, Phillips, and Milo 2018) and the increasing areas of land devoted to human activities. Not surprisingly, the species composition of the mosquito community is affected by the presence of humans and human influences on habitat. A study from Thailand has shown that even over short distances, the diversity of species and the relative abundance of disease vectors varied across forest and different anthropogenic habitats, with vectors of disease lowest in intact forest (Thongsripong et al. 2013).

A number of pathogens have evolved to exploit mosquitoes feeding on humans, including the single-celled plasmodium parasites which cause malaria; several viruses, such as Dengue, Zika and yellow fever; and various parasitic nematodes, which cause filariasis. Of these, malaria parasites cause the most infections and the highest mortality, contributing to an estimated 430,000 deaths in 2015 (WHO 2016). The two most significant malaria parasites, *Plasmodium falciparum* and *Plasmodium vivax*, are responsible for the vast majority of infections globally, with *falciparum*, which is common in sub-Saharan Africa, by far the most deadly form. The health impacts of other mosquito-borne pathogens are also substantial; for example, Dengue is reported as being responsible for tens of thousands of deaths every year (ECDC 2019).

Co-evolution of humans, pathogen and vectors

Inevitably, vector-borne pathogens are involved in an evolutionary 'arms race' with their human hosts, and it should be considered how the use of gene drives to spread disease refractory genes in mosquitoes might affect this process.

The evolutionary relationship between humans and the two most significant malaria parasites is now at least partly understood. In fact, resistance to malaria is thought to be the strongest selection pressure in recent human evolution, driving some of the most rapid evolutionary changes known. For example, over the last 40,000 years a variant in a gene known as *DARC* has swept through African populations (McManus et al. 2017), apparently because it gives protection against *Plasmodium vivax*. Given that *P. vivax* is rarely lethal in modern humans, the

strength of the selection pressure driving *DARC* into the human population is difficult to explain from today's situation, and it has been suggested that this form of malaria was more deadly in the past and that humans have evolved considerable resistance (Price 2017). The most deadly parasite, *Plasmodium falciparum*, originated in gorillas and is thought to have been transmitted to humans relatively recently in evolutionary terms, probably around 10,000 years ago (Loy et al. 2017). Since then, mutations providing resistance have been strongly selected for in human populations, including the variant in the haemoglobin-gene that gives rise to sickle cell anaemia. It is believed that in exposed populations, additional resistance variants are present that have yet to be identified (Hedrick 2011). In turn, however, the parasites also evolve to evade human resistance, with some strains of *P. vivax* now apparently gaining the capacity to infect humans who carry the protective *DARC* mutation (Mendes et al. 2011).

Like humans, mosquitoes can evolve a high level of immunity to the malaria parasite, but intriguingly this strong immune response is only present in some species: the species Anopheles quadriannulatus, widely considered a non-vector, shows a robust immune response to Plasmodium falciparum, whereas the important vector, Anopheles gambiae, shows little immunity (Habtewold et al. 2008). Similar results were found when these two species were infected with the Plasmodium berghei parasite, and it was also shown that other *Anopheles* vector species showed a weak immune response (Habtewold, Groom, and Christophides 2017). The most probable explanation for the absence of immunity in these cases is that the costs to the insect of deploying an immune response can outweigh or balance out the costs of infection (Hurd et al. 2005).

Humans, mosquitoes and malaria parasites are thus involved in a dynamic three-way process of co-evolution that is unlikely to end with the modification of certain vector mosquitoes through gene drives. If gene drives do succeed in spreading disease refractory genes in mosquitoes, and even if they only partially or temporarily succeed, this alteration would interact with powerful evolutionary forces. It seems appropriate to reflect on the uncertainties and potential consequences this might entail.

How many species could be affected?

Given the ambition of gene drive developers to deliver health outcomes by modifying or suppressing disease-vector mosquitoes, it is worthwhile to consider how many species this could reach. To our knowledge, at least four (and probably five) species, representing three major genera, are being targeted by gene drive development. However, given the number of species implicated as vectors, which we estimate at 160 to 190, there is clearly scope for many more (Table 3). Here we consider the total numbers of known disease vectors, the species targeted, and the scope for gene drives to spread beyond target species by hybridisation for each of the three affected genera (*Anopheles, Aedes* and *Culex*).

Anopheles

Whilst attention is often given to a handful of prominent vector species[17], there are in fact 40-70 species of *Anopheles* that are capable of transmitting the human malaria parasite. Among these are two of the principal targets for gene drive projects: *Anopheles gambiae*, the major vector in sub-Saharan Africa, and *Anopheles stephensi*, a major vector in the Indian sub-continent. Anopheles gambiae has seven closely related species that together form a 'species complex', which, whilst almost identical in appearance, exhibit different behaviours in their choice of host, have different capacities to transmit malaria, and have different, yet overlapping, preference of habitats. *Anopheles gambiae*, for example, prefers to feed on humans and is susceptible to infection with the malaria parasite, whereas *quadriannulatus* shows no preference for humans over livestock, is relatively resistant to infection, and is not considered a vector for human malaria (Pates et al. 2001; Habtewold et al. 2008). However, a synthetic

17 Figures for the total number of *Anopheles* species which can transmit disease vary in the literature. The Malaria Atlas Project states that 'Approximately 40 *Anopheles* species are able to transmit malaria well enough to cause significant human illness and death' (MAP 2019). Neafsey et al give a figure of 60, while Manguin et al state that around 70 species are of 'epidemiological significance'.

Table 3: Mosquito disease vectors. Sources: (Harbach 2013); (Wilkerson et al. 2015); see text for sources on numbers of vector species for *Anopheles*, *Culex* and *Aedes*; (Ughasi et al. 2012) describes 2 *Mansonia* vectors in West Africa, while (Chiang 1993) lists 6 additional vectors in South and South East Asia.

Genus	Number of species	Number of known vectors of human disease	Examples of human pathogens carried	Gene drive targets
Anopheles	475	40-70	Malaria, filariasis	Anopheles gambiae; Anopheles stephensi
Culex	769	≥15	West Nile virus, filariasis	Culex quniquefasciatus
Aedes	931	≥84	Dengue, yellow fever, Zika	Aedes aegypti, Aedes albopictus
Psorophora	49	≥10	West Nile virus	Currently none
Haemagogus	28	≥4	Yellow fever	Currently none
Armigeres	58	≥2	filariasis	Currently none
Mansonia	25	≥8	filariasis	Currently none
Total		**163-193**		

gene drive has the potential to spread into this species and to affect, suppress or potentially eliminate it, because *gambiae* and *quadriannulatus* are capable of hybridising and producing fertile offspring, as are most other species in the complex (Pates, Curtis, and Takken 2014; Fontaine et al. 2015). Genetic studies show evidence of extensive historic gene flow between members of the complex (Fontaine et al. 2015; Coluzzi, Sabatini, Petrarca, and Di Deco 1979), observations that illustrate the inherent difficulty in defining separate species by reproductive isolation. Genetic comparisons of *Anopheles gambiae* with *quadriannulatus* have also revealed that *gambiae* has adapted to feeding on humans, for example by evolving a capacity to detect human odours (McBride 2016; Rinker et al. 2013), another aspect of the triangular evolutionary relationship between mosquitoes, humans and the plasmodium parasite.

Aedes

The *Aedes* are the largest mosquito genus, with over 900 species (Wilkerson et al. 2015)[18], and are the dominant group globally, with a range extending from the tropics to the arctic (Harbach 2013). More than 80 of these are known vectors for human diseases, including viruses such as Dengue and the nematodes which cause filariasis (Wilkerson et al. 2015). Prominent among them is the gene drive target *Aedes aegypti*, a species that acts as a vector for viruses such as Dengue, yellow fever and Zika (Guerbois et al. 2016; Wilkerson et al. 2015). Aegypti originally evolved in Africa but has adapted to feed off humans (Ponlawat and Harrington 2005), allowing it to spread alongside its human host and to become established in tropical and warm temperate regions around the globe (Powell and Tabachnick 2013; Kraemer et al. 2015). According to one source, research on gene drives in another invasive species, *Aedes albopictus*, a vector for many of the same diseases, is also underway (Darrow et al. 2016). Like *Anopheles gambiae*, *Aedes aegypti* can produce fertile hybrids with closely related species (Motara and Rai 1977).

Culex

After *Aedes, Culex* are the second largest genus, with nearly 800 species and a range reaching from the tropics up to cool temperate latitudes (Harbach 2013). At least 15 species have been shown to act as vectors for human pathogens, including West Nile virus, encephalitis viruses, and filarial nematodes

18 The taxonomy of the tribe *Aedini*, which includes the genus *Aedes*, is controversial, and the number of species included in the genus has changed as a result. For example, Reidenbach et al. state 363 species; however Wilkerson et al. revise this to 931 (see Mosquito Taxonomic Inventory for count).

(Harbach 2013)) as well as acting as vectors for other diseases in mammals, birds and reptiles. The well-known species *Culex quinquefasciatus*, which is found in tropical and sub-tropical regions around the world (Samy et al. 2016), has become a focus for gene drive development, owing to its role in human disease and avian malaria. As with *Anopheles gambiae* and *Aedes aegypti*, *Culex quinquefasciatus* (Gomes et al. 2012) can produce fertile hybrids with closely related species.

Technical issues

Without downplaying the possibility that drives could have major and potentially very harmful impacts, it must be noted that a variety of technical hurdles create a significant likelihood that drives won't behave as expected or deliver the promised outcomes.

Resistance: technical and behavioural issues that may thwart planned outcomes

At least three mechanisms could give rise to resistance to gene drives, preventing them from propagating in the target population and suppressing or modifying populations as planned (Sarkar 2018): natural genetic variations at the target site may block the drive; mutations can arise that generate evolved resistance; and selection pressures against the drive may result from non-random mating behaviours, (see Chapter 1). One example of 'behavioural resistance' would be the evolution of sibling mating behaviours, which modelling studies show could emerge in response to gene drives (Bull, Remien, and Krone 2019).

In the case of suppression drives, it is obvious that there is a huge evolutionary pressure for resistance to emerge. However, if modification drives were ever released in the wild, it is rather uncertain how rapidly they would spread. In this case, the payload gene is not intended as a burden to the mosquito, thus avoiding selection pressure. However, if either the gene drive or the payload gene confer a high fitness cost which is counter to the design criteria, resistance to the drive could spread faster and selection pressure could reduce the presence of the payload gene.

Implementation in wild populations will be challenging

There are also numerous difficulties in modifying populations in the wild, as opposed to a cage. For example, success would be dependent on a level of geographic mobility of mosquitoes to spread the drive, and could be undermined if gene drive mosquitoes are less successful at finding mates than their unmodified counterparts. In addition, there are significant practical difficulties, such as mass rearing of mosquitoes for release and in most scenarios ensuring that biting females are not released.

Risks and uncertainties

There are a number of different issues and risks with gene drive technology that need to be brought into the foreground (see also Section 3 on risk assessment); in particular, its unpredictable nature must be emphasised.

A wide spectrum of unplanned outcomes is possible

The likelihood of some form of resistance emerging to a mosquito gene drive makes the actual outcomes of a drive in the wild very difficult to predict. Figure 2 illustrates the range of possible outcomes in a highly simplified case of a single use of a suppression gene drive against one species. Even in this case, a wide range of outcomes are possible, depending on how widespread resistance is in the initial population or how rapidly it appears through evolutionary and behavioural processes. At the two extremes of the range of possibilities are: complete collapse of the drive; or complete eradication of the target species. Perhaps more likely than either is a partial suppression of the target, ranging from a limited drop in the population to near complete eradication, followed by the spread of resistance and the rebounding of the population to near its original level, with notable public health implications (see below). Depending on how the drive behaves at a molecular level and how it is impacted by mosquito behaviour, the new population could

also contain a large number of genetically modified mosquitoes, bringing additional risks (see below). In reality, this scenario is overly simplistic, and factors such as geographic limitations on its spread and the locations and timings of probable multiple releases would all add additional layers of complexity to predicting outcomes.

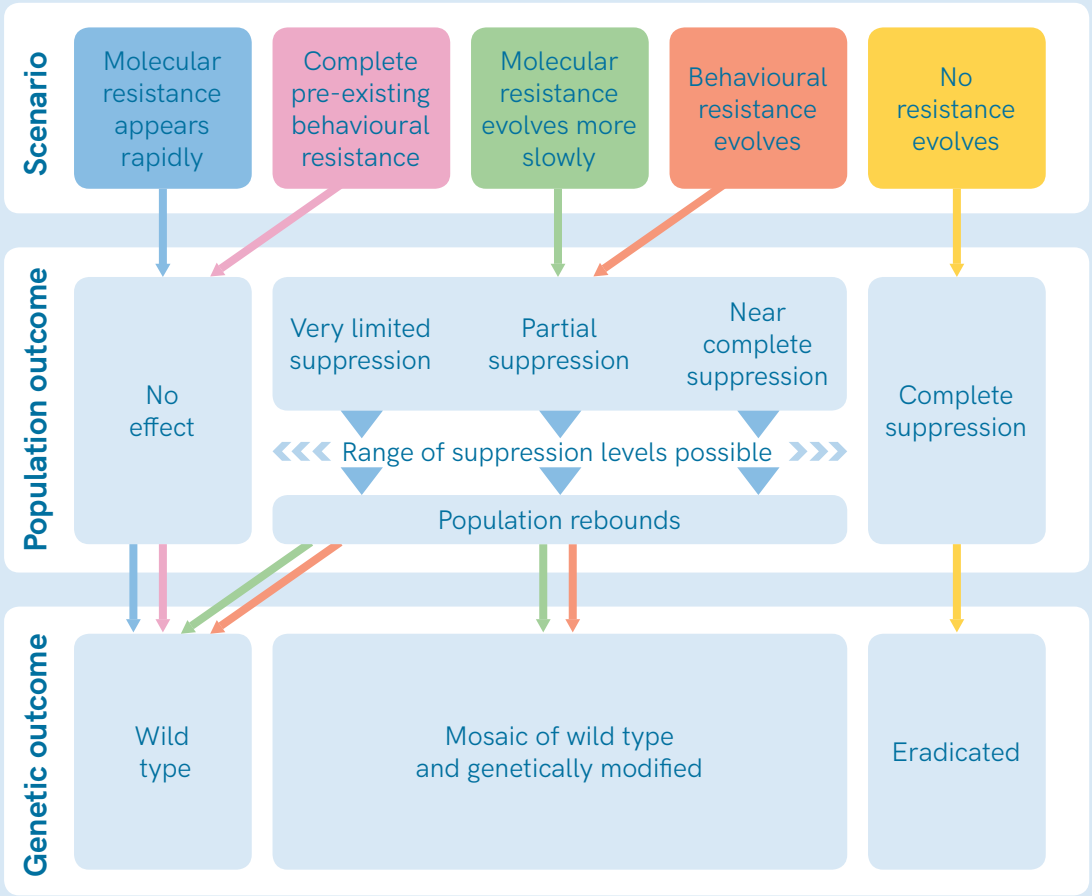
For example, in the case of gene drives containing active CRISPR/Cas9 (either as a homing system or a simple endonuclease for cleaving DNA), the development of resistance will not stop this machinery from cutting alternative target sites. The presence of an active CRISPR/Cas9 system in the population has the potential for frequently setting new and unintended mutations, thus potentially constantly adding to the genetic alteration or modification of the population in a way that most likely cannot be predicted.

Geographic range and species scope are difficult to control

If drives do propagate as intended, there is considerable uncertainty about concerns such as the extent of the geographic areas they will eventually reach and the numbers of species that might be affected. Many gene drive technologies have the potential to become highly invasive, which could lead to impacts that are both global and irreversible (Noble et al. 2018). Even with proposals for theoretically self-limiting drives (many of which have not yet

Figure 3

Spectrum of outcomes for a suppression gene drive
(assuming it remains in one species)



been demonstrated even in a laboratory), the scope of the effects is difficult to predict and could be far wider ranging than intended (Dhole et al. 2018).

Given that most of the mosquito species being targeted are known to hybridise with closely related species, the capacity to confine a drive within one species is also questionable. Significantly, the doublesex gene sequence (targeted by the suppression drive developed by Crisanti and co-workers) is completely conserved across the *Anopheles gambiae* species complex, which means the drive would function just as effectively in these sibling species. Members of this complex are known to hybridise, so if this drive were released in the wild, it could potentially affect the entire species complex alongside *gambiae* – and the ecosystems linked to them.

Risks from generating GM mosquito populations

One significant issue is that drives could generate vast populations of GM mosquitoes, potentially carrying genes encoding the genome editing agent CRISPR/Cas9. This would of course occur with intentional modifications designed to alter or suppress mosquitoes, and these alterations may have unexpected or unintended effects and consequences that will need to be investigated and risk assessed prior to release.

More difficult to risk assess are unintended alterations; as every time a CRISPR/Cas9 gene drive is active in the cell, it could theoretically cut the DNA off-target with a non-homologous end joining (NHEJ) mutation arising (see Chapter 1). With replacement drives, these modifications could well spread. In the case of suppression drives, if resistance arises, then unintended modifications may get fixed in the population. In all cases these GM insects would constitute a risk of their own, one that has not been assessed and in fact probably cannot be assessed beforehand. The question arises, how this could be adequately addressed in a risk assessment, especially when no data are available.

Several mechanisms could confound any health benefits

The consequences on human health of attempting to eradicate or of eradicating a mosquito population or species are likely to also be difficult to predict. Whilst we are not experts on public health, we believe it is important that certain scenarios are considered, in which gene drives do not give the intended results. We therefore wish to draw attention to important questions in this area and to highlight relevant concerns that have been raised by others.

Could other disease vectors occupy empty ecological niches?

The response of the ecosystem to the eradication of a mosquito species is one important unknown quantity in predicting health outcomes. One possibility would be that other related species of mosquitoes or other insects would simply fill the newly empty niche. It is known, for example, that *Aedes albopictus* competes with *Aedes aegypti* in many settings (Braks et al. 2004); so removal of *aegypti* would perhaps simply result in dominance of *albopictus*, which, as stated already, is a vector for many of the same diseases. If other mosquito or insect species expanded to fill emptied ecological niches, then it could be possible they could adapt to feed on humans in a similar way as *Anopheles gambiae* has done. Humans account for a large proportion of vertebrate biomass in many contexts, pointing to a plausible evolutionary pressure or advantage for such specialisation.

Impacts of partial or temporary removal

As already discussed, there is a possibility that drives could suppress vector mosquitoes temporarily or even for some substantial time, with populations later rebounding. What might the consequences for public health be for such a scenario? According to reports, with regular exposure to malaria adults develop a natural acquired immunity to the disease (NAI), in addition to the various levels of genetic immunity that already exist in exposed populations. The authors of one review argue that NAI "should be appreciated as being virtually 100%

effective against severe disease and death among heavily exposed adults" (Doolan, Dobaño, and Baird 2009). This review goes on to state:

"*Interventions that reduce exposure below a level capable of maintaining NAI risk the possibility of catastrophic rebound, as occurred in the highlands of Madagascar in the 1980s, with epidemic malaria killing more than 40,000 people. (Romi et al. 2002).*" (Doolan, Dobaño, and Baird 2009) p14, emphasis added.

In light of this, we would recommend that the risks associated with temporary population suppression of vectors are investigated and assessed by those with relevant expertise.

Evolution or replacement of pathogens

The capacity of pathogens to evolve in order to evade immune responses is well documented, and arboviruses such as Dengue have already evolved mechanisms to suppress mosquito host defences (Sim, Jupatanakul, and Dimopoulos 2014). Thus it could be asked: if efforts to modify populations to generate immunity to pathogens succeed, would pathogens not simply evolve in ways that avoid this immunity? Similarly, if existing vectors were wiped out, then couldn't selection pressure push pathogens to evolve to spread via other vectors, which might be just as difficult to control. Mosquito species can in many cases transmit more than one pathogen, and as the Convention on Biodiversity (CBD) guidance on living modified (LM) mosquitoes (Andow 2012) states, a mosquito in which the 'capacity of transmission of one of these pathogens has been modified, may enhance the transmission of other pathogens.'

Overview of existing and proposed alternatives

Mosquito-borne diseases have been impacting human health for tens of thousands of years, and human ingenuity has developed approaches, both ancient and modern, to counter them. This is a field where we cannot offer expertise, and so we are not seeking to give advice on public health strategies. We are aware however that an overview of current practices, as well as current developments, would be helpful in giving a sense of the wider context in which mosquito gene drives are being developed.

Current malaria control methodology

A concerted global programme of malaria control saw deaths from malaria halve in the period from 2000 to 2015 (Gulland 2015), and even included complete eradication of the disease in countries such as Sri-Lanka (in 2016) and Paraguay (as recently as 2018). This progress was based on widespread implementation of policies recommended by the WHO, principally the use of: long lasting insecticide-treated bed nets (LLINs); indoor residual spraying (IRS) of insecticides in homes at risk for malaria; preventative treatments for children and pregnant women; and access to diagnosis and treatment for malaria infections[19] (WHO 2016). Progress since 2015 has stalled, however, with deaths remaining around 430,000 (WHO 2018). The reasons for this are not fully clear, although the WHO is highlighting reductions in funding for malaria control in many countries with a high disease burden (Kelland 2017; WHO 2018).

Vaccination

Vaccination has made substantial impacts on the incidence of yellow fever, and many view it as a promising approach for tackling other mosquito-borne diseases (Frierson 2010; WHO 2017; Draper et al. 2018). A relatively safe and effective vaccine was developed against yellow fever in the 1930s, and mass vaccination campaigns resulted in the eventual disappearance of the disease in many areas (Frierson 2010). Development of a vaccine against Dengue involves significant technical challenges, and whilst the currently licenced vaccine is only recommended in certain circumstances, the WHO states that "the current Dengue vaccine pipeline is advanced, diverse and overall promising" (WHO 2017). Malaria vaccine research has also encountered considerable difficulties, yet much pro-

19 Treatment contributes to reducing malaria transmission: people who have been treated with anti-malarial medication are less likely to infect mosquitoes and thereby transmit the parasite to others (WHO 2015).

gress is being made; one vaccine has now been approved which is said to offer effective protection for infants and young children (although the immunity is partial and not long-lasting), and over 20 other vaccine candidates are in clinical trials or advanced pre-clinical trials (Draper et al. 2018; WHO 2019).

Emerging mosquito control methodologies

Public health specialists are also drawing attention to a variety of new and existing techniques that could supplement the two current existing foundations of vector control, LLINs and IRS (Barreaux et al. 2017; Killeen et al. 2017). A recent review (Barreaux et al. 2017) highlights five complementary approaches, each with an evidence base, which could begin to be deployed immediately:

- **Attractive toxic sugar baits (ATSBs):** These take advantage of mosquito sugar feeding to administer an oral toxin and are capable of locally reducing malaria vector populations.
- **Swarm sprays:** Many vector mosquitoes form swarms when mating which can be sprayed with insecticide by local volunteers, giving reductions in vector density and mating success.
- **Housing improvements:** Modern housing and modifications to existing homes can provide protection against malaria transmission.
- **Treatment of livestock:** Many mosquitoes also target livestock, so treatment of livestock or the structures housing them with insecticides can reduce mosquito numbers.
- **Spatial repellents:** These are airborne chemicals that cause changes in insect behaviour and which show potential for reducing transmission.

Other perspectives on malaria control

A detailed review of the malaria control literature is beyond the scope of this report, but it should be highlighted that there are many potentially valuable perspectives that could be further explored. Laporta and colleagues, for example, are considering the protective role that healthier ecosystems might play. On the basis of modelling studies, they have suggested that in tropical forest areas where biodiversity of both mosquitoes and wild warm-blooded animals is high, humans are to some extent protected from malaria (Laporta et al. 2013). There is also the consideration that traditional medicines and healers are widely used in many communities affected by malaria (Suswardany et al. 2015), and that some researchers have proposed that giving them a greater role in public health programmes could improve outcomes (Graz, Kitua, and Malebo 2011).

Conclusions

Gene drives are an inherently risky mosquito control technology. The considerable enthusiasm of some actors is drawing attention away from both the risks of the technology failing to deliver the promised benefits, but also, more crucially, from its unpredictability. This obscures the potentially serious and irreparable harms that may be caused by the release of gene drive mosquitoes on ecosystems and biodiversity, and tends to ignore the possibility of negative human health impacts.

If drives fail to suppress or modify mosquito populations as planned, then clearly the health benefits will not be realised. Equally, even if drives do achieve these goals in the short term, shifts in the composition of the mosquito community, adaption of feeding preferences and evolution of pathogens could all potentially rapidly counteract any benefits and perhaps pose new risks.

Mosquitoes and their larvae are likely to be an important component of ecosystems in many circumstances. If major mosquito species are removed, the ecosystem will shift in complex patterns that are not fully predicable, but because other species rely on them in various ways, are likely to be harmful to biodiversity. Deployment of these drives could easily lead to knock-on effects that impact predators such as birds, bats or dragonflies, which may already be under stress because of other damage to ecosystems, resulting in further declines in their numbers. Similarly, impacts on the microbial community and nutrient recycling could, for exam-

ple, harm the photosynthetic phytoplankton at the base of food chain, leading to further chains of consequences. So whilst swatting an individual mosquito is no threat to biodiversity, taking a similar step at an ecosystem level would be dangerous leap into the unknown.

The question also arises of just how many mosquito species may eventually become gene drive targets? Will gene drives be deployed against a handful of major vectors, or all disease vectors, or even all mosquitoes? The consequences would be different in each of these scenarios, yet we must reflect on all of them because no one, including the developers, knows where this technology may ultimately lead us. As stated earlier, at least 160 mosquito species are known to transmit human pathogens, and given that many species have not been well investigated, there could be more, all in addition to species that may be poor vectors, or could potentially adapt to act as vectors. Given that even when they are not disease vectors, mosquitoes are considered a nuisance, it is not hard to imagine a situation where gene drives are used against a large proportion of the mosquito family, normalising an unprecedented level of intervention in the natural world and opening up the prospect of 'designer ecosystems' starting to replace natural ones.

There are a wide range of approaches for controlling mosquito-borne diseases, with some proven methods not receiving enough investment. In this context, and in line with the Precautionary Principle, it would be wisest to avoid any approach that risks failing to deliver health benefits and could also cause significant collateral damage to ecosystems.

2.4.2 Case study 2: Mice

Introduction

In one of Aesop's fables, a sleeping lion is woken by a mouse and is so angered by the disturbance that he threatens to kill the mouse. The mouse replies that he would not be worthy prey, and so the lion agrees to spare his life. To the lion's amusement, the mouse responds that he will one day return the favour, and they go their separate ways. Sometime later, the mouse finds the lion caught in a hunter's net and on recognising him, chews through the threads to free him and save him from the hunters' spears.

This story, which dates back to ancient Greece, illustrates not just the benefits of mercy and how beings can be interconnected in unexpected ways, but also the long-standing place mice have in the human imagination. This is hardly surprising, given that the house mouse (*Mus musculus*) has lived in close association with humans at least since the development of agriculture about 12,000 years ago (Auffray, Tchernov, and Nevo 1988), accessing human food supplies in houses, out-buildings, stores and cropland. Whilst the species originated in the Indian sub-continent, their commensal relationship with humans probably emerged in the Middle East (Weissbrod et al. 2017), and this association, combined with remarkable adaptability, has allowed them to spread widely: first travelling with bronze-age traders around the Mediterranean and into Europe (Cucchi, Vigne, and Auffray 2005), and more recently to the Americas and other landmasses along shipping routes (Boursot et al. 1993). Indeed, together with rats, they are now probably the most widely distributed vertebrate in the world, after humans (GISD 2019), inhabiting environments from the tropics to the Arctic and sub-Antarctic (Musser 2016).

Methods to control commensal rodent populations have been actively pursued at least since the domestication of the cat, and considerable investment is now being made to add eradication via gene drive to the existing range of tools. At least three research teams are pursuing gene drives intended to be capable of suppressing or eradicating wild mouse populations, either by biasing sex ratios or spreading infertility. As the most intensively studied mammalian laboratory organism, the development of effective gene drives in *Mus musculus* is also being pursued as an intentional step towards engineering drives in other mammals. Here we give a brief overview of the biology of the house mouse, and review the motivations behind mouse drives along with the current state of research, so as to

better comprehend the spectrum of potential hazards and multitude of risks in the application of this technology.

Overview of ecological role and relevant biology

House mice are very widespread globally and stow away easily

Whilst the house mouse has thrived in this close relationship with humans, the species has existed much longer than modern *Homo sapiens*[20] and populations continue to flourish in wild and semi-wild environments. The house mouse is generally very successful in anthropogenic habitats, yet can also occupy grasslands and shrublands at a wide range of latitudes, as well as some coastal and wetland habitats (Musser 2016). In many contexts, including the Americas, Southern Africa, most of South East Asia, Australia, New Zealand, and many smaller islands, they are considered an invasive species (Musser 2016). The wide range of new territories colonised by *Mus musculus* reflects its remarkable capacity as a stowaway. A small study in the United States found mice in transported hay, straw, grain, dog food, and even a vehicle cab, leading the author to estimate that thousands of mice are unintentionally transported globally each year (Baker 1994).

Diet and influence on invertebrates

House mice are omnivores, and this dietary flexibility is important in allowing them to occupy such a range of habitats. Their diet comprises a variety of plant material, which can include grains, seeds, fruits, leaves, stems and roots, in addition to insects and other invertebrates (Tann, Singleton, and Coman 1991; Shiels et al. 2012b; Wilson et al. 2006). The range of invertebrates found in mouse stomachs is considerable, and includes true flies (*Diptera*), true bugs (*Hemiptera*), beetles (*Coleoptera*), caterpillars (*Lepidoptera*), spiders (*Araneae*) and earthworms (*Annelida*), suggesting that mouse predation may be a significant influence on some invertebrate populations.

The relative fraction of invertebrates and plant matter varies considerably depending on their habitat. In some contexts, for example croplands in Australia, cereal seeds have been shown to make up the majority of their diet (Tann, Singleton, and Coman 1991). In other environments, including the sub-Antarctic Marion Island (Gleeson and Van Rensburg 1982), the Hawaiian Islands (Shiels et al. 2012a), and in alpine and coastal New Zealand habitats (Wilson et al. 2006; Miller and Webb 2001), they have been shown to be predominantly insectivores.

An important food source for many species

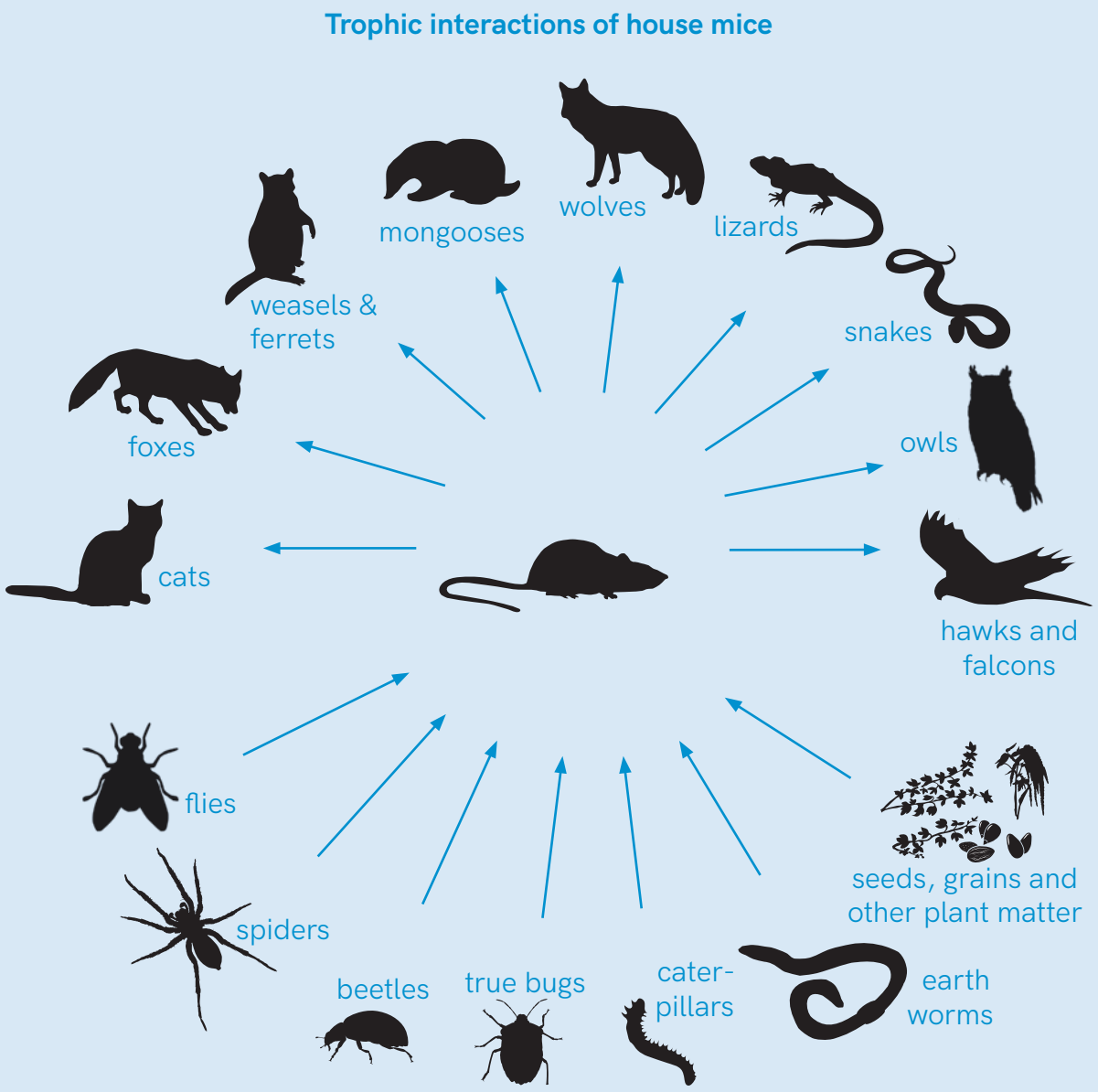
A great variety of carnivores and omnivores eat house mice in all of their many habitats; they include domestic cats (*Felis silvestris*), foxes (*Vulpes*), weasels (*Mustela*), ferrets (*Mustela*), mongooses (*Herpestidae*), wolves (*Canis lupus*), large lizards (*Squamata*), snakes (*Serpentes*), hawks (*Accipitridae*), falcons (*Falconidae*) and owls (*Strigiformes*) among others (Ballenger 1999; Alberto et al. 1991) (see Figure 4). The predators of *Mus musculus* will of course be different in different environments, and knowledge of how important the species is in sustaining different predators is limited to certain narrow contexts that have been studied in detail. For some, like wolves, house mice are one food source among many (Alberto et al. 1991). For others, for example barn owls, long eared owls and kestrels, which were studied in urban environments, they form a large proportion of their diet (Charter et al. 2007; Laiu and Murariu 1998; Kečkéšová and Noga 2008). So whilst house mice can be considered pests in cities, they are also important in sustaining birds of prey in these habitats. In the light of the number of species that prey on them, what might be the effects of suddenly removing mice?

Closely related species, scope for hybridisation and spread of gene drives

House mice belong to the genus mus, which contains about 40 species, and are closely related to genera such as field mice (*Apodemus*) and rats

20 The subspecies of *Mus musculus* are estimated to have diverged from a common ancestor around 500,000 years ago (Geraldes et al. 2008)

Figure 4



(*Rattus*) (Chevret, Veyrunes, and Britton-Davidian 2005). Mus musculus itself has diverged into at least three sub-species, all of which show commensal behaviour: *M. m. domesticus*, which is present in Western Europe, the Americas, Africa and Australia; *M. m. musculus*, in Eastern Europe and much of Asia; and *M. m. castaneus*, in India and South East Asia. (Geraldes et al. 2008). Whilst these are sometimes considered separate species, their reproductive isolation is by no means absolute. Hybridisation between *M.m. musculus* and *M.m. domesticus* is known to occur in the wild (Payseur, Krenz, and Nachman 2004), generally producing fertile offspring. *M.m. domesticus* can also produce fertile female hybrids with closely related species such as *Mus spretus* (Orth et al. 2002) and *Mus spicilegus* (Zechner et al. 1996). Indeed, some gene flow has been shown to have occurred between *M.m. domesticus* and *spretus* (Liu et al. 2015). The capacity for interbreeding between subspecies and closely related species, and the overlap in their distributions (Phifer-Rixey and Nachman 2015), therefore makes

it uncertain whether any gene drive could be confined to a particular target species or subspecies. It is not clear exactly which subspecies are being targeted for gene drive development: it is probable that initial experiments would use standard inbred laboratory mice, which are hybrids largely derived from *M.m. domesticus* (Yang et al. 2011).

Knowledge of ecological roles is limited

Inevitably, given the limitations of what has been or can be systematically studied, knowledge of the ecological roles of *Mus musculus* is limited. So it is possible, and even probable, that the species is interacting with and sustaining other species besides those listed, and contributing in other manners to ecosystems, in ways that have not yet been observed. For example, it has been proposed that mice could play a role in formation of new soils, by transporting oribatid mites - an important component of soil - to locations where new soils are forming; and these mites have indeed been found on other mice in field studies (Teunkens 2016). It is also possible that house mice play a role in seed dispersal. Rodents of the muroid family (which includes house mice) have been shown to pass intact seeds through their digestive systems (Corlett 2017), and at least in some cases these seeds are viable (Duron et al. 2016). Thus the impacts of any sudden reduction in house mouse populations may not be limited to the obvious effects on their predators and prey.

Might closely related species also be vulnerable to gene drives targeting *Mus musculus*? This possibility is discussed in more detail below, but if this risk was present then the ecological roles of related species would also need to be considered. For example, a related species, the western Mediterranean mouse (*Mus spretus*), buries acorns in scattered hoards, and has been shown to be important in dispersing acorns of the holm oak (*Quercus ilex*) (Muñoz and Bonal 2007) the dominant tree species in many western Mediterranean forests (Sheffer 2012).

Drivers for mouse gene drive research

Whilst house mice cause a number of undesirable effects for humans, including minor damage to building fabric and in rare cases the spread of pathogens, it is the consumption of crops, stored food and animal feed that is likely one of the foremost drivers of gene drive research to suppress this species. Unstated assumptions underlying the logic of suppressing mice and other pests should be carefully examined: namely, that humans societies are entitled to maximise harvests by eliminating any species that seek to use even a small fraction of those same resources. To consider the point of view of those wishing to maximise economic returns, the reported monetary costs that *Mus musculus* brings are certainly significant, creating powerful incentives to employ new 'pest control' measures. An explosion in numbers in Australia in 1993/4 is estimated to have caused damage to crops totalling U.S. $60 million (Brown and Singleton 2000). In farms and other anthropogenic environments, they often co-exist with black and brown rats (Rattus rattus and Rattus norvegicus), with the annual costs incurred by rodents to farmers estimated at around U.S.$30 billion in the United States (Pimental 2007) and U.S.$2 billion in South East Asia (Nghiem le et al. 2013). It is clear in at least some cases that suppressing pest populations is the primary motivation of this research. The UK's Roslin Institute states that they are exploring how disruption of fertility in mice and rats via gene drive could 'curb pest rodent populations' (Roslin Institute 2017).

On many islands *Mus musculus* can become a problematic invasive species; in one unusual but high profile case, Gough Island in the South Atlantic, by predating chicks of ground-nesting birds (Cuthbert et al. 2016). The eradication of mice on certain islands has therefore become a conservation goal. Elimination of rodents, especially rats, has been achieved on many islands through the use of toxicants (Campbell 2015), but this approach cannot presently be applied in all circumstances. Advocates of mouse gene drive research therefore argue that a drive capable of eradicating mouse populations should be developed as a conservation tool (Leitschuh et al. 2018), and a consortium

calling itself Genetic Biocontrol of Invasive Rodents (GBIRd)[21] is now seeking to deliver gene drives which they state are for conservation purposes. However, it is questionable if any future mouse gene drive would remain exclusively as a conservation tool. Communications between researchers obtained through open record requests show that the research community is well aware of the potential to use this technology in agriculture and elsewhere. A memorandum of understanding between the partners in the GBIRd consortium (Gene Drive Files 2017a) from April 2017 states:

"The Participants seek to assess the potential of this technology for advances in agriculture, food security, and human health."

Emails between GBIRd Steering Committee members sent later, in July 2017[22], reveal a discussion about whether communications should be "noting the potential future benefits in other areas" or "focus solely…on eradication of invasive rodents from islands…" (Gene Drive Files 2017b)

Current state of gene drive research

Mice have been chosen as the first candidate for gene drive development in mammals for several reasons; they are the foremost mammalian laboratory organism, and researchers possess well-developed molecular genetic tools, a complete genome sequence, and a high level of understanding of their physiology and development. Significant funding is being committed to achieve this goal, from institutions that include the US National Institutes of Health (NIH), the US Defence Advanced Research Projects Agency (DARPA) and the UK Biotechnology and Biological Science Research Council (BBSRC), and in January 2019 results were published from a team at the University of California San Diego describing a mouse gene drive (Grunwald et al. 2019). In this case, the technology is a homing CRISPR/Cas9 drive using a visual trait (white coats) to test the feasibility and performance of such an approach. However, so far the method has only limited efficiency: the drive increases the probability of an individual inheriting the desired allele from 50% to 73% on average, and only functions in the female germline. Whilst higher efficiency would be needed for a gene drive to function in the wild, the authors suggest that the technology could be useful for constructing new strains of laboratory mice for medical research.

At least three other groups are working on mouse gene drives, with the aim of suppressing or eradicating populations of mice in the wild. One proposal is to construct drives that cause mice to produce all male offspring. This could in theory be achieved by constructing drives to propagate a gene named *Sry*, that leads to the development of male characteristics. A team at the University of Adelaide is seeking to achieve this with a homing CRISPR/Cas9 drive (Gene Drive Files 2017b), whereas a group at Texas A&M University are coupling *Sry* to a naturally occurring selfish genetic element named the T-haplotype, which behaves much like a synthetic gene-drive (Leitschuh et al. 2018). A drive based on the X-shredder method could also bias sex ratios towards males, and this is one of the proposals being explored by a group at the Roslin Institute, UK (McFarlane, Whitelaw, and Lillico 2018). Alongside this, that group have proposed a second approach, which would use a homing CRISPR/Cas9 drive to disrupt female fertility genes (McFarlane, Whitelaw, and Lillico 2018). Given that the Grunwald study indicates there are additional technical barriers to constructing efficient gene drives in mammals as compared to insects, there is uncertainty if any of these methods can reach high enough levels of efficiency to eradicate wild populations. Equally, with the current levels of investment in this technology, a mouse gene drive for population suppression could soon be a technical possibility.

21 This consortium includes the U.S. Department of Agriculture, The University of Adelaide, Texas A&M University, The University of North Carolina, the Australian Commonwealth Scientific and Industrial Research Organisation (CSIRO), New Zealand's Landcare Research and the NGO Island Conservation.

22 Also obtained through open record requests.

Risks and uncertainties of using a gene drive against mice

Risks from use exclusively on islands

Mouse gene drive developers are promoting a scenario where the drive would be used to eradicate mouse populations from certain islands, and would thus be contained by water and could not spread to other land masses. Such a scenario in itself already holds direct and indirect problems and risks. Should mice suddenly, within a few generations, be eliminated from islands, what would be the knock-on effects? While removal of (recently) invasive species often benefits a native ecosystem, unpredicted and negative effects can occur where interactions between different invasive species are present (Zavaleta, Hobbs, and Mooney 2001). For example, because rats and mice are competitors, one scenario would be a competitor release effect, where elimination of the mice would result in an increase in the population of rats. Such effects have been observed in the opposite scenario, where rats have been eliminated, thus causing an increase in mouse numbers (Caut et al. 2007). Further complexity arises from interactions with predators[23], as described by Leitschuh et al.: "The presence of an invasive species, especially species that are food sources for predators, can attract other species in search of food, as seen on the Channel Islands and the Farallon Islands [Collins, Latta, and Roemer 2009, SouthEastFarallonIslandsEIS 2013] .If the invasive food source is removed too quickly, the predator may turn to consuming endemic species rather than leave the island [Courchamp, Woodroffe, and Roemer 2003, Collins, Latta, and Roemer 2009]." (Leitschuh et al. 2018, S125)

The potential to spread to continental landmasses

The most dangerous possible outcome of releasing gene drive mice on islands, or indeed anywhere else, is that they may escape, stow away, and migrate to other landmasses, resulting in uncontrolled spread of the drive and widespread elimination or suppression of the species. This is a very significant risk, and the difficulty in containing gene drive mice is well recognised. In a preliminary risk analysis on the use of gene drives in Australia, Australian government scientists concluded that "… biocontainment of house mice and black rats will be challenging to manage because of their propensity to stowaway and survive among cargo and vessels." (Moro et al. 2018). There are other scenarios that could result in spread of gene drive mice on continental landmasses. Many actors have an economic interest in controlling mouse populations, and it is not hard to imagine an unauthorised release of gene drive mice, or of a state using them unilaterally. Accidental release from a laboratory is also a possibility.

Risks from a gene drive in continental mouse populations

What might the consequences be of the arrival of a gene drive in mainland populations? One scenario would be a crash in mouse numbers, which would likely have serious negative impacts on the predators that rely on them, and could well be disastrous. Often these predators are already under pressure from other factors, for example barn owl populations in the UK have declined due to road mortality, a loss of nesting and roosting spots, and intensive farming practices that have reduced food availability (Meek et al. 2003; Toms, Crick, and Shawyer 2001). Given the wide geographic range of the house mouse and the number of predator species it helps sustain, effects from suppression or eradication could be very widespread and harmful to a large number of species. Other ecological effects, for example complex changes in the invertebrate communities the house mouse feeds on, are also possible, and similarly could be very wide ranging.

Because dynamics within ecosystems are complex and multi-layered, many possible scenarios must also be considered. If a predator suddenly finds a proportion of its usual prey is absent, which other species might it turn to? What would be the

23 There is an interesting case reported from Italy of how one prey species can protect another species. In this example, introduced crayfish were found to protect native amphibians from consumption by the invasive American bullfrog (Bissattini, Buono, and Vignoli 2018)

consequences of reductions in populations of these alternative prey species? And what species might increase in numbers to fill the gap left by mice?

Risks from hybridisation

The scope for hybridisation of *Mus musculus*, both with other subspecies and with the closely related species *Mus spretus* and *Mus spicilegus*, widens the potential range of impacts further. What might the consequences be of a gene drive spreading to such other species? Hybridisation between subspecies makes the possible geographic impact of a gene drive global, while suppression of related species that live in natural habitats would bring further ecosystem consequences. The dispersal of acorns by *Mus spretus* is a good example of the sort of relationship that might not be obvious, but which if disrupted could bring significant and harmful results.

A drive could have complex effects on mouse populations and genetics

The effects of any eventual engineered gene drive on both mouse populations and genetics would be highly uncertain and unpredictable. Over time, resistance to the drive could emerge through various mechanisms (see Chapter 1), which could create scenarios where the population first drops and then rebounds. What might the ecosystem consequences of such an outcome be? What about a situation where the gene drive becomes ineffective, yet the mice are all genetically modified, and - depending on which gene drive system was used - might actually have more and different alterations than at the point of release (as CRISPR/Cas9 for example, when acting as an endonuclease, has a capacity to cut off-target.)

There are many scenarios that need to be considered and that people - that means all of us - haven't yet envisaged, as well as many possible consequences that no one has yet been able to perceive.

What are the alternatives?

The control of rodents is a significant area of study and it is not our intention to recommend particular approaches, nor do we have the expertise to do so. We do wish to highlight though that there are many existing technologies for controlling rodent populations, and some proposed new methods, which do not carry the risks that come with gene drives.

Island ecosystems

At the time of writing, more than 560 islands have been successfully cleared of invasive rodents, almost all through the use of toxicants, with success rates for eradication campaigns relatively high[24] (DIISE 2018). The ambition of rodent removal projects is also increasing as expertise develops. In 2005 New Zealand's Campbell Island, at 117 km^2, became the largest island to be successfully cleared of rodents (Howald et al. 2007). Yet by 2018, South Georgia, with an area of more than 3500 km^2, was also declared free of mice and rats, after a 10-year elimination project (Harvey 2018). Whilst there are legitimate animal welfare questions to be asked about toxicants, relative to gene drives they do at least avoid the risk of uncontrolled elimination of target species beyond the intended area.

Rodent control in other settings

Rodent control in agricultural environments, in food storage and transport and in domestic settings, is a well-developed science, drawing on long established traditional techniques as well as more modern ones. Methods include physical barriers, various forms of trapping and stalking, using cats or other predators, and removal of cover, alongside the more recent development of toxicant usage. Practices in rodent management continue to evolve. Since the 1990s, Ecologically Based Rodent Management (EBRM) has emerged as an approach to design more effective control strategies, by drawing on knowledge of animal biology and behaviour (Singleton et al. 1999); it has been shown to be ef-

24 For comparison, failures have been reported on 100 islands

fective in various farming communities (Singleton, Brown, and Jacob 2004; Taylor et al. 2012). Alongside the push towards gene drives, other more predictable new technologies are also in development (Campbell 2015), for example self-resetting traps have shown promise in controlling rats and mice at landscape scale in New Zealand (Carter et al. 2016; Carter and Peters 2016).

Beyond gene drive mice – what's next?

Current efforts to construct a mouse gene drive are motivated in large part by the desire to apply gene drives to other mammals. The comments in an opinion piece accompanying Grunwald and co-workers' mouse gene drive study in the journal Nature illustrate this: "Grunwald and colleagues' work is an important proof-of-concept that will surely be followed by modifications that might lead to improvements in future mammalian gene drives. If gene drives become efficient in mammals, one possible way in which they might be used is to tackle pests or disease-causing agents." (Conklin 2019).

Funds are already being directed for preliminary research towards gene drives to eradicate populations of other mammals. For example, the Australian Wildlife Conservancy and the Australian government agency CSIRO are funding a project to sequence the genome of feral cats (AWC 2018) - an invasive species in Australia. Gene drives have also been proposed for the eradication of invasive populations of rats, stoats and brushtail possums in New Zealand (Dearden et al. 2018), for the elimination of rats, mice, red foxes, and rabbits in Australia (Moro et al. 2018), and for control of indigenous rats in the UK (McFarlane, Whitelaw, and Lillico 2018). If mammalian gene drives can be made more efficient, a rapid proliferation of target species is very probable, similar to that which is already starting with insects (see Table 2a). It is also being suggested by some that mammalian gene drives might be used in the wild as a test case before insect ones; the opinion piece cited above goes on to propose that they could be a better test case because the movements of mammals might be "more easily restricted" – a statement which is of course debatable for mice and rats, which are the most likely targets. Nevertheless, the enthusiasm with which some funding agencies and researchers view mammalian gene drive technology is apparent. If the use of gene drives to eradicate mice proves technically possible and gains regulatory approval, the house mouse is likely to be just the first of many species targeted.

Concluding remarks

A highly unpredictable technology

Much like proposed gene drives in mosquitoes, the behaviour of any drives deployed against mice or other mammals, and the ecological consequences they would bring, is very difficult to predict with any confidence. As discussed for mosquitoes in this chapter, various molecular mechanisms or behavioural tendencies could give rise to resistance, causing the drive to either fail completely or only partially supress populations. However, there is the risk that drives could be highly invasive and spread rapidly, and given that species of *Mus musculus* are present over much of the globe, can hybridise with each other, and frequently stow away, the geographic reach of any drive could prove to be impossible to control. The removal, or even temporary suppression of mice, could also have powerful ecological effects, which are difficult to predict with any accuracy, but could be harmful to biodiversity, agriculture or human health. A spectrum of predators could decline or even disappear in some circumstances; invertebrate communities could increase or shift in composition due to reductions in predation; and other species could eventually expand to occupy the empty ecological niche, bringing further consequences.

Functional gene drives would tighten human control over the biosphere

Whilst the consequences of experimental releases of gene drive organisms are highly unpredictable, it is necessary to consider the scenario humanity would reach if researchers succeed in their intention of building operational gene drives in mammals. Through agriculture, humans have gained control over the types of plants produced in the biosphere and the species that feed on them, to the extent that

humans and their livestock now account for more than 95% of all land mammals by biomass (Bar-On, Phillips, and Milo 2018). Animals like *Mus musculus*, whilst from one perspective considered pests, divert biomass out of human control into the sphere of the remaining wild animals. To put it another way, the limitations of current 'pest control' methods are valuable in maintaining biodiversity. For example, a study of barn owls living on agricultural land in California found that 99.5% of their prey were 'pest' species (Kross, Bourbour, and Martinico 2016). If gene drives do fulfil their developer's ambitions, they would instead offer a new level of pest control, potentially going as far as wide-scale eradication. Would it be possible to control the use of these tools against mice and other vertebrate 'pests' in the face of strong economic pressures to employ them? If some individuals or organisations did use them, could they be contained—and if not, what might be the consequences? It is possible that drives could crash not just mouse populations, but also greatly reduce the numbers of snakes, lizards, owls, hawks, falcons, foxes, stoats, weasels, and many others that feed on them. Thus gene drives could have the capacity to further shrink the already much diminished realm of the wild animals. We find the prospect of this further tightening of human control over the biosphere extremely disturbing.

2.4.3 Case study 3: Plants in agriculture – Palmer amaranth

Introduction – Brief description of the biology of Palmer amaranth (*amaranthus palmeri*), and the broader agricultural context

Palmer amaranth (PA) is a member of an important group of annual plants found in North America and other parts of the world. There are several aspects of the biology of the species in the PA group that makes them of high interest as crops and as food sources for animals. However, in instances which include certain industrial agriculture systems, this same biology is responsible for their classification as agricultural 'weeds', candidates for biological controls.

The current interest in using gene drives to control PA weeds could lead to several harmful results. Gene drives created in an attempt to eradicate the weed could spread into non-agricultural populations, potentially damaging their role in native ecosystems. This means that the potential of this species as a human food source, or potentially as a source of conventionally bred genes for related crop species, could thereby be threatened. The highly desirable traits possessed by Palmer amaranth described below, especially its nutritional value and ability to adapt to high temperatures and drought, both of which are exacerbated by climate change, illustrate some of the risks of eliminating this species, either intentionally or accidentally.

On the other hand, there are systems-based solutions for controlling pests such as PA that can be achieved by following the principles of agroecology, the widely recognised and sophisticated science that applies ecology to the design and management of agricultural systems (Altieri 1995, Gliessman 2014; UN Food and Agriculture Organization 2011; Abate et al. 2008). It emphasises the optimisation of biodiversity of crops and supportive organisms, as part of strategies to build long-term, healthy agroecosystems and secure livelihoods. Generations of indigenous and peasant farmers' knowledge and skills pioneered this practice, and they continue to contribute to the growth and use of agroecology. Because local farming communities must be healthy and adaptive to local ecosystems for agroecology to be effective, it is a form of agriculture that recognises the importance of climate justice, food justice and food sovereignty to its functioning (Altieri 1999; Francis et al. 2003).

The agroecological approach avoids the risks and uncertainties of gene drives and also provides multiple co-benefits for the environment, including much cleaner water, increased biodiversity and substantially reduced greenhouse gas emissions (Dooley et al. 2018; Han et al. 2017; Isbell et al. 2017; Kremen and Merenlender 2018; Kremen and Miles 2012; Liebman and Schulte 2015; Ramankutty et al. 2018).

Indeed, one of the more general and usually unmentioned risks presented by gene drives is that if they succeed, they may further lock agriculture into a chemically dependent industrialised system that is causing multiple, global scale environmental challenges. The harm that results from industrial agriculture includes hundreds of coastal hypoxic zones ("dead zones") and toxic algal blooms, heavy reliance on pesticides, major contributions to the largest loss of biodiversity in millions of years, and a quarter to a third of greenhouse gas emissions (Breitburg et al. 2018; Dudley et al. 2017; Garnet 2011; Kremen and Miles 2012; Maxwell et al. 2016; Ramankutty et al. 2018; Scavia et al. 2014; Smith et al. 2014).

Gene drives aimed at reversing resistance to herbicides, glyphosate in particular, could simply further lock in an herbicide-dominated approach to weed control that has been shown to cause direct and indirect harm to the environment and to people.

Characteristics of Palmer Amaranth and its Value

In addition to the use of some species of amaranths as domesticated crops, wild species, including Palmer amaranth, have been used by indigenous peoples and native farmers globally as important food sources. Several native American tribes in the Southwest US used PA seeds and foliage as food (Moerman 1998). Species in Sub-Saharan Africa are similarly used. Not only are the seeds highly nutritious, but the foliage contains 25 percent protein (in the leaves of *A. cruentus*), as well as vitamins and minerals such as calcium (National Academies of Sciences 2006). These can be particularly important for subsistence farmers as supplements to their cultivated crops, providing important nutrients.

The family *Amaranthaceae* contains 79 genera globally, while the closely related *Chenopodiaceae* contains 104 genera (Hernandez-Ledesma et al. 2015). These two families are often considered to make up a single taxonomic clade (having a mutual ancestor). The genus *Amaranthus* contains about 75 species (Ward et al. 2012), including the important grain amaranth (*A. hypochondiacus*), a highly nutritious crop containing high quality protein. The Chenopodiaceae contains quinoa (*Chenopodium quinoa*), which was domesticated in South America about 3,000+ years ago and is highly nutritious, also containing high levels of high-quality protein. The amaranth family also contains several important weed species, including Palmer amaranth (also known as Palmer pigweed), and several other species (often known as pigweeds).

Palmer amaranth is dioecious, meaning that it typically produces male and female flowers on separate plants, while several other species of amaranths are monecious, as are many other plant species, producing both male and female flowers on the same plant.

The dioecious characteristic results in high genetic adaptability through obligate outcrossing (Ward et al. 2012). This characteristic also makes it a good potential target for the use of gene drives, since it facilitates the spread of the drive. Many plants that are monecious can be self-fertile, and this trait reduces the dispersal of the drive during reproduction.

Palmer amaranth is native to the arid areas of the Southwestern U.S. and northern Mexico, typically living in or adjacent to the washes (seasonal streams and rivers) (Saurer 1957). As a species adapted to desert conditions, it is capable of growing at high temperatures and tolerating drought.

It does not do this primarily by resisting desiccation, as do species like cacti (in the western hemisphere) or euphorbs (in the eastern hemisphere). Those species use several characteristics to retain water, such as thick cuticle covered by or permeated by wax, and broad stems that hold substantial amounts of water. Palmer amaranth also does not rely on a deep root system to tap deeply buried groundwater. Instead, it takes rapid advantage of limited seasonal precipitation by growing extremely quickly and developing huge numbers of seeds before soil moisture is lost. It also maintains high solute levels that help to retain water in its tissues to temporarily resist wilting when water is not plentiful in the environment (Ward et al. 2012).

This allows it to grow quickly by using substantial amounts while water is available, and to continue growing for some time beyond, when many plants, including crops that do not develop high solute levels, would fatally wilt. Since it produces seed before water is completely gone, it avoids the worst conditions of drought. In fact, PA can respond quickly to loss of water by accelerating seed production. This can be a highly desirable ability to adapt to climate change.

Another important characteristic of amaranths is that they use C4 photosynthesis (Wang et al. 1992). This mechanism greatly improves photosynthetic efficiency by largely avoiding a process called 'photorespiration', that occurs in C3, the other main type of photosynthesis. C4 plants typically grow faster than C3 plants, at least under historic atmospheric carbon dioxide levels and higher temperatures. They also tend to be more drought- and heat-tolerant. C4 metabolism evolved separately in monocots such as grasses, and dicots, such as PA.

Much more common among monocots, C4 metabolism is unusual among dicots. Important examples of C4 monocot crops are corn, sorghum, and millets (but this metabolism is not found in several other grains, such as rice, wheat, barley, oats or rye). Corn is known for its extremely high productivity, and sorghums and millets for their drought and heat tolerance.

The C4 property, as well as the others described above, makes PA and other amaranths of particular interest. There is work and consideration focused on potentially further developing several amaranths as food crops, due to such properties and high nutritional value (National Academies of Sciences 2006). At the same time, these physiological and genetic properties of PA and other amaranths have also made them invasive weeds under certain conditions (see below).

Outcrossing between Palmer Amaranth and Related Species

Hybridisation between PA and other related species could provide a route for a gene drive to enter the population of these other species, with unknown, potentially harmful consequences for the species and their ecosystems. For this to occur, some of the hybrids must be fertile and have the ability to backcross with that species in order to cause the introgression of the gene drive into the population.

Plants have higher potential to outcross and produce viable hybrids and fertile offspring more commonly than do most animal species. It was believed as recently as several decades ago that crops would rarely outcross to wild relatives, but this has now been shown to commonly occur (Ellstrand 2003). Plants have been sometimes found to produce fertile hybrids, not only with other species in the same genus, but occasionally even with species from other genera in the same family.

The ability to hybridise with other species is important both for evolution and crop breeding, in providing important sources of genetic diversity and adaptability (Baack and Rieseberg 2007). It is also as a concern for the potential unwanted spread of gene drives from one species to another, or to a crop, and could entail serious potential health and ecological consequences.

Palmer amaranth has been shown to most readily hybridise and produce fertile progeny with the sympatric monecious species called spiny amaranth (*A. spinosus*) (Gaines et al. 2012). One report provided evidence of hybridisation and introgression of a herbicide resistance gene through backcrossing from PA into common waterhemp (*A. rudis*) (Wetzel et al. 1999). Hybridisation was also found with tall waterhemp (*A. tuberculatus*), and at very low rates with smooth pigweed (*A. hybridus*) (Gaines et al. 2012). However, I could find no research on its sexual compatibility with amaranths from other regions.

The ability of PA to form fertile hybrids with other species could extend the geographic range or ecological impacts of a gene drive. While PA was originally found in arid areas of the U.S. Southwest and Mexico, the natural range of several sexually

compatible species extends farther north and into more humid areas.

Ward and colleagues summarise several studies of interspecies hybridisation attempts, showing differing results in different experiments, with some producing fertile progeny and others, although using the same species, failing to do so (Ward et al. 2012). This may be attributed to the very low hybridisation frequencies found in these studies, as well as differences in methodology or the genetics of the specimens used in the studies. This could result in rare fertile hybridisation events, with various species being missed in such studies.

As Ward et al. recognise when referring to the potential for herbicide resistance to be transferred to other amaranths, even low levels of gene flow between these species could be cause for concern. This statement could also be applied to low levels of transfer of a gene drive to other species. If a gene drive is effective at spreading through the genome, even very low frequencies of gene flow through hybridisation and backcrossing to another species could result in the effective interspecies spread of the drive.

It should also be noted that the previous research on natural hybridisation and gene flow cited above does not address whether PA may be a source of genes for improving cultivated grain amaranths. Techniques such as protoplast fusion or embryo rescue have sometimes been used successfully to breed crops with wild relatives, techniques which may allow fertile hybridisation in cases where it may not occur naturally or is exceedingly rare without such assistance. These techniques were not used in studies of natural hybridisation.

To summarise the available research, hybridisation and gene flow between PA and other sympatric species has been demonstrated. But these data are limited, and it is unknown how many other species, whether in North America or elsewhere, might be sexually compatible with PA. Even when it comes to the potential spread through species already known to be sexually compatible with PA, there could be significant risk from a gene drive, since these species are common native members of North American ecosystems.

Ecology of Palmer Amaranth

As a fast-growing seed-producing plant in the US Southwestern deserts, PA has a role in providing food for numerous seed-eating species. Desert birds are reported to use this food source, with recovery from 11 bird species' digestive tracks (Proctor 1968). It is also consumed by multiple duck and goose species, with seed remaining viable after digestive track recovery (Farmer et al. 2017). Survival in bird digestive tracks may facilitate long distance dispersal of this plant.

It is important to note that its adaptive strategy of emphasising fast growth, rather than high conservation of water, compared to the typically slower growth of many other desert species, may complement the latter's ecological function. Its small seeds and large seed production also facilitates colonisation of new and disturbed sites, which may facilitate later succession to slower-growing species.

Perhaps because of its dual food and weed roles, much of the research on PA focuses on these aspects of its biology. The research on its wider roles in ecosystems is more limited. Therefore, the consequences of gene drives that may impact whole populations or species like PA is very difficult to predict. This limited ecological understanding makes adequate risk assessment difficult at best.

How Palmer Amaranth became a Serious Weed Problem in Agriculture - The Bigger Picture

Palmer amaranth is an example of a plant that has become a major weed only recently, largely due to technological changes in US and South American agriculture in the last few decades. In particular, the advent of genetically engineered glyphosate-resistant crops, in the mid-90s, led to the large majority of corn, soybean and cotton acreage in the US containing this trait, which resulted in the extreme overuse of this herbicide (Mortensen et al. 2012). Prior to that time, PA was not considered to be a highly important weed. Besides the US, engineered her-

bicide-resistant crops are most common in South America, where PA and other resistant weeds have also become a substantial problem.

Many other countries have been reluctant to grow these crops. However, they are nonetheless part of trends toward further industrialisation of agriculture and emphasis on reducing dependence on labour, being dependent on chemical fertilisers, large machinery and pesticide use, along with various other technologies. In this broader sense, this trend toward industrialisation and reduced biological diversity can also be found in many parts of the world, including Europe. This is due in part to international neoliberal trade regimes that emphasise productivity and price, at the expense of more multifunctional aspects of agriculture. Crop and habitat diversity support predators of pests and pollinators, and continuous plant cover of the soil enhances fertility and water quality and also helps to limit soil erosion. In other words, technologies that emphasise herbicide and other pesticide use are the antithesis of agricultural systems such as agroecology, that are based fundamentally on diversity—biological and genetic, as well as cultural.

As such, there is continuing pressure globally to further adopt policies and technologies, such as engineered crops, that have coincided with falling crop and landscape diversity in the United States (Lark et al. 2015; Plourde et al. 2013; Stern 2012). Gene drives, by enhancing herbicide overreliance or avoiding systems based on ecological diversity, could well increase this trend.

The widespread planting of herbicide-resistant crops and overuse of glyphosate-based herbicides led to the development and rapid selection for PA and several other weeds resistant to this herbicide (Webster and Nichols 2012). Their spread through many states has been facilitated, especially in PA's case, by its production of large numbers of small, easily dispersed seeds.

Therefore, although PA is widely established now, making it hard to control, measures not highly dependent on glyphosate or other herbicides that were previously used, as well as newer measures, can be useful to regain control of this weed.

In fact, as discussed below, integrated weed management using the principles of agroecology could not only resolve the PA problem, but also provide other important co-benefits for the environment and rural communities. Gene drives aimed at ridding the agroecosystem of PA or making it susceptible to glyphosate again might instead, if successful, allow industrial agriculture to avoid needed changes. These needed changes include achieving broad environmental goals such as cleaner water, reduced water use, greater biodiversity and lower greenhouse gas emissions.

This points to a general problem that afflicts narrowly targeted strategies like gene drives: They do not address the often complex and broader issues that led to the problem in the first place. This in and of itself does not mean that technologies could never have a positive role in solving agricultural problems; but it does suggest that they may obscure more systemic problems and foreclose better systemic solutions that have multiple benefits.

Specific Origins of the Glyphosate-Resistant Weed Problem

Palmer amaranth was reported to begin moving from its regions of origin in the early 20th century (Ward et al. 2012). However, except for a few southeastern states, it was not recognised as a major agricultural weed until the adoption of conservation tillage (reduced tillage with crop residues left in the field) and no-till farming became more common following incentives in the 1985 U.S. Farm Bill, and also after glyphosate resistant crops became widespread after the mid-1990s. With the reduction of tillage, which can substantially contribute to effective control of PA, weed control became even more dependent on herbicides, especially glyphosate used in conjunction with the major crops corn, soybeans, and cotton.

This led to the massive overuse of the single herbicide, glyphosate, and to PA's subsequent resistance to it and its geographic spread (Mortensen et

al. 2012). For example, while not listed among the important US weeds of corn in 1994, it was ranked 7th by 2009. It was ranked 23rd in soybeans in 1995, and rose to 2nd in 2010 (Webster and Nichols 2012). This means the main reason for the increased importance of PA as a weed was the development during this period of glyphosate resistance, with reduced tillage also playing a role.

In the several decades prior to HR crops and incentives to reduce ploughing and tillage, along with several herbicides, were commonly used to control weeds by the industrial farms that dominate commodity crop production in the US and Western Europe. This includes crops like corn, soybeans and cotton that are grown on huge areas of land. Palmer amaranth is susceptible to tillage in part because it is an annual and so does not grow back from root fragments that may occur after ploughing, as many perennial weeds can. Moreover, its seeds are very small; when buried by ploughing, they cannot germinate and sprout. However, because, unlike many other weeds, new PA seedlings emerge throughout most of the growing season, control measures like tillage or herbicide applications often need to be repeated.

Gene Drives for Palmer Amaranth

Because of its importance as a weed and its biological characteristics, PA is considered one of the primary targets for CRISPR/Cas9 based gene drives in plants, as noted by the U.S. National Academies of Sciences (National Academies of Sciences 2016). Because it is dioecious, it is an obligately outcrossing species. However, there are reports of low level agamospermy (seed produced from ovules without fertilisation) that could short-circuit a gene drive system (Ward et al. 2012). The large number of seeds produced by PA plants, on the other hand, could facilitate faster spread of the drive.

There are several recognised challenges that would affect the performance of gene drives in weeds or other plants. First, it could take several years for a gene drive to adequately penetrate a population, and persistent seed banks can add to that time period—seed banks are the seed left in the soil (Neve 2018). Depending on the plant species and environmental conditions, these may last from a few years to decades. Seed banks are an important consideration in weed control, because once they have built up to significant levels, weeds will continue to emerge in a field, even if no further immigration of seeds from elsewhere occurs. PA does not have a very persistent seed bank. In one experiment, after four years of burial in soil, only about 0.01 – 0.03 percent of seed remained viable. On the other hand, a single plant can produce 600,000 seeds, which still means many viable seeds after several years even with low persistence rates (Jha et al. 2014). Resistance, as reported above, is also a possibility for several gene drives and could readily occur in the field (Unckless et al. 2017 – and see Chapter 1).

More fundamentally, homologous recombination does not seem to function as well or as readily as a DNA repair mechanism in plants as it does in many other organisms (Neve 2018). The predominant repair mechanism for DNA double strand breakages in plants is the NHEJ mechanism (non-homologous end joining), which, instead of facilitating the insertion of the gene drive construct, results in small random mutations at the DNA breakage point. A homologous repair pathway is required to ensure a functioning gene drive system, whether the goal is to disrupt a target gene with insertion of CRISPR/Cas9 as a "genetic chain reaction", or to spread an effector gene through the population. Low rates of homologous recombination repair could greatly slow the spread of the drive, which is already a challenge with weeds because of relatively low rates of reproduction and/or lack of reliable outcrossing. If low enough, these rates could prevent the drive from working (e.g., if lower than any possible reduction in fitness resulting from the drive). Research to date has not been found that demonstrates any proof of concept for gene drives in plants.

Risks and Other Issues

Two general types of approaches for gene drives in PA have been suggested, 1.) drives altering the sex ratio (e.g. reducing or eliminating female plants), which would aim for eliminating weed populations,

2.) sensitising drives, to make subsequently treated plants susceptible to a treatment, likely a proprietary chemical, that would then kill them (Neve 2018). The latter would also include re-sensitising weeds that have become resistant to a herbicide, such as glyphosate. These approaches would be based on CRISPR/Cas9 methods.

The most commonly discussed sensitising drive for PA is to restore its original sensitivity to glyphosate-based herbicides. Theoretically this could be possible, since the genetic mechanism for resistance to the herbicide has been discovered. It has been found that gene duplication has created numerous copies of the native *EPSPS* gene, part of the aromatic amino acid biosynthesis pathway. The EPSPS enzyme is the target of glyphosate herbicidal activity. The effect of multiple *EPSPS* gene duplications is to dilute the herbicide relative to its target to the point where it no longer can kill the plant at normal or even very high application rates (Gaines et al. 2010).

However, a substantial limitation with this approach, in addition to those already discussed above, is that the herbicide could not be used for a number of years while the drive was spreading through the weed population, and while viable seed remained in the soil seed bank. Otherwise, the plants with the drive would be killed prior to all plants acquiring the drive. If some plants escaped the drive, they would ultimately be strongly selected for by the use of the herbicide.

But more fundamentally, this approach would maintain the heavy use of this herbicide, with all its attendant harms to the environment, biodiversity and human health. The heavy use of glyphosate is likely the primary cause of the decimation of monarch butterflies in the US by nearly eliminating the milkweeds necessary for larval growth (Pleasants et al. 2017), and herbicide drift generally harms important uncultivated habitat near treated crop fields. Glyphosate has also been determined to be a probable human carcinogen by the International Agency for Research on Cancer (International Agency for Research on Cancer 2015; Levin and Greenfield 2018). As such, a gene drive restoring sensitivity of PA to glyphosate would also further forestall the implementation of truly sustainable weed control methods like agroecology, and could have other negative consequences to the environment and human health.

The second approach, population suppression, neglects the fact that PA is only a weed in agricultural systems. Its other properties, discussed above, make it a potentially valuable plant as a human food source or as a source of valuable genes for breeding in related species. In particular, its adaptation and fast growth in hot and water-limited environments, and its highly nutritious seed and foliage, means that it may have enhanced value as a potential crop in the future.

Given how easily dispersed the seed of this plant is, both by wind or animals but also farm machinery, it seems highly possible that a gene drive could invade native populations of PA in the US southwest and Mexico. Palmer amaranth is now found widely in the lower 48 mainland US states, so there are no major geographic barriers such as oceans to prevent its invasion of the native range of the species, which could threaten the species' existence.

PA also has ecological significance that is not well understood. The ability of PA to hybridise with several other species of amaranths means that the drive may eventually spread to related species. Even if PA and related species are not driven to extinction, reduced populations in wild habitats could have negative ecological consequences. As for the potential of these species to provide genes useful for crop breeding, population reduction short of extinction could reduce their genetic diversity, possibly reducing the number of valuable genes or alleles. The collective impact could cause significant harm to the environment.

Agroecology as a Way to Control PA Sustainably and as an Alternative to Gene Drives

Agroecology relies on biodiversity and a diversity of farming practices and management methods like long crop rotations, cover crops and provision of habitat for pest predators, in order to control

pests and weeds. It relies on knowledge developed by farmers over millennia to sustainably grow crops, along with application of modern ecological sciences (Altieri 1999). Modern ecological research can help to optimise systems and breed crop varieties adapted to those systems and to the needs of farmers. For example, the ecological sciences recognise that ecosystems vary locally and regionally, and therefore optimisation of cropping systems for productivity and co-benefits can best be achieved by designing such systems to best take advantage of local conditions.

In essence, all organisms, including pests, are adapted to particular environmental conditions and plants they can feed on or crops they can infest as weeds. By varying those conditions over time and space through practices like crop rotation and the use of cover crops, pests are usually prevented from building up to harmful levels. Using these strategies have been shown to be effective in controlling weeds (Liebman et al. 2004). Similarly, crops can be bred to better compete with or suppress weeds (Worthington and Reberg-Horton 2013). In addition, the increased biodiversity created by these crops and nearby uncultivated areas, together with limited use of pesticides, encourages the proliferation of organisms that reduce pest and weed numbers (Altieri 1995; Liebman et al. 2004).

For example, long-term experiments in Iowa have shown that herbicide use can be reduced by about 90 percent or more to obtain weed control, and crop yields for corn and soybeans as high or higher than for typical herbicide-dependent industrial agriculture (Davis et al. 2012). Others have demonstrated similar results in Europe and elsewhere, especially under drought stress (Gaudin et al. 2015; Lechenet et al. 2014). While more labour is often required, the cost of chemical treatment is reduced, so the net profit to the farmer is as high or higher than for chemical-and GMO dependent industrial agriculture. PA was not found in the area of these experiments, but a related amaranth, waterhemp, is a major weed in Iowa. Even though limited tillage was used in the system of Davis et al. and others, water quality is substantially higher than for industrial agriculture, due to the incorporation of the perennial alfalfa (lucerne) and cover crops in the winter (Davis et al. 2012; Isbell et al. 2017).

More specifically, separate experiments have shown that winter rye cover crops, combined with modest tillage, can effectively reduce PA, providing the biomass of the cover crop is high enough (Aulakh et al. 2012; Aulakh et al. 2013; Price et al 2016). Combined with the positive weed control effects of greater crop diversity in agroecological systems, these practices have promise to provide long-term control of PA, as well as providing the multiple benefits noted above (Liebman et al. 2004). At present however, there appears to be no research on the use of diverse agroecology specifically to control PA.

Although agroecological systems provide substantial co-benefits in reduced pesticide and fertiliser use, increased soil fertility, higher biodiversity, and cleaner water, also in reduction of greenhouse gas emissions, farmers are often locked into current industrial practices for several reasons. These include: inexperience with knowledge-intensive agroecology; peer pressure; farm policy that discourages them (e.g. insurance or loan unavailability); higher labour requirements; and debt service due to the purchase of expensive specialised equipment (Roesch-McNally et al. 2017; Vanloqueren and Baret 2009). These could be remedied over time with proper policies and incentives, along with more research to optimise agroecological systems (Delonge et al. 2016). These measures would be highly justified, given the large public benefits of this kind of farming.

Summary and Conclusions

There is considerable interest in developing gene drives to address the substantial challenges of agricultural weeds. Palmer amaranth in particular has been discussed as a desirable target. This is due both to its great importance as a weed in the US and South America, and also because of its biology of obligate outcrossing. On the other hand, there are so far no proof-of-concept examples of gene drives functioning in plants, and there are several considerable biological barriers, which are greater than

for some other organisms (such as mosquitoes), for such an approach to work.

Despite the current barriers, the potential attractiveness of commercial gene drives that control weeds like PA or other crop pests is likely to drive further research projects seeking to overcome these challenges. It is therefore important to consider the many potential harmful consequences of agricultural gene drives such as might be used for PA.

In doing so, this chapter finds many ways that such gene drives could cause harm, as well as too little information about how such gene drives could negatively affect either the environment or human health. Some of this harm could result from reduction or elimination of populations or PA in the natural environment, or through damage to populations of related species via gene flow. This is an area for which there is far too little information.

Substantial harms and dangers could also occur through the re-sensitisation of PA to glyphosate herbicide, which is something that will probably find financial backing, as such a gene drive would hold considerable interest to the companies that sell this chemical.

This re-sensitisation pathway is often considered to be less risky than population elimination. However, the analysis here finds that there are considerable indirect risks that are not often well considered by regulatory agencies. These include the established harms of supporting forms of agriculture overly dependent on herbicides, along with other ecologically and socially harmful technologies or practices.

The risks of using gene drives in these contexts also include the potential opportunity costs of forestalling movement to more agroecologically-based systems, which are needed to address the multiple harms caused by industrial agriculture, currently propped up in part by overuse of herbicides. These kinds of concerns, although they have huge social and environmental implications, are rarely considered by risk assessment agencies.

This also points to a general concern about gene drives as an example of a piecemeal techno-fix, rather than a systems-based, holistic approach to solving complex environmental and social problems. Because specific problems in agriculture are inevitably part of complex interconnected systems, they are often symptoms of much larger problems. Addressing these as individual issues alone can lead to other unanticipated harms.

Our starting point should therefore be a broad analysis of the biology and ecology of the organisms that may be considered to be targets of gene drives. We also must evaluate the social systems with which these organisms interact, and understand exactly what kind of systems in which these drives would be used, or could facilitate. We must also evaluate systems-based alternatives before gene drives are considered for use in the environment.

2.4.4 Agricultural insect pests as Gene Drive targets

In considering pest insects as potential gene drive targets and in order to adequately determine other potential options for pest control, it is important to first understand how these insects became significant pests in the first place. Instead, the starting point for considering whether gene drives might be appropriate is typically the current severity of the pest and whether typical conventional options such as pesticides are sufficient to control it. In particular, the industrial agriculture production system itself may have played a large role in terms of whether an insect became a pest in the first place, as well as how severe its effects might be. Therefore, consideration should be given to whether altering the production system might also be able to provide opportunities for control that would avoid the risks and uncertainties associated with gene drives. A second important consideration in evaluating the use of gene drives for agricultural insect control is the state of knowledge about the ecological role of the pest in the wider environment, including the different geographies into which the gene drive may spread. These considerations will be evaluated below.

Because in practice a very large number of species might eventually be considered by proponents of this technology as gene drive targets, in order to briefly illustrate these issues, the focus here is on only a few examples. However, it needs to be emphasised that to date, only some proof of concept research has been published, which is a long way from showing that gene drives can work in the complex context of the open environment or that they can be safe.

Several of the species that have been mentioned as potential targets are listed in Table 2a and references cited therein, while several others are considered by Scott and colleagues (Scott et al. 2018). These include: spotted wing drosophila (SWD, *Drosophila suzukii*); the wasp species *Vespula vulgaris* and *V. germanica*; Argentine stem weevil (*Listronotus bonariensis*); Australian sheep blowfly (*Lucilia cuprina*); red flour beetle (*Tribolium castaneum*); and the Asian citrus psyllid (*Diaphorina citri*; the New World screwworm fly (*Cochliomyia hominivorax*); diamondback moth (*Plutella xylostella*); Western corn rootworm (*Diabrotica virgifera virgifera*); and silverleaf whitefly (*Bemisia tabaci*).

The Role of the Agriculture System in the Development of Insect Pests

Many important insect pests cause substantial damage because current intensive agriculture production systems are particularly vulnerable to pests due to their limited biological and genetic diversity, which can be exacerbated by heavy dependence on chemical pesticides (Bennett et al. 2012; Douglas and Tooker 2016). Research showing that biologically diverse organic farming systems tend to have less pest damage also demonstrate productivity in these organic systems at near industrial farm levels (Ponisio et al. 2015). In contrast, low-diversity organic systems that are similar to industrial systems in respects other than pesticide use, had yields approximately 19% less than comparable intensive industrial plots. Overall, more diverse organic systems yielded only about 8-9% less than industrial systems (Ponisio et. al. 2015).

As these authors point out, this is despite the fact that only a few percent of US research dollars currently being spent is supporting the improvement of organic and other agroecological systems (Delonge et al. 2015). Ponisio and colleagues suggest that with adequate research support, even the small yield gap between the two systems might be eliminated. At least one other study at the global scale suggests that organic can be close to, or sometimes more productive than, conventional agriculture, especially in developing countries (Badgley et al. 2007). These agroecological systems can apply advances in ecological science to augment more traditional systems, but currently receive little research funding compared to industrial methods, despite their notable successes.

Although factors other than reduced insect pest damage could likely have contributed to these results, it is unlikely that high yields could have been produced alongside substantial insect damage. Similarly, diversified farms in Europe maintained yields as high as industrial systems, despite dramatic pesticide reduction in these more diversified farming systems (Lechenet et al. 2014). Long-term experiments at farm scale have shown that agroecological systems in the US Midwest can be as, or more, productive than industrial systems, while dramatically reducing pesticide use and fertilisers, thus conferring large benefits to biodiversity and water quality (Davis et al. 2012; Liebman and Schulte 2015).

A substantial factor in higher yields in more diverse systems is biological insect pest control by pest predators and parasitoids, which are also known as pest natural enemies (Grab et al. 2018; Rusch et al. 2016). Current simplified industrial systems generally have lower abundance and diversity of pest enemies than more diverse farming systems (Letourneau et al. 2011).

A proposed gene drive target, Western corn rootworm (WCR) (Scott et al. 2018) provides a well-studied example of how current simplified cropping systems lead to higher crop damage. Western corn rootworm is considered the worst corn insect pest in the US, but in most areas crop rotations eliminate the need either for insecticides, or gene drives, to

control it (Gray et al. 2009). These rotational systems are as, or more profitable than, monoculture corn (Davis et al. 2012). In some areas WCR has developed resistance to the common corn-soybean rotation. This rotation, however, consisting of only two crops, is considered too simple to fully qualify as agroecology, and is part of typical industrial crop systems heavily reliant on chemical pesticides (Davis et al. 2012).[25]

Invasive Species as Agricultural Insect Pests

Many of the most challenging insect pests, and most of those noted in Table 2a and elsewhere as gene drive targets, are actually invasive species where they occur as agricultural pests (Scott et al. 2018). A substantial reason for the damage they cause may be the lack of adequate local biocontrol (in terms of natural predators) in their new habitats (Tscharntke et al. 2016). It is therefore important to note that the lack of diverse habitats may reduce the efficacy of introduced biocontrol agents. For example, strawberry farms embedded in less diverse habitats had more damage and lower yields because of the tarnished plant bug (*Lygus lineolaris*), due to reduced populations of an introduced wasp biocontrol parasitoid in the less diverse landscape (Grab et al. 2018).[26]

Similarly, insecticides used in simplified industrial systems are known to harm biocontrol agents (Douglas and Tooker 2016; Tscharntke et al. 2016). This has been demonstrated for an increasingly important introduced wasp parasitoid of the invasive Asian soybean aphid[27], the most important insect pest of soybeans in the US (Frewin et al. 2012; Frewin et al. 2014).

These examples may have important implications for accepted biocontrol methods that could be more viable and desirable approaches than the creation of targeted gene drives. For example, several parasitoid wasps, both domestic and from the region of origin of the spotted wing drosophila (SWD) (another target of gene drives), could be more or less effective depending on both farm landscape diversity and insecticide use (Staccconi et al. 2017; Wang et al. 2018).

In particular, the efficacy of an introduced biocontrol agent could be hampered in the simplified industrial farm landscapes common in the U.S. and parts of Europe. This could mask the potential of some of these agents, and thereby encourage the use of gene drives, if care is not taken to determine the suitability of the farm landscape, and to encourage a favourable environment for the biocontrol agents. Unlike gene drives, which target only one particular pest at a time, agroecologically diverse farming systems also provide multiple environmental and social benefits that include better water quality, climate adaptation, and biodiversity (see Case Study 3 on Palmer amaranth), as well as their basic pest control function.

Those who oppose biocontrol methods may point to how long it takes to develop them, but gene drives may take fully as long and could be far more dangerous. Pest natural enemies also may adapt over time to reduce harm to crops or livestock from an invasive pest. It is important, therefore, to consider how long an invasive pest has existed in its new environment, and how long efforts other than gene drives have been under development. For example, invasive SWD first was identified in Europe and the US just over 10 years ago, and potentially effective biocontrol agents have only been identified in the past 3 or 4 years and require more testing (Wang et al. 2018). By comparison, the Asian soybean aphid was first found in the U.S. in 2000, and the unintentionally introduced biocontrol parasitoid wasp, *Aphelinus certus*, has been increasing in abundance and efficacy in recent years (Kaser and Heimpel 2018). There is also evidence that generalist pest predators may adapt over time for greater control of some invasive insect pests (Symondson

25 It is not known whether WCR would have developed resistance to longer crop rotations, but it seems likely that such rotations would impose higher fitness costs to rotation-resistant variants, reducing this possibility.

26 A parasitoid is an insect, especially wasps, that lay their eggs in other insects, including pest insects. The larvae of the wasps grow in the insect host and kill it.

27 The soybean aphid is not a target for gene drives because it frequently reproduces asexually. It is used here as an example of an important invasive insect species, which provides important relevant similarities for gene drive targets.

et al. 2002).[28] Other helpful approaches to invasive pests also take time to develop, such as breeding for crop resistance (McCarville et al. 2014), or cultural methods such as soil micronutrient additions, which show promise for remediating harm from the Huanglongbing (citrus greening) pathogen transmitted by the invasive Asian citrus psyllid, another potential gene drive target (Table 2a) (Corchrane and Shade 2019).[29] In fact, gene drives themselves may take several years to develop, and more years to adequately test and assure their safety (if their safety, or adequate testing, is even possible). This means that they have no obvious advantage in terms of how quickly they may be safely deployed.

Risk Assessment of Gene Drives for Agricultural Insect Pests

An important component of risk from gene drives is the harm they may cause to the ecosystems from which the agricultural pest originated. In most cases we know little about these risks, because we know little about the role of many of these pests in non-farming ecosystems. In their review of potential agriculture insect targets of gene drives, Scott et al. (2018) note that eradication of the New World screwworm (NWSW) from Texas by using sterile insect technology may have contributed to increases in whitetail deer populations—and deer overpopulation can result in harm to tree understories and tree reproduction, as well as to the spread of Lyme disease. They also note that little is known about the ecology of New World screwworm, probably because research emphasis has been on its control, not its ecosystem purpose. These authors also note that there is similar need for more ecological research for other insect pest targets of gene drives: "Further, the screwworm experience highlights the need for more basic ecological studies for other pest insects before and after a population suppression program."[30]

In research for this report, it was similarly noted that the preponderance of the research on *Drosophila* has been on *D. melanogaster*, a model organism for genetics research since the early 20th century, and now again for gene drives (see Table 2a). Proof of concept was demonstrated in *D. melanogaster* for a "mutagenic chain reaction" using CRISPR/Cas9 (Gantz and Bier 2015). More recently, Buchman et al (2018) used a MEDEA-based maternal gene drive to achieve near 100% population supression in lab in Spotted Wing Drosophila, including several wild-type populations from different regions, although this is still far from demonstrating function in the environment.

But knowledge of *D. melanogaster* cannot substitute for understanding the actual ecological functions of the pest species SWD, including behavior, effects on plant species composition, role as a food source and other factors. Research for this report was unable to identify substantial research on the role of SWD in its native habitats; there seems to be very little. Some aspects of the physiology or anatomy of SWD that make it a particular pest problem, such as its serrated ovipositor (egg laying organ), which facilitates egg laying in ripening fruit, unlike many other species of better known *Drosophila*, also may have implications for its ecological roles that differ from better known species. The same processes that would spread SWD could be reversed, to bring gene drive individuals into contract with non-target populations (i.e. in region of origin) (Webber et al. 2015). Further, recent modelling suggests that efficient gene drives could be highly effective and spread through all populations, even if introduced at low frequencies (Nobel et al. 2018). Several species of drosophila have been shown to be able to hybridise, resulting in gene flow (Kaneshiro 1990).

This all means that, in addition to possible extinction of the target pest SWD, it may be that other species, especially closely related species sympatric to the region of origin of SWD, might be driven to extinction as well, without researchers having, or

28 Parasitoids often have only a few species that they attack, which makes them attractive as imported biocontrol agents. They are therefore specialised biocontrol agents. Generalist biocontrol agents, by contrast, prey on many species, including pests and others.

29 It is too early to determine how effective this approach may be, but the main point is that these approaches take some time to develop and test.

30 Scott et al. 2018, S104

even attempting to have, a clear understanding of their role in their ecosystems.

Ecological assessments of environmental risks by or for regulatory authorities and agencies for other pest control technologies have been shown in recent years to be inadequate. For example, resistance to glyphosate herbicide and the weed control crisis (see Case Study 3 on Palmer amaranth) resulting from the commercialisation of genetically engineered herbicide resistance crops, was not predicted or prevented by authorities in the US.[31]

More recently, widespread harm to invertebrates, such as pollinators, from the use of systemic neonicotinoid insecticides, was not foreseen by regulators in any country. This is due at least in part to the inadequacy and difficulty in determining harmful sub-lethal and trophic level effects of these insecticides in the broader environment, for example, identifying harms to behavior, fecundity, or immune function of invertebrates (Pisa et al. 2015). It has taken years of research by dozens of scientists to begin to determine these effects. While the precise types of ecosystem effects caused by gene drives would not be identical to the effects of a pesticide, they are likely to also be at least as complex and take considerable time and effort to understand. The history of the regulation of pest control technologies does not provide comfort that adequate complex ecological assessments will in fact be undertaken before application if they are developed. And while pesticide use can be discontinued, gene drives intended to spread through the environment, or those that spread beyond their intended range, so far cannot be recalled or reversed.

A general problem with piecemeal approaches like gene drives is that even if nominally successful in controlling some particular pests, they could leave intact harmful industrial agriculture and perhaps forestall systemic ecological changes in these activities that are needed in order to reduce water pollution and climate change emissions, conserve biodiversity, and improve resilience to climate change (i.e. temperature and moisture extremes). Agroecology has been shown to benefit all of these societal needs. Although it is not necessarily inherent in the development of gene drives that its use would replace efforts to pursue agroecological systems, new technologies need to be considered in a current social context, one which already favours industrial agriculture in terms of research and funding, and which could be propped up and further entrenched with gene drive technologies (Roesch-McNally et al. 2018; Vanloqueren and Baret 2008).

2.4.5 Dual use - military (& civilian) research & potential use

As already outlined in the introduction, this is a powerful technology that has high potential for misuse and destruction, and is as such recognised as a 'dual-use technology', that is, a technology that can be utilised for peaceful civilian purposes as well as for military ones. The National Academy of Sciences report on gene drives makes an important point under "biosecurity considerations", explaining that gene drives add a new dimension, a new opportunity for weaponising insects, because of their self-sustaining nature: "The actual and potential use of insects as weapons has been discussed; for example, by releasing insects infected with human pathogens or releasing agricultural pests (Lockwood 2012). However, the availability of a gene drive provides a new opportunity for malicious use because its self-sustaining nature poses a perhaps more significant threat." (NASEM 2016, 161). Kenneth Oye has also repeatedly warned about the potential ease of misuse of this technology, e.g. (Oye and Esvelt 2014).

When looking at potential dual use scenarios, the US National Academy of Sciences, Engineering, and Medicine (NASEM) argues in their 2016 report on gene drives: "Yet, with a better understanding of the basis of mosquito—pathogen interactions, it is not inconceivable that rather than developing a resistant mosquito, one could develop a more susceptible mosquito capable of transmitting a specific pathogen more efficiently than wild-type mosqui-

31 Weed resistance was predicted by environmentalists, but even they did not anticipate the scale of harm from this process.

toes. It might even be possible to develop mosquitoes that could transmit a pathogen that is not normally vector-borne, or that could even be able to deliver a toxin." (NASEM 2016, 161) There are in fact many scenarios one could conceive of, especially for insects, given the recent research advances in that field. Whilst spreading toxins and diseases to humans, livestock or plants is a serious prospect, it would be of equal concern to intentionally weaken or eliminate beneficial insects. NASEM hence states in its conclusions: "Governance mechanisms need to be in place to address questions about the biosecurity implications of gene drive research and consider developing mitigation strategies that are not dependent on the underlying technology." (NASEM 2016, 171)

The DARPA Safe Genes programme and possible military applications

The US Defense Advanced Research Projects Agency (DARPA) is investing at least $65 million over four years into research on gene drives and genome editing technology through a programme named 'Safe Genes' (DARPA 2017). The programme was announced in July 2017, along with outlines of seven major research projects it would support, five of which are wholly or partly focused on gene drive research. The goals are broad and include: overcoming the remaining technical barriers to creating gene drive systems capable of modifying wild populations; development of control systems to allow limitation of their geographic range; and finding methods for reversing drives, including counteracting drives released by other actors. DARPA emphasises that no gene drives will be released in the wild as part of this programme, though many of the projects include public consultation elements or engagement with policy makers which are likely to be aimed at achieving consent for an eventual release.

Who is being funded?

'Safe Genes' is directing funding to most of the leading figures in gene drive research, alongside high profile individuals in the CRISPR/Cas9 genome editing community. Whilst many of these projects have been described, an overview is helpful to illustrate the reach of the programme:

- Omar Akbari at UC San Diego is leading a $14.9 million project to engineer gene drives to modify or eradicate populations of the mosquito *Aedes aegypti* (Warren 2017), alongside the development of drives in *Saccharomyces cerevisiae* as a model system (Aguilera 2017). His collaborators include Ethan Bier, Valentino Gantz, Anthony James and others.

- A consortium led by John Godwin at NCSU is receiving $6.4 million to develop gene drives capable of eradicating mouse (*Mus musculus*) populations (NCState 2017). Collaborators include David Threadgill and Paul Thomas, who are spearheading the mouse genetics work.

- Kevin Esvelt at MIT is leading a collaboration to validate 'daisy chain' drives and related concepts in the nematode *Caenorhabditis brenneri* (Esvelt 2017), and along with Luke Alphey, to apply them in the mosquito species *Culex quinquefasciatus* and *Aedes aegypti* (BBSRC 2018).

- Andrea Crisanti's team at Imperial College are continuing their development of gene drives in *Anopheles gambiae* mosquitoes (Neslen 2017), as part of an $11 million project led by CRISPR/Cas9 expert Keith Joung at Massachusetts General Hospital (MGH 2017).

- A project to develop controllable gene drives in *Anapholes stephensi* mosquitos is going ahead, led by CRISPR/Cas9 specialist, Amit Choudhary at the Broad Institute (DARPA 2017). It has not been announced who is directing the mosquito work, though it is likely to be Valentino Gantz and Ethan Bier who work with *A. stephensi* and have stated they are involved in a second 'Safe genes' project (Aguilera 2017).

As well as focussing on gene drives, 'Safe genes' is funding efforts to develop new CRISPR/Cas9 technologies, including: engineering small molecule regulated forms; expanding methods to inhibit CRISPR; improvement of genome editing specificity; increas-

ing the range of sites on the genome that can be targeted; and the development of new applications for CRISPR beyond genome editing. These efforts involve Joung's and Choudhary's teams, alongside projects led by George Church of Harvard Medical School and Jennifer Doudna of UC Berkeley.

What are the motivations?

To speculate on the underlying logic of 'Safe Genes', consider first how a gene drive could be weaponised, for example to crash populations of insect pollinators for important crops, or to suppress fish populations in an important fishery. Even if the US was not interested in gaining this capacity, there would be motivation to find out how to counteract a gene drive released by a hostile actor. Given that the most plausible strategy to counteract a gene drive is another gene drive (as discussed in Chapter 1), this creates an imperative for US defence agencies to develop a functioning gene drive before any rival states or other actors do. Therefore, from a military perspective, there are powerful motives for the US and others to develop this technology, and to do so as rapidly as possible.

The Safe Genes programme should also be seen in the light of another recently announced DARPA programme named 'Insect Allies' (DARPA 2016). This $27 million programme seeks to develop methods to genetically modify crops using infectious viruses that would be delivered by insects (some of the methods being explored to do this would use CRISPR/Cas9) (Reeves et al. 2018). Whilst the stated motive for this programme is to be able to directly modify crops whilst they are already growing in the field to protect them from stressors such as drought, disease or insect attack, it has been observed that the proposed technology could be weaponised in various ways, for example to disrupt the formation of viable seeds from targeted crop varieties (Reeves et al. 2018). There may then be the view in the defence community that it would be desirable to gain the capacity to modify crops, insects and perhaps other organisms on a very large scale, whether through viruses or gene drives, and to be one step ahead of rivals in terms of being able to counteract these measures. This is a disturbing prospect, and concern about proliferation of such biological weapons has led to calls for the Insect Allies programme to be scrapped (Reeves et al. 2018).

3 Risks, potential negative impacts and risk assessment limitations

3.1 Risk assessment of GDOs[32]

Current risk assessment (RA) of GMOs is mainly focused on crop plants. With increased research into gene drives we may expect a shift that has already started with the development of GM-sterile insect technology: environmental release of organisms carrying a gene drive will be in wild living animals.

Risk assessment of GM crops is mainly focused on toxicological effects of the expressed transgenic components. Environmental risk assessment (ERA) is complex even for sessile ('classical') GMOs like crop plants, which are cultivated in field sites. The release of gene drive differs from these 'classically' genetically engineered crops in the following ways, which add additional layers of complexity to any effective ERA, since it means that first release will most likely be:

1. With mobile animals (mosquitoes or rodents);

2. in natural or semi-natural environments (island ecosystems);

32 The term GDO was coined by van der Vlugt et al. 2018 and is also used in Simon et al. 2018

3. carrying a transgene designed to outcross and spread in natural populations;

4. with the intention to either wipe out or persist and permanently genetically modify populations.

The competent authority for ERA in the EU is the European Food Safety Authority, EFSA. In the past, it has published guidance for ERA of crop plants (EFSA 2010), as well as on GM animals (EFSA 2013), which briefly covers gene drives. It has to be noted, however, that this guidance has been developed in the pre-CRISPR era and so will not be fully applicable to recent developments, especially the ability to create global gene drives (global is used in the sense that they might cover the whole geographic range of the affected species).

Risk assessment and especially environmental risk assessment of gene drives will be concerned with multiple layers of effects, caused either directly by the genetic modification or by the direct effects of this modification. For low threshold (global) drives, like most CRISPR-based systems, an intrinsic problem with field testing will occur: namely, that a small release can easily escalate into a full release (Noble et al. 2018). CRISPR-based gene drives can act as "mutagenic chain reactions" (Gantz et al. 2015a), which spread exponentially by inheritance in the given population or species. To obtain field data to support the actual ability to do proper RA of gene drives will thus be difficult, and in some cases might even prove impossible. Modelling effects are seen as an attractive alternative to extensive field testing. However, most modelling approaches for gene drives have so far been performed in order to evaluate efficacy and spread of the desired genetic modification e.g. (Unckless et al. 2015), not in order to anticipate risks. Modelling of ecological effects caused by gene drives which would be useful for ERAs has yet to be developed. In comparison to the modelling of efficacy for purpose, approaches to simulate ecosystem effects are far more complex. Complexity of ecological modelling will be determined by the questions asked in RA/ERA.

The potential full release resulting from an intended small (test) release has another striking consequence for RA/ERA: Limits of concern[33] for possible risks have to be defined before first releases are authorised. Only then may intolerable adverse effects on a global (species)-wide level be prevented.

3.1.1 Molecular considerations

Currently, the most promising concept leading to the creation of an effective gene drive would be a global CRISPR gene drive. Synthetic CRISPR gene drives differ significantly in their concept and make-up from current GMOs released into the environment, in that they have a mutagenically active component integrated into their genome. Furthermore, in eukaryotic or complex organisms, the stable integration of CRISPR, a component of an anti-pathogenic system in bacteria[34], creates a high level of complexity, opening many questions on the molecular level. With regards to CRISPR/Cas as a genome editing tool, it is currently used in research as well as in the development of GM organisms for commercialisation. After application, the CRISPR/Cas system is intentionally removed from the organism to prevent unintended effects. Cas itself is an endonuclease, which are "restriction" enzymes that in their original context cleave foreign DNA in an organism, thus eliminating foreign DNA from outside. Stable insertion of an endonuclease into an organism might create toxic effects, a finding that is related to the question of why a defence system based on homing endonucleases is very successful in single-celled prokaryotes, but absent in multicellular eukaryotes. Data on the influence of a permanent, long term exposure of homing endonucleases (such as the CRISPR/Cas based gene drives) on eukaryotic genome stability is currently lacking.

33 Definition: "…the minimum ecological effects that are deemed biologically relevant and that are deemed of sufficient magnitude to cause harm." (EFSA 2010, 110). Defining limits of concern of LOC is difficult and not even done for effects of classical GMO. One effect could be a decrease of population size of a predator of mosquitoes. LOC is then defined as the maximum decrease of population size that would be accepted as a result of wiping out the mosquito population.

34 CRISPR/Cas9 is basically a bacterial defence system. It was transformed by molecular biologists into a tool.

3.1.2 Outcrossing and spreading

Spreading of the molecular construct is another important consideration in the ERA of organisms carrying a gene drive. The inheritance of the transgene is crucial for the functionality of any given synthetic gene drive, and therefore is a desired trait of an organism with a gene drive. Outcrossing of transgenes into closely related taxa is commonly assessed in RA of GMOs. Important for the evaluation of outcrossing is the likelihood of the event, but also the potential of the transgene to establish in feral or natural populations. Even with a high potential to cross into wild relatives, certain GM traits may not be advantageous or favoured by selection, and therefore are expected to disappear over time. For organisms carrying a global gene drive, the chance of transfer for a single transgene into a closely related wild relative is comparable to that of a GMO release, and the likelihood might even increase with the spreading of the gene drive into many organisms.

The important difference is that gene drives do not need to confer a selective advantage in order to spread. The likelihood of an unlimited spread of that given gene drive into the whole geographic range of that species is vastly increased. In the case of an intended population suppression gene drive, this could have fatal consequences for an entire species. Global gene drives, like CRISPR/Cas based systems, are sequence specific. For efficacy reasons, those gene drives will most likely be based on conserved gene sequences, thus increasing the risk of any outcrossing event becoming established. Therefore, any assessment of the outcrossing potential needs to take into consideration the DNA sequence space at the target site(s) of potential crossing partners of the desired species, in order to be capable of evaluating a given risk. This data is not even available for most target organisms currently discussed, and has to additionally be generated for all potential crossing partners of the potential crossing partners. Because of these facts, performing RA/ERA for gene drives is not possible, given currently available data.

3.1.3 Risk assessment of the intended effects

Population suppression using gene drive organisms will have ecological consequences for the entire ecosystem into which it is released. In a best-case scenario, e.g. rodents eradicated from islands, the gene drive will relieve the ecosystem of the target species (in this case invasive) and help to balance the existing ecosystem and strengthen ecological diversity, with little or no detrimental effects. In practice, however, effects on ecosystems have not proven to be so easily predictable, not even in rather simple examples such as the eradication of rabbits and cats from islands (Bergstrom et al. 2009).[35]

Eradication of mosquitoes or weeds poses more complex scenarios, as such efforts will affect not only organisms when they are invasives, but organisms within their native environments. Data and knowledge about their roles in ecosystems is often lacking, but experts warn the likelihood of severe effects on ecosystems (Hochkirch et al. 2018). Evaluation of the impact of any given species' demise relies on the interaction of the target species within the food web and its full ecological context. Besides being a pest or disease carrier, the target species may provide many positive ecosystem services such as: pollinator, food source (prey), predator, ecosystem builder.

As ecological effects are often long term, the proper problem formulation, data acquisition, modelling and/or practical testing will be both complex and demanding for any gene drive.

3.1.4 Risk assessment of the unintended effects through escape

What happens if the gene drive "escapes" its geographic area of application? Eradicating invasive alien species from their non-native habitat has proven to be a difficult task. Using gene drives to solve this problem is a tempting quick-fix. But one has to carefully consider the fact that in cases where an

35 In this example, the influence of eradicating invasive cats on rabbit populations (which were under biological control as well) was underestimated and resulted in an explosion of the rabbit population, causing substantial damage by herbivory.

invasive species might potentially be removed from say an island ecosystem where they are considered a problem, might then, under similar circumstances of spread, unwitting carriers, etc., be able to return to their native or other habitats, now carrying a deadly gene drive.

This point leads to one of the most pressing questions posed by developers and risk assessors: Is it even possible to efficiently contain a gene drive? Containment of gene drives is not trivial. Even using island ecosystems for rodents as an example cannot be considered sufficient protection against GDO spread. Alternatively, concepts for containment can also be based on the molecular design (e.g. high threshold, or 'local' CRISPR drives). But those concepts (once fully developed in the laboratory) have yet to be proven safe, which might be impossible considering the myriad of unforeseen effects that can occur in nature.

As population suppression is the most widely proposed application of gene drives today, escape scenarios will be a primary focus of RA/ERA. Evaluations for assessing escape are coupled to space (geographic ranges of populations and species and migration boundaries, unintended movements, etc.); but time is also an important factor. The self-perpetuating nature of gene drives does not allow predictions about the timely spread of a given synthetic construct. In fact, spread of the gene drive depends on migration and reproduction parameters of the target species and population, which can result in very different dynamics (i.e., fast and exponential, vs. slow and steady, as well as all mixtures). Alongside the intention that gene drives persist infinitely in the wild, or until the goal of suppression is reached, time becomes an important factor for RA, especially because, even with low likelihood, the probability of an escape event will increase with time.

Factors to consider in the risk assessment of escape scenarios are:

1. molecular design of the gene drive (global vs. local gene drive, specificity for a given population)
2. life history of the population and species
3. space (geographic characteristics) and time (infinite persistence) dynamics

3.2 Monitoring

Monitoring of GDOs has to be able to identify and detect a given gene drive in the wild. Due to its molecular mechanisms, a simple detection might not be sufficiently able to determine whether a gene drive is active. CRISPR gene drives harbour a complex copy/paste mechanism, which is error prone. Fragments of inactive gene drives can nonetheless be inherited and thus be detected in monitoring approaches. An in-depth molecular characterisation, potentially by sequencing, might be needed to monitor active gene drives.

A second layer of monitoring could aim at detecting gene drives that have outcrossed in untargeted populations and species. For this task, sampling and molecular characterisation has to extend well beyond the target population and species.

Finally, monitoring has to be able to detect the effects on the environment that are caused intentionally and unintentionally by the gene drive and the GDOs. Those effects also have to be investigated, even if a gene drive has already vanished (due to failure or success). Hence monitoring will need to be complex and long-term.

Should a GDO be released (intentionally or unintentionally), early and efficient monitoring would be crucial, as risk management procedures are aggravated due to the intrinsic properties of gene drives, that is, the spread of a GM trait independent of time and space.

As there is a strong call for not releasing gene drives unless they can be reversed, recalled or overwritten, monitoring will also need to be able to assess the effectiveness of such counter-measures as well as to monitor for environmental impacts of these measures.

4 Conclusions

In this chapter we have addressed numerous points linked to the application of synthetic gene drives and their potential negative impacts. We have carefully explained why categorisation based on the different areas of intended application (agriculture, health etc.) and desired or claimed benefits, which so often is used as the starting point for introducing the topic of gene drives, is problematic and often misguided. We believe it must be stringently examined, and the possibility seriously considered that this technology may not be desirable, for either ecosystems or its stated purposes. Given the potentially severe and undeniable negative impacts that can arise from the release of gene drive organisms, we find it inappropriate to be guided by the excitement of technical advances or the lure of benefits only. We have noted that it is often the case that the underlying causes of the problems gene drives are intended to solve have actually been self-created by human practices and activities, or could be addressed by less problematic means; yet the necessary political or economic support has not been available. As we have illustrated in the case studies, modern agriculture is vulnerable to pests in large part because of the biological and genetic simplification involved in industrial agricultural practices, which also harm the natural predators of pests through pesticides and by limiting habitat. More diverse farming systems based on agroecology collectively present substantial defences against pests.

In our approach, we have thus placed the organism itself and the ecosystems linked to it centre stage. Understanding the full biology of an organism, including its genetic diversity, its mating behaviour, speed of dispersal, feeding patterns and sources, its place in the foodweb, its role in the ecosystem and its ecological value, are all essential for understanding the hazards, and for identifying the negative consequences that may arise from the release of a GDO. This also requires detailed knowledge of the respective ecosystems and their many complexities.

To illustrate and investigate this more closely, we have provided three case studies focusing on taxonomic categories, namely, mosquitoes, mice and Palmer amaranth, all of which highlight the lack of sufficient knowledge and understanding of the organism, its behaviour in the wild and its roles and functions in the ecosystems associated with it. Whilst the data are insufficient and the complexities too intricate to currently (if ever) allow for clear and reliable predictions of the outcomes and the impacts from a release of invasive gene drives, this is additionally confounded by the inability to identify and address various concerns. Such concerns are among others: how the wild populations will behave in response to the gene drive (e.g. altered mating behaviour, unintended behavioural effects due to the modifications); how the gene drive will behave at the molecular level within the wild populations and under real life conditions; whether the gene drive will fail to work, either at once or gradually, causing unpredictable population rebounds and changes; which genetic modifications will arise in response to the presence of active CRISPR/Cas9 elements in the genome; and how, in turn, to predict the consequences of these. We also discussed the possible spread of the engineered gene drives into closely related species, the consequences of which would additionally need to be addressed in any risk assessment.

Given the high level of unpredictabilities, the lack of knowledge and the potentially severe negative impacts on biodiversity and ecosystems, including agroecosystems, we recommend that there should be no intentional releases into the environment (including experimental releases) of GDOs; and that such releases should only be considered if and when it is demonstrated that there is full knowledge and understanding that allows for robust and reliable performance and risk assessments that can verify that no serious or irreversible negative impacts will arise as a consequence of the release of gene drives and also that there are no other, possibly safer options for dealing with the problem (and its underlying causes) that each drive is intended to solve.

This places the search for, development and support of other sustainable approaches high on the agenda. As shown for example in our agricultural case studies for Palmer amaranth (pigweed), systems-based, agroecological approaches have been shown to provide substantial control. Applying gene drive technology to Palmer amaranth, only recently considered a major pest due to industrial and especially herbicide practices which are largely linked to GMO crops, could put its useful and nutritious related species at risk. And in fact, Palmer amaranth itself has traits and food qualities that would be lost if it was driven to extinction. At present, CRISPR/Cas-based homing gene drives have not been shown to be viable for plants, due at least in part to the fact that the levels of homology directed repair in plants are too low for gene drives to spread. Therefore any potential use of gene drives in plants remains highly speculative at this point.

Similarly, insect pests are more of a threat in simplified industrial agroecosystems. Most of the current insect pests under consideration or mentioned as possible targets for gene drives are invasive. Invasive species may be less susceptible to control by natural pest enemies in the geographies where they have spread. But introduced biocontrol agents like parasitoid wasps to control such pests also depend on suitable habitat that may not be adequately provided in simplified industrial systems. This is yet another reason why more diverse agroecosystems are needed. Of course, it takes time to find and test new biocontrol agents and methods that often prove effective against established invasive insects over time. Therefore, these methods need time and investment to develop, rather than a precipitous resort to gene drives. In fact, gene drives themselves take time to develop and test for safety, and therefore have no obvious advantage in that respect. Furthermore, at this stage, gene drives in pest insects have not been shown to be reliable in the environment or safe for a variety of alarming possibilities, including spread throughout the species or even to other species.

It must also be emphasised that the history of risk assessment (as exemplified by herbicide resistant GMOs leading to extremely problematic resistant weeds like Palmer amaranth, harm to monarch butterflies, or neonicotinoid insecticide harm to non-target invertebrates), raises serious doubts about whether risk assessment authorities are equipped to adequately evaluate the risks of gene drives. In the case of neonicotinoids, several types of sub-lethal effects have caused widespread harm at the population level and at multiple trophic levels. These kinds of complex problems, even if different in specifics, will be difficult for risk assessment to evaluate in gene drives.

The case study on gene drive mice also revealed the unpredictability and limits of this technology. It highlights that even if gene drives were only ever used for eradications on islands, there would be serious risks from (stow-away) gene drive mice unintentionally ending up in and decimating mainland wild populations. It also showed that the deliberate use of a gene drive in mainland populations is likely, given that a major motivation for developing gene drive mice is the intention to eradicate pest populations that cause economic damage to crops, seed and feed. We pose the questions: Were it possible to make gene drives work reliably in small mammals, would they be seen as the next level of pest control, potentially going as far as wide-scale eradication? And, given the economic pressures involved, would it be possible to control the use of these tools against mice and other vertebrate 'pests'?

In considering mosquitoes, we draw attention to the complex web of relationships with other species, and potential of severe knock on effects to ecosystems of suppressing mosquito species. Also important is the very real possibility that gene drives will not achieve their intended results in terms of human health: the behaviour of synthetic gene drives in the wild is difficult to predict but population rebounds are one very plausible outcome; similarly the interaction of drives with the many evolutionary forces at play is extremely difficult to foresee. However, if gene drives do achieve population suppression, even temporarily, the ecological implications could be profound. The high level of uncertainties and unpredictabilities is further confounded by the multitude of scenarios arising from the wide spectrum of possible performance and behaviour of gene

drive technologies and gene drive mosquitoes in real life – also raising concerns regarding negative implications for human health. We further raise the question of how many species may eventually be targeted, as there are at least 160 known for being vectors of human diseases, and 40-70 of these transmit Malaria. Setting aside their individual roles and functions in the ecosystems, how much of the total mosquito biomass would these species represent in particular ecosystems? An important concern is that the vectors targeted by gene drives may be among the more abundant species in some contexts. Given the large numbers of mosquito species involved in human disease transmission, mosquito gene drives could eventually be employed against numerous species representing a significant proportion of the total mosquito population, escalating and broadening the likely ecological consequences, including negative impacts on species that depend on mosquitoes for food.

We have also covered the aspect of dual use, the use of gene drive technology for military and harmful purposes. This in particular needs urgent attention.

The range of organisms intended as gene drive targets is broad and continuously growing. As discussed, the intention is to make the technology widely applicable for small mammals and for a wide range of insects, which we regard as alarming, both as an approach to dealing with problems, as well as with regards to the impacts of such practices.

In conclusion: in terms of the science and current knowledge, we cannot see how to make the release of gene drive organisms safe, or even how to perform an adequate and robust risk assessment that would cover all the points we have raised and that we regard as essential to safeguard biodiversity as well as human health. For the present, the strict application of the Precautionary Principle might be our best guide in terms of this new and potent technology.

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for references for the tables and case studies see sections below

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Felis silvestris

Darekk2, using the IUCN Red List spatial data: IUCN (International Union for Conservation of Nature) 2015. Felis silvestris. In: IUCN 2015. The IUCN Red List of Threatened Species. Version 2015.2. http://www.iucnredlist.org. Downloaded on 01 September 2015. https://commons.wikimedia.org/wiki/File:Wild_Cat_Felis_silvestris_distribution_map.png

Mus musculus

Osado, (corresponds to IUCN Red List data though source not cited) https://commons.wikimedia.org/w/index.php?curid=9482429

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Rattus norvegicus,

Oknazevad, does not correspond well to IUCN data, source not cited https://upload.wikimedia.org/wikipedia/commons/archive/2/20/20190402152405%21Brown_rat_distribution.png

Rattus rattus

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Sturnus vulgaris

MPF using: Snow & Perrins BWP Concise, del Hoyo et al. Handbook of the Birds of the World 14: 724, and Harrison, Atlas of the Birds of the Western Palaearctic; introduced range, Sibley North American Bird Guide, Australia, South Africa https://commons.wikimedia.org/wiki/File:Sturnus_vulgaris_map.png

Trichosurus vulpecula,

Chermundy using the IUCN Red List spatial data: IUCN Red List of Threatened Species, species assessors and the authors of the spatial data. https://commons.wikimedia.org/wiki/File:Common_Brushtail_Possum_area.png

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Chermundy using UCN Red List spatial data - IUCN Red List of Threatened Species, species assessors and the authors of the spatial data https://commons.wikimedia.org/wiki/File:Stoat_area.png

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Chapter 3

Social issues

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1 Introduction

Gene drive organisms (GDOs) are a new biotechnological development that currently has no final product available to be assessed for its risks and benefits to society. In the first part of this chapter, we look at where investment in gene drive R&D is coming from, along with how conflicts of interest may arise. We examine the promises made about what products we can expect from this technology, especially in terms of claims about how they would benefit society and the economy. We also discuss how such promises influence public understanding of the technology and help to secure research funding. We then examine gene drive patent applications. In the second part of this chapter, we examine how issues such as consent and risk assessment have been tackled by existing projects using genetically modified (GM) mosquitoes (currently without gene drive, but with some plans to include it in the future) and discuss liability and the Precautionary Principle. Finally, we discuss what more meaningful public engagement about these issues would require.

2 Gene Drive science in context: science in society

Research and development of gene drive organisms (GDOs) is taking place in different social and economic contexts across the globe. For gene drive organisms (GDOs), the initial investment in R&D occurs mainly in rich economies (notably in the USA, Australia, the UK and some other European countries). In contrast, some of the first open releases of GDOs are planned in resource-poor countries, with the claim that they will tackle diseases of poverty such as malaria. For example, Beisel and Boëte note that the transfer of genetically modified (GM) mosquitoes from lab to field, potentially including GDOs in future, "also involves a transfer from North to South, from laboratories in high-tech knowledge economies to (often) resource-poor developing countries" (Beisel and Boëte 2013, 47).

In wealthy OECD countries, the idea of the knowledge-based economy[1] has become a key driver of research investment. The 'knowledge' embedded in a product is seen as adding value to it. Compared to physical goods, knowledge is less tangible and hence more difficult to value, trade and control. Thus, industries depending on knowledge want to pin it down and build walls around their own knowledge, in order to control and protect it from competitors. Intellectual property rights became these walls. They give value to this knowledge and allow it to be traded rather than freely used (Gold et al. 2008, 17).

With the general decline in public structural funding during the last decades, universities have experienced increasing pressure to diversify their

1 The term 'knowledge-based economy' (KBE) was first coined by the Organisation of Economic Co-operation and Development (OECD) in a 1996 report which argued that the OECD economies were increasingly based on knowledge, information and technological innovations, underpinned by scientific research and development and patents (OECD, 1996).

financial sources and to rely more on competitive funds (Geuna and Nesta 2006, 791). In theory, patents act as a reward for invention that is supposed to stimulate investment, creativity and economic growth. While originally inventions made with public funding in the USA belonged to the federal government, the adoption of the Bayh-Dole Act in 1980 made it possible for universities to own and commercialise publicly-funded, in-house inventions, and to license their intellectual property to private firms (see Section 6.1, Box 2) (Tofano, Wiechers, and Cook-Deegan 2006, 54). With this change in policy, which has since been copied elsewhere in the world, huge amounts of private capital have been invested in certain types of R&D. As a result, researchers started to think about commercial uses of their work and pressure to file patents rose, with some researchers even being bound by contract to tell their funders about any invention that could be patented and commercialised (Tofano, Wiechers, and Cook-Deegan 2006, 57).

In this context, it is not surprising that 'hype', or exaggerated promises about valuable future commercial applications and social benefits, started to appear in scientific research studies, in an effort to help secure research funding. Additional issues arising from this development relate to conflicts of interest and transparency; for example, ties to industry and the incentive to patent may be problematic for the independence and autonomy of researchers (Geuna and Nesta 2006, 796). Patent applications are often not declared in scientific papers (Mayer 2006). Scientists who are named as inventors on patents will in some cases have a direct financial interest in promoting the claims of 'industrial applicability' made in the patent. In other cases, the patent may not confer a direct financial reward, but defending the claims made in it may still be important for the scientist's career and future funding.

Biotechnology is an important part of this fundamental change to science. For example, Joly notes that the privatisation of agricultural research and development is related to economic policies and to reductionism in science, i.e. to "the promises associated with the biotechnology revolution, and specifically the 'molecularisation' of life sciences, which prompted major changes in research and development (from the experimental field to the research laboratory, increasingly disciplinary and reductionist research and development, concentration of research in a small number of institutions), and the patentability of life forms…" (Joly 2005, 619).

Commercial biotechnology emerged at the same time as the above-mentioned change to US and international patent policy (Tofano, Wiechers, and Cook-Deegan 2006, 54). Biotechnology became a business when the knowledge emerging from scientific research became classified as intellectual property (IP) that was valued and could be bought and sold (Pisano 2006). Many countries followed suit and brought their IP laws in line with those of the US, in order to benefit from the biotechnology boom (Gold et al. 2008). A watershed moment was when venture capitalists learned that IP could be bought and sold independently of the final product (Pisano 2006, 142). This has allowed hype around new technologies to influence both public and private R&D investments, and allowed money to be made from simple promises, even when useful final products are often not delivered and when there is no net benefit to society or the economy.

More recently, philanthropic donations have begun to play an increasing role in the research and development of new technologies, for example in the case of GM mosquitoes, including those with gene drive. Thus, Beisel and Boëte argue that "GM mosquitoes render the mosquitoes themselves as a commercial product; a commercial product in a political economy funded by philanthropic initiatives, shaped by private university spin-offs and characterized through economic inequalities" (Beisel and Boëte 2013, 54).

3 Funding for Gene Drive research and development

The biggest investments into gene drive research and development (R&D) come from the US military, large philanthropic donors and government-funded research agencies. In the following sections, we will look at who the main gene drive funders are, what they are funding and how this may be relevant for public engagement exercises.

3.1 Military and intelligence agencies

The U.S. Defence Advanced Research Projects Agency (DARPA) announced in 2017 that it will invest $65 million over four years in the 'Safe Genes' programme that funds seven major research projects focusing on gene drive and genome editing R&D. (DARPA 2017). The *Gene Drive Files*, a trove of documents and emails obtained by civil society investigators through a Freedom of Information request, reveal that the total amount DARPA invests into the 'Safe Genes' programme is $100 million, likely making them the largest single funder of gene drive R&D (Gene Drive Files 2017a, 1). One of the 'Safe Genes' projects, led by Keith Joung at the Massachusetts General Hospital, receives $11 million from DARPA, and part of the project funding goes to Target Malaria investigators, at Imperial College in London. The team at Imperial College for the first time achieved complete population suppression of caged mosquitoes using gene drives (Kyrou et al. 2018). That research was funded not just by DARPA, but by the Bill & Melinda Gates Foundation and the UK Biotechnology and Biological Sciences Research Council (BBSRC) as well (Kyrou et al. 2018, 1066).

Other military and intelligence organisations involved in gene drive R&D are the Intelligence Advanced Research Projects Activity (IARPA) and the US Army Corps of Engineers (ACE) (Gene Drive Files 2017b).

3.2 Philanthropic foundations

The Bill and Melinda Gates Foundation (BMGF), the largest philanthropic foundation in the world (Belluz 2015), has long had a leading role in funding GM mosquito research (Enserink 2010). Beisel and Boëte (2013, 47) note that: "Before the establishment of the Gates Foundation, research on genetic manipulation of insects was a small niche field…" They also highlight how one of the foundation's strategic aims now focuses explicitly on developing insect technologies, thus accelerating the development and testing of GM mosquitoes. BMGF provides the core funding, $75 million so far, for the Target Malaria project (Regalado 2016a). Target Malaria is a research consortium that aims to control the spread of malaria by releasing genetically modified gene drive mosquitoes. Target Malaria has progressed R&D on gene drive mosquitoes further than other groups and is currently operating in Burkina Faso, Mali and Uganda (Target Malaria n.d.a).

The Open Philanthropy Project (OPP), whose major funders are the couple Cari Tuna and Dustin Moskovitz (co-founder of Facebook and Asana), is another major philanthropic donor that has awarded an additional $17.5 million to Target Malaria (Dunning 2017). OPP has also awarded $1.2 million to the Foundation of the National Institutes of Health (FNIH) to form a working group of approximately twenty experts tasked with developing a consensus pathway for field-testing gene drive mosquitoes (Open Philanthropy Project 2016).

The FNIH itself is another key actor supporting the development of gene drives. In collaboration, again with the Bill and Melinda Gates Foundation, along with numerous research institutions around the world, the FNIH managed the *Vector-based Control of Transmission: Discovery Research (VCTR) programme* (Foundation for the National Institutes of Health n.d.). The VCTR programme supported Target Malaria's R&D on gene drive mosqui-

tos (see for example Eckhoff et al. 2017, E264 and Hammond et al. 2016, 82).

In addition to the funding from such philanthropic organisations, Target Malaria has also received direct governmental funding from the European Commission, the UK Department of Environment, Food and Rural Affairs (DEFRA) and the Ugandan Ministry of Health (Target Malaria n.d.b).

Tata Trusts are among the top philanthropic organisations in India and have awarded $70 million to create the Tata Institute for Active Genetics and Society (TIAGS), in collaboration with the University of California, San Diego (UCSD). UCSD announced they would match the trust's award with a further $70 million. The institute aims to develop mosquitoes that are unable to propagate malarial parasites using gene drives (Philanthropy News Digest 2016).

Other philanthropic organisations that fund gene drive R&D include, among others, the Wellcome Trust (UK), the Burroughs Wellcome Fund (US), the Rainwater Foundation (US), the Greenwall Foundation (US), the Alfred P Sloan Foundation (US), the WM Keck Foundation (US), the Kinship Foundation (US), the Pew Charitable Trusts (US), the David and Lucile Packard Foundation (US) and the Paul G. Allen Frontiers Group (US) (Esvelt 2018a, 8; Gantz et al. 2015, E6742; Grunwald et al. 2019, 109; Sculpting Evolution n.d.a; Target Malaria n.d.b).

3.3 Governmental science and research agencies

The Australian Commonwealth Scientific and Industrial Research Organisation (CSIRO) is a partner in the DARPA-funded 'Safe Genes' project that aims to develop and test a mammalian gene drive system in rodents (Godwin 2017). According to the *Sydney Morning Herald*, CSIRO has allocated $3.5 million for "community research related to synthetic biology" to secure "social licence" for its gene drive ambitions (Wilson 2018). The goal of this social engagement seems be securing social acceptance, rather than fostering true democratic decision-making (see Section 10). According to an email obtained by a Freedom of Information request, CSIRO has also been promoting the rodent gene drive technology to various government agencies and other stakeholders (Wilson 2018).

Furthermore, the UK Biotechnology and Biological Sciences Research Council (BBSRC) is funding mouse and rat gene drive research at the Roslin Institute at the University of Edinburgh as well as mosquito gene drive research at Imperial College (BBSRC 2017; Kyrou et al. 2018, 1066).

The US National Institutes of Health (NIH) awarded $1.5 million to Kevin Esvelt for the development of 'daisy' gene drives (National Institutes of Health 2017; Sculpting Evolution n.d.a). With support from DARPA and the Bill & Melinda Gates Foundation, NIH and FNIH sponsored the National Academies of Sciences, Engineering, and Medicine (NASEM) gene drive report "Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values" (2016), that intended to "…create a consensus committee to summarize current understanding of the scientific discoveries related to gene drives and their accompanying ethical, legal, and social implications" (National Academies of Sciences, Engineering, and Medicine [NASEM] 2016, viii & 1). NIH further support Target Malaria (Target Malaria n.d.b) and various gene drive studies (see for example DiCarlo et al. 2015, 12; Gantz et al. 2015, E6742; Gantz and Bier 2015, 444; Grunwald et al. 2019, 109).

Other governmental science and research agencies involved in gene drive funding include the Uganda National Council for Science and Technology (UNCST) (Target Malaria n.d.b) and the National Science Foundation (NSC) (see for example DiCarlo et al. 2015, 12; Dhole et al. 2017, 806; Min et al. 2018, S60).

3.4 Guiding principles for the sponsors and supporters of Gene Drive research

As a response to the US National Academies of Science, Engineering and Medicine Report that provided recommendations directed at researchers,

funders and policy-makers (NASEM 2016, 106, 128, 142, 170-172, 177-178), Emerson et al. (2017, 1136) published five guiding principles for sponsors and supporters of gene drive research:

1.) advance quality science to promote the public good;

2.) promote stewardship, safety and good governance;

3.) demonstrate transparency and accountability;

4.) engage thoughtfully with affected communities, stakeholders and publics;

5.) foster opportunities to strengthen capacity and education.

These guiding principles have been endorsed by prominent gene drive funders, including the Bill & Melinda Gates Foundation, Tata Trusts and the US FNIH. Such a pledge to ensure safe and responsible gene drive research is laudable; but can we conclude that further development of the technology will always follow these guidelines and be in the best public interest? Boëte (2018) argues that the list of Guiding Principles is a "voluntary undertaken code of ethical and scientific conduct" (Boëte 2018, 18), which is not legally binding. This means that the signatories cannot be held accountable for actions that do not honour the code.

While governmental funding is, at least formally, accountable to the public, philanthropy is still largely free from public accountability mechanisms and democratic control. The Bill and Melinda Gates Foundation, for example, is only accountable to its three main trustees, that is, Bill and Melinda Gates, alongside Warren Buffet. Although philanthropic and charitable organisations, by definition, aim to serve the public interest, foundation trustees are the ones to decide a.) what the public interest is (e.g. global health), b.) what a problem is (e.g. malaria), and c.) how they want to fix it (e.g. with gene drives) (Barkan 2013).

Today, more and more funders have preconceived notions about social problems and their solutions. In an approach called "strategic philanthropy", they develop specific policy or outcome agendas to be fulfilled by their grantees; thereafter, the grantees seem to take on the role of contractors (Rourke 2014, 2). Academic experts have questioned the Bill and Melinda Gates Foundation's global health research priorities. Some in particular critique the emphasis on technology and technological fixes (Belluz 2015). The growing influence wealthy philanthropic organisations, such as the Bill and Melinda Gates Foundation, have on funding for global health (Belluz 2015) and the lack of real public accountability, raises the question of whether, and how, the public can be truly involved in the discourse on gene drive R&D.

As the *Gene Drive Files* have revealed, the principle on transparency, which is key to the guiding principles, has already been violated by important signatories. They have been officially named as having engaged in coordinated "closed door" efforts to influence UN agencies' support of gene drives, and also in avoiding media engagement (Boëte 2018; Gene Drive Files 2017c). This gives the impression that instead of genuine stakeholder engagement, which could theoretically result in the rejection of the gene drive approach, the aim of these signatories is simply to gain acceptance for their agenda.

Another issue is that DARPA, as probably the largest funder of gene drive R&D, is missing from the list of signatories. There seems little interest on the part of DARPA to engage thoughtfully with stakeholders and the public in discourse on gene drive R&D. At the first public meeting of the Committee on Gene Drive Research in Non-Human Organisms, Col. Daniel Wattendorf stated: "…we may not have the time in this case to actually wait for, and make calls for, certain scientific actions and communities to deliberate. We actually may need to be working on technology solutions right now. And the alacrity of our [DARPA] institution to be able to do that is at hand" (Wattendorf 2015).

Lastly, while the five guiding principles could become very important for responsible R&D, they currently do not allow for discussion about how a problem should be tackled and what research is

being done in the first place. As we discuss under consideration of the Precautionary Principle (PP) later (Section 8), and as the European Environment Agency has noted, thorough practice of the PP would always include inter alia assessment of what may be the multiple alternative trajectories which could meet the same social goals and needs as the prevailing trajectory. Thus, even a thorough enactment of the five guiding principles would fail to meet the internationally established Precautionary Principle requirements.

4 Conflicts of interest in science

Conflicts of interest may play a major role in what is communicated about a technology, what research is conducted, and how the results of scientific studies are communicated and used in practical investment and regulatory decisions.

It is well established that commercial conflicts of interest in science can jeopardise the independence of research. The discussions in this area have focused on the field of medicine, where compromises have repeatedly occurred in research participants' well-being, research initiatives, publication of results, interpretation of research data, and scientific advancement, all because of industry funding for research (Tereskerz et al. 2009). Industry funding can also skew the research agenda, with major implications for what kind of research gets funded and how this is communicated and used (Wallace 2009). Adverse effects, among many others, may include biasing the research and associated policy agendas towards false or ineffective solutions to a problem, potentially leading to major negative impacts on public health (Wallace 2009; Kearns 2016).

Conflicts of interest are not limited to scientists working in the commercial sector. Krimsky (2003) describes how university science is now entangled with entrepreneurship, and investigates the effects of modern, commercialised academic science. Vallas and Kleinman describe how "the structural reconfiguration of academic science generates an increasing tension between the 'ideal' culture of academic science and the 'real' culture of market-oriented logics governing the pursuit of capital in one or another form" (Vallas and Kleinman 2008, 306). Patents held by academic scientists are also a recognised source of conflicts of interest (Mayer 2006). In relation to GDOs, Brossard et al. note that "relevant conflicts of interest can go beyond the financial ones and can include how the topic at hand relates to our worldviews, the success of our next grant proposal, or the positive views of our administrators and colleagues" (Brossard et al. 2019, 5).

In addition, bias is not limited to commercial interests. Scientific bias has been well studied in the medical research literature, where several types of interpretative bias (bias in the analysis of data, rather than in the measurements themselves) have been identified (Kaptchuk 2003). These also include "confirmation bias" – evaluating evidence that supports the scientist's preconceptions differently from any evidence that challenges these convictions (Kaptchuk 2003, 1454).

A major problem is scientists 'over-promising' in order to secure research funding, which is now almost routine (Gannon 2007). Hype and 'over-promising' are discussed further below. Other impacts of conflicts of interest in GM insect research are discussed further in Section 7.

5 The role of hype in the Gene Drive discussion

5.1 The role of hype in securing research funding (for Gene Drive research)

Hyperbole or "hype", in terms of scientific research, means "extravagant or exaggerated promotion" of whatever one protagonist is attempting to sell to another. Promises about future benefits play an important role in securing (competitive) investments in R&D. In some cases, the grant being sought is corporate or venture capital investment, underpinned by intellectual property (IP). In other cases, funding for research, whether academic or private, may be coming from governments, philanthropic organisations or a combination of the above.

Writing more than a decade ago, Gannon (2007) argues that "hype" in science is spreading for several reasons, including: the increasing pressure on institutions and researchers to secure funding from diverse sources; the requirement that scientists explain the relevance of their work to the general public; and the fact that many grant applications require the applicant to explain the impact of their work on society. Scientists are in a fierce competition to maintain and increase public as well as private support and funding, and therefore, "…scientists over-promise by sending messages of being close to their goals, even if this is not true" (Gannon 2007, 1087). Gannon notes that the promise that a cure is just around the corner, if only a few million more in funding is forthcoming, more often than not is an exaggeration. However, when it comes to scientific publications and grant applications, reviewers do not usually comment on the credibility of the claims made for future benefits that might arise from the research. Furthermore, they do not ask for the same level of proof for these speculations as they do, for example, for speculations on a step in scientific methods. This has led to overstretched expectations of what science and technology can achieve, both among the public and among funders.

Future releases of GDOs have been claimed to bring tremendous benefits to society, for example the end of malaria or Lyme disease. Even though R&D is still in its infancy and far from any field trials, gene drive researchers have informed potential philanthropic funders that "gene drive research has the potential to make enormous positive impacts on global human health" (Darrow et al. 2016, 3). Whilst this recommendation comes with extensive caveats about the need to also fund "gene drive safety and control", little doubt is expressed about the ability of open releases of GDOs soon being able to play a major future role in tackling serious infectious diseases. In some academic journals, in contrast, numerous doubts are expressed about the potential of GDOs to deliver on any of these promises.

One issue is the likely evolution of resistance to the introduced trait. For example, Brossard et al. note that most of the public discussions of gene drives relate to one type of gene drive, where the release of a small number of individuals could, in theory, cause the spread of the gene drive through entire populations of the engineered species worldwide. They state that "It is important to recognize that this is only one type of gene drive and that it will be very difficult to develop such a gene drive to function indefinitely without pests evolving resistance to it" (Brossard 2019, 2). They also note that an alternative approach involves the use of a GDO which produces many unviable offspring; but this would theoretically require enough individuals to be released so that the engineered individuals are initially more than 25% of the total population. In practice, there might be significant practical difficulties in achieving this, in addition to the complexities of how ecosystems might respond.

In relation to GM mosquitoes, including those incorporating gene drive mechanisms, Beisel and Boëte ask "How might a control strategy that is embodied in the mosquito genome play out in the

face of ecological complexity, adaptability and resistance? Which risks might the strategy entail and how are risks and benefits distributed?" (Beisel and Boëte 2013, 40). They also raise the question of "how to think about biological adaptability of GM mosquitoes in relation to the coexistence of mosquitoes, parasites and humans over time?" (Beisel and Boëte 2013, 42). The same authors also note that the basic relationship between the density of mosquitoes, human infection and disease is poorly understood. More than 450 species of *Anopheles* mosquitoes are known worldwide; around 70 are malaria vectors (of which 41 are thought to be dominant vector species or species complexes), and the rapid reproduction and evolution of mosquito populations makes them dynamic and adaptable (Beisel and Boëte 2013, 46; Sinka et al. 2012, 1). Moreover, new species continue to be identified with the aid of molecular techniques (Coetzee et al. 2013). Hybridisation occurs between major vector species, with hybrids typically occurring at rates of about 1% in most areas, but up to 24% in others, for reasons that are not fully understood (Lee et al. 2013; Mancini et al. 2015). This poses a risk of gene flow between species, if gene drive *Anopheles* mosquitoes were to be released. However, the fact that hybridisation is limited also implies that releasing one species of gene drive mosquito is unlikely to suppress the population of another species, which may therefore expand its range and continue to transmit malaria. This multi-species challenge is rarely discussed in public.

5.2 The role of hype in framing the public discourse

Public support is a very important factor contributing to the success of a technology and its capacity to become economically viable (Esvelt 2018a, 5). Since the 1990s, when there were major concerns amongst policy, commercial and scientific elites about indiscriminate public mistrust in science, cultivation of public acceptance of science-based innovation of almost any kind has become a policy and industrial mantra. For example, the perceived worth and benefit of potential applications have always played an important role in public acceptance of biotechnology. "The relatively low levels of public support for a variety of gene transfers change dramatically when a gene transfer is tied to achieving a specific goal that is deemed worthy" (Amin et al. 2007, 42).

Media, including scientific media, often overemphasise the potential future benefits of any given technology while downplaying the risks. While the media's desire to tell an interesting story may be partially responsible for reporting exaggerated promises, journalists are not always the source of such exaggerated claims. Bubela and Caulfield (2004, 1399) found that the majority of 627 analysed newspaper articles accurately reflected the claims made in scientific and medical journals. Although media sources can be at fault as well, pressure by industry and funding entities may lead researchers to make claims about future benefits of gene drives in order to secure research funding. Picked up by media journalists, these claims may then also frame public understanding of the technology and what it might do long before it is ready to be applied. In the end, it is important to note that researchers, media and industry all play a role in framing the public discourse of gene drives.

In the following sections, we will have a closer look at some examples of exaggerated and overly optimistic promises made about this technology in newspaper articles, as well as in scientific journal articles and patent applications; and we will discuss how erroneous descriptions and perceptions contribute to framing the public discourse.

5.2.1 Headlines

Headlines are a source of information for the many people who do not have the time to read full articles. Of course, headlines tend to exaggerate and use catch-phrases in order to gain the reader's attention. Gene drive-related headlines often include exaggerated and sometimes quite unsubstantiated promises, for example making claims about being able to offer public health or conservation benefits:

- The CRISPR machines that can wipe out entire species (Ryan 2019).

- Argument builds around a genetic tool that can erase an annoying species (Meador 2016).

- Genetically modifying Zika virus out of existence (Flam 2016).

- Powerful 'Gene Drive' Can Quickly Change an Entire Species (Stein 2015).

Since to date no open releases of gene drive organisms have taken place (nor are such releases planned), it is too early to say what GDOs "can" do, or that they will be able to predictably wipe out a species. The gene drive research currently being done is lab and modelling work. As Oxitec's failed open release experiments with GM mosquitoes in the Cayman Islands have shown (GeneWatch UK 2018), results from the lab or models can be insufficient predictors what will happen in the field. However, much confidence was invested by the scientists in those partial methods. Using a headline that strongly implies what the technology can do once ready to be applied may be less of an informative description and more of a mechanism for influencing public understanding of the technology.

5.2.2 Terminology

In a subtler way, the language and terms used to describe gene drives can themselves convey promises which influence how the technology is perceived. Different terms are being used to portray what gene drives are supposed to be able to do: *modification drive, suppression drive, sensitising drive, global drive, local drive or daisy chain gene drive, reverse drive or daisy restoration drives*, etc. Some of these terms, especially "local drive" or "reverse drive", intentionally convey a promise of safety, containment, control, reversibility and redress, even though none of these concepts has ever been proven. Kevin Esvelt has often publicly stated that he opposes closed-door science and that gene drive research must be open and transparent (see for example Esvelt 2016; 2018b). Therefore, he wants to inform the public about the experiments his research group is planning to do before they are actually conducted. As a result, before actually successfully developing them, Esvelt's 'Sculpting Evolution' research group has presented its concept of so-called 'daisy chain gene drives' and what different versions could do. By doing so, they helped to establish many of the above-named terms, although all are hypothetical. Not only do we not know whether these theoretical concepts will behave as intended and promised in the field, they have not even been demonstrated in a lab.

Nevertheless, many speculations have already been made, for example: that the daisy drive system will "return power to the hands of local communities" (Sculpting Evolution n.d.b), who, once (and if) it is operational, will be able to decide whether or not to use gene drives to solve local ecological problems; or that they could be used to restore a population to its original genetic state (Sculpting Evolution n.d.c). While these researchers find it problematic to release GDOs that are designed to "spread indefinitely" (Sculpting Evolution n.d.b.), they see no problem in releasing daisy drives, which are intended to have a limit to their spread. In their patent application on daisy chain gene drives (see Section 6.2) they promise: "Daisy chain gene drives designed using methods provided herein can be used to address otherwise intractable ecological problems, with a level of safety inherent in their design, that reduces or eliminates a likelihood of global effects as occurs for conventional gene drive organisms that are released into the wild", and: "Unlike previous global gene drive system, methods of the invention provide designs for daisy chain gene drives that can be safely tested in field trials" (Esvelt, Min, and Noble 2017, 55-56).

A side-effect of this supposed open and transparent approach to research is that a.) promises about future benefits of a hypothetical, untested concept are made very early in development; b.) the language and terms conveying these promises, as if they were already-proven reality, are already established in society well before a technology actually exists.

5.2.3 Application promises

As discussed above, a specific goal or application perceived perhaps as dangerous but also as *worthy*, for example in saving human lives, can increase public support for that technology. Therefore, it is important to show the public how they personally, or the world as a whole, can directly benefit from this technology: "Although many questions about this technology remain unanswered, we are optimistic about the potential of gene drives in strengthening the public health arsenal and reducing worldwide human suffering" (Darrow et al. 2016, 2).

Although any form of gene drive technology is far from being tested in the field and further yet from its promises of beneficial applications becoming reality, a lot of emphasis has already been placed on future beneficial applications being delivered once the technology is made available. For example, the following quotes paint an overoptimistic picture of the potential health, environmental and agricultural applications of gene drives: "The ability to edit populations of sexual species would offer substantial benefits to humanity and the environment. For example, RNA-guided gene drives could potentially prevent the spread of disease, support agriculture by reversing pesticide and herbicide resistance in insects and weeds, and control damaging invasive species" (Esvelt et al. 2014, 1); "...it could be used to conserve threatened or endangered species, combat invasive species, or control agricultural pests. It is particularly tantalizing as a potential weapon against vector-borne infectious disease" (Abbasi 2016, 483); "Effective gene drives may enable us to control invasive species, re-sensitize organisms that have developed resistance to insecticides and herbicides, and reduce or eliminate many types of vector-borne diseases, all at a low cost" (Champer, Buchman, and Akbari 2016, 147).

As the examples above show, three areas of applications of gene drives are most prominent: public health, conservation and agricultural applications, with hoped-for eradication of vector-borne diseases currently being the most commonly hyped potential application of gene drives. In addition to these direct benefits promises about the results of gene drive R&D, it is sometimes argued that the gene drive approach might actually be the more sustainable alternative for other already applied technical solutions, for example by decreasing the numbers of GM mosquito releases: "To date, trials [with GM mosquitoes] have used a self-limiting approach, requiring repeated mass release of GM males. But a self-sustaining control would be possible using a gene drive system, eliminating the need for ongoing releases..." (Piaggio et al. 2017, 102); or by decreasing the use of toxic pesticides: "For example, a gene drive to suppress non-native rodent populations on remote islands could reduce the need for alternative forms of control such as the use of rodenticides. The cost of administering rodenticides is estimated to be in the millions of dollars and rodenticides may also harm non-target species" (NASEM 2016, 5). Not mentioned is the question of whether gene drives will work in mammals at all, and what practical and social implications the release of gene drive rodents on these islands might have: for example, how many GDOs would have to be released to efficiently control the island population, how long would that take and what damage could the GDOs cause in the meantime?

Furthermore, it has even been argued that Gene Drives "could make the world a more just place", thereby adding a moral, ethical component. According to the MIT technology review, Esvelt considers evolution a blind, amoral process, whose only goal is to survive, comparing it to a "larger failing of the universe". This should be rectified with gene drives and the ability of experts like himself to "fine-tune the battle for survival" (Regalado, 2016b). This shows the immense confidence of some gene drive researchers that they are not only able to alter organisms and eventually populations, but the evolutionary process itself. Fittingly, Esvelt called his research group at the MIT media lab in Massachusetts "*Sculpting Evolution*".

Below we will take a closer look at the specific promises made in these three sectors.

Public health promises

Where biotechnology is concerned, human medical and health applications are generally better accepted by the public than are agricultural applications (Amin et al. 2007, 40). In the gene drive discourse, a great deal of emphasis is being put on potential public health benefits. The most common promise is that gene drives, once applied, will have the potential to eradicate vector-borne diseases such as malaria, dengue fever or Zika, either by suppression of the vector population or by rendering the vector population resistant to the parasite, virus or bacteria. This is illustrated with the following quotes: "With gene drives, it may be possible to kill off a mosquito population or make the population resistant to malaria parasites" (Wade 2015a); "Gene Drive mosquitoes have tremendous potential to help eliminate malaria, and multiple gene drive approaches have recently shown promise in laboratory settings" (Eckhoff et al. 2016, E255); "These findings could expedite the development of gene drives to suppress mosquito populations to levels that do not support malaria transmission" (Hammond et al. 2016, 78); "In the U.S., scientists are racing to develop similar genetic suicide vests for mosquitoes that spread Zika and dengue fever" (Regalado 2016b).

When gene drives are proposed as potential solutions for public health concerns, the proponents build their narrative by citing the large numbers of people suffering and dying each year from specific illnesses: "Malaria alone kills over 650,000[2] people each year, most of them children, while afflicting 200 million more with debilitating fevers that economically devastate their societies. Dengue, yellow fever, trypanosomiasis, leishmaniasis, Chagas disease, and Lyme disease are caused by other pathogens that spread using vectors. All of these can potentially be reduced or even eliminated by driving changes in the vector that prevent transmission" (Esvelt and Smidler 2015, 28-29); "A large region, at least in principle, could be freed from malaria, which kills almost 600,000 people a year" (Wade 2015b).

Sometimes the promises are highly specific and ambitious: "Such genes, if successfully propelled throughout a wild mosquito population, would render a region free of the malarial parasite, which could no longer spread via mosquito bites" (Wade 2015a); "the inserted genes are expected to *spread rapidly and take over a wild population in as few as 10 generations, or a single season*" (Wade 2015b, emphasis added). Another, equally optimistic one states: "Although all vector species must be targeted in a given area in order to stop transmission, the disease will be permanently eradicated if the newly vacated ecological niches are filled by competing non-vector species. Significantly, this strategy requires little or no understanding of the vector's molecular biology, but *unavoidably entails the local or possibly global extinction of the vector species*" (Esvelt and Smidler 2015, 29, emphasis added).

Such statements convey the impression that once this technology is applied, it will work predictably, as intended, and also that it will work rapidly, thereby being a sensible or the only solution to combat vector-borne diseases. Missing are all the varied caveats about what might go wrong if the technology doesn't work as intended; for example, when the mosquitoes develop resistance to the gene drive. Anyone conversant with biology knows that there is no guarantee that the vacated ecological niche will be filled with a non-vector species, as Esvelt and Smidler (2015) suggest, and not by another mosquito species (Wilke et al. 2018, 5-7). Furthermore, potential ecological problems arising if an ecological niche is filled with a species that previously played a minor role in that particular ecosystem are not brought up. In the case of genetically modified Bt crops, we have seen that reducing the numbers of a specific pest in an area often leads to the establishment of secondary pests that may be just as destructive (Lu et al. 2010; Wang et al. 2008; Wu et al. 2002; Zhao 2011). In the case of mosquitoes which transmit dengue, the former Chief Scientific Officer of GM insect company Oxitec, Luke Alphey, has stated: "Since *Ae. aegypti* and *Aedes albopictus* are known to compete…it is possible that the successful implementation of…gene drives could lead

2 The World Health Organisation's World Malaria Report 2018 speaks of 435,000 deaths in 2017.

an existing *Ae. aegypti* population to be displaced by *Ae. albopictus* where it would not otherwise have been. This would likely hamper efforts to eliminate viruses such as dengue since *Ae. albopictus* are also competent vectors…" (Edgington & Alphey 2018, 21-22).

Conservation promises

It is often promised that synthetic biology and especially gene drives could make a significant contribution to conservation efforts. In 2017, Piaggio et al. published a paper called "Is it Time for Synthetic Biodiversity Conservation?" in which they claim that synthetic biology might be the long-desired solution for many conservation problems. They state: "The field of synthetic biology, which is capable of altering natural genomes with extremely precise editing, might offer the potential to resolve some intractable conservation problems…", adding: "It has become apparent that synthetic biology holds tremendous potential across numerous fields, including conservation biology" (Piaggio et al. 2017, 97).

One promise often mentioned is that gene drives could help control invasive alien species, such as rodents on islands, resulting in protection for the endangered species threatened by them. Although this is highly theoretical and far from any experimental validation, gene drives are already being treated by some science reporters and gene drive researchers as known working tools in the conservation toolbox: "What's more, the technology also offers a new way to delete invasive species from islands like Hawaii, something that could rescue native birds at the edge of extinction" (Regalado 2016b). As seen above with promises about public health, proposals to use gene drives as solutions often portray the severity of the situation and then propose gene drives as potential technical fixes, without appropriate time or research going into whether they will work as intended, what could go wrong on the ground, how we would deal with that and especially, what the alternatives are: "One of the most environmentally damaging consequences of global economic activity is the transport of invasive species, which often causes ecological disruption and the extinction of native species. Isolated ecosystems such as those on small islands are especially vulnerable. Cas9 Y-drives have tremendous potential to promote biodiversity by controlling or even eradicating these species from individual islands or possibly entire continents" (Esvelt and Smidler 2015, 29).

Another promise is that gene drives could immunise endangered species, such as amphibians, against pathogens: "Although not yet developed, other payload genes of great practical importance may immunize threatened or agriculturally important organisms against pathogens, such as…genes that render amphibians immune to the killer Chytrid fungus, which is responsible for the decline of amphibian species all over the world" (Champer, Buchman, and Akbari 2016, 147) or "Such RNA guided Cas9 gene drives may be used to quickly spread protective alleles through threatened or soon-to-be-threatened species such as amphibians" (Esvelt and Smidler 2015, 28).

The extremely speculative nature of such statements is rarely highlighted, and readers (the public and the funding bodies) are likely to infer the scientists' excitement and confidence reflects imminent breakthroughs, rather than what is more likely, a desire for public approval and further funding. Statements about the practical implementation of these approaches are mostly lacking. Grunwald et al. (2019), for example, indicate that there might be additional technical hurdles to develop efficient gene drives in mammals, compared to insects, stating "… it appears that both the optimism and concerns [that gene drives could be used to reduce invasive rodent populations] are likely to be premature" (Grunwald et al. 2019, 108). Moreover, alternative methods to control invasive species that are, or with better understanding, could be available to society, may be equally cost-effective and much more within the realm of predictability and control than these as yet non-existent technical fixes. But this basic dimension of responsible democratic social appraisal and choice seems largely ignored. Gene drives are portrayed as an added or even only possible solution to different conservational issues in the above mentioned statements, although many of the species mentioned have never even been tested in the lab.

Agricultural promises

Gene drive patent applications also include many potential agricultural applications. In his 2003 patent application, Burt already stipulated that gene drives could be used to control pest populations or to render pest and weeds that have developed resistances to certain pesticides susceptible again, stating: "The method may also be used to interrupt other, non-lethal genes, e.g. a gene that confers a pesticide resistance onto a crop, thus making the pest susceptible to the pesticide again" (Burt 2003, 31). Nevertheless, agricultural applications, such as gene-drive mediated pest control, are less widely discussed in the media than potential health or conservation related applications (Courtier-Orgogozo et al. 2017, 878). As stated above, human medical and health applications are generally better accepted by the public than agricultural biotech applications. Potential agricultural applications being mentioned – mostly gene drive-mediated pest control, or the reversal of pesticide resistance, using so-called "sensitising drives"- are portrayed as sensible or sustainable solutions to current agricultural problems: "Additionally, the versatility of RNA-guided endonucleases may allow for other suppression approaches, such as the reversal of resistance to pesticides or herbicides by specifically targeting resistance alleles and replacing them with sensitive ones — a process that could be repeated if resistance is reacquired" (Champer, Buchman, and Akbari 2016, 147), or: "Compared to other pest management techniques, it [gene drive-mediated pest control] is cheaper, more precise, and, so far, less controversial as, say, the use of pesticides", adding that gene drive-mediated pest control may "easily eradicate a species" (Courtier-Orgogozo et al. 2017, 878). However, these are still approaches within the prevalent industrial agricultural system, likely to be attractive to major agrochemical companies (further discussed in Section 6.2). Moreover, gene drives so far have not been tested and might not work in plants. For example, the cell repair mechanism predominant in plants[3] might prevent the gene drive element to be copied to the damaged chromosome (see Chapter 1 for more details). As for other GDOs, ecosystem responses may also be complex and unpredictable.

5.3 Implications of hype for alternatives

Hype about new technologies can undermine existing or more practicable alternatives, by diverting resources from promising approaches. For example, Beisel and Boëte note that "beyond the question of whether or not GM mosquitoes can work, we should be asking what other kinds of techniques they replace or marginalize by directing resources away. As a tool of transfer and an instrument of eradication, they entangle malaria in institutional and economic calculations—between companies, philanthrocapitalist endeavours, macroeconomic models and global health agendas. At the same time, GM mosquitoes disentangle malaria from more local forms of control—the low-tech labour-intensive forms of management that belong to place" (Beisel and Boëte 2013, 47).

However, the body organising public engagement in new technologies is often the same one that has developed and/or invested in the technological fix being promoted. As such, it does not have proper incentives to explore alternatives as part of any public engagement exercise. Although alternatives are often mentioned, this is usually in a way which highlights their limitations and diminishes or dismisses the role that they can play. In the agricultural GM crops domain, Vanloqueren and Baret (2009) have explained in detail how this anti-scientific lock-in to a particular technology occurs, and how it correspondingly locks out what may well be more sustainable, more ethical, and more acceptable, alternative technical, scientific and social trajectories.

For example, for dengue control, the GM mosquito company Oxitec restricts discussion of alternatives to GM mosquitoes to the use of larvicides and adult spraying, with most focus on adult spraying (which is widely recognised to be ineffective), although they do mention wearing a long-sleeved shirt and using mosquito repellent (Parry 2012).

3 Called Non-Homologuous End Joining (NHEJ)

They do not discuss existing methods of control, such as destruction of breeding sites by government-employed inspectors or local communities; or social and environmental measures, such as improving water and sewage systems and shredding waste tyres (which provide potential breeding sites). Absence of a tap water supply is correlated with an increased incidence of dengue, because water storage containers used by households without tap water supply provide mosquito breeding sites (Schmidt 2011, 6), and the presence of a good primary health care system can significantly reduce the incidence of dengue (Roriz-Cruz et al. 2010). World Health Organization research has also focused on utilising new non-insecticidal intervention tools (such as rectangular water container covers in India, sweeping nets or dragon fly nymphs in Myanmar, and copepods and screen covers for earthen jars in Thailand), and on engaging local communities in these methods (TDR 2013).

Reis de Castro and Hendrickx (2013, 121) use the concept of 'ordinary treasure' to describe how releases of Oxitec's GM mosquitoes in Brazil were characterised as both ordinary (and hence unproblematic) on the one hand, and as valuable treasures (embedding hopes and expectations of tackling disease). Reis de Castro and Hendrickx (2013, 123-124) describe a 'rhetoric of hope', in which arguments about the possible negative effects of releasing GM mosquitoes in Brazil are perceived as a threat to the economy, and moreover, in the case of new technologies designed to tackle disease, as equivalent to not caring for people who are suffering. Reis de Castro and Hendrickx note (2013, 123) how the GM insect technique "follows a deep-rooted logic that focuses on the mosquito, rather than analyzing and improving social conditions, health care or medical interventions" and conclude (2013, 124) that "In this sense, the case of the transgenic mosquitoes in Brazil evidences a technological fix that proposes to overcome not only a problem in the individual attitude [to mosquito control] or the government's actions, but an entire deficient infrastructure". This analysis raises questions about the wisdom of spending time and money on unproven technology, rather than fixing the social structures that caused the problems in the first place.

The same rhetoric is now evident in claims about GDOs, including the potential use of gene drive in mosquitoes to tackle diseases such as malaria, as detailed above.

Failure to properly include alternatives can lead to significant opportunity costs, especially if large sums of money - and other resources, as well as time - are wasted on unrealistic future promises rather than implementing existing interventions effectively and conducting more cost-effective, diverse, and appropriate R&D. For example, Beisel and Boëte argue that "Funding silver bullet solutions such as GM mosquitoes diverts resources away from more low-cost and local measures in malaria control like mosquito nets, larviciding, or increasing health systems capacities in order to improve access to malaria treatment" (Beisel and Boëte 2013, 54).

5.4 Implications of hype in current public engagement exercises

There are no current open releases of gene drive organisms. However, there have been open releases of genetically modified (GM) insects on an experimental scale, conducted by the commercial company Oxitec, which is now owned by the US company Intrexon (Intrexon n.d.). In Burkina Faso, the research consortium Target Malaria aims to begin experimental open releases of GM mosquitoes over the next year, with a view to beginning open releases of gene drive mosquitoes in five to ten years' time. In the US, MIT researchers are proposing releasing hundreds of thousands of GM mice into the environment of Nantucket Island. This project is also seen as a possible step towards releasing gene drive mice in the future: however, the researchers say they do not intend to build gene drives in this organism until field trials of non-drive mice are completed and local communities request a drive system (Esvelt n.d.). Genetic Biocontrol of Invasive Rodents (GBIRd) is another research consortium, focused on developing gene drive organisms in rodents, with a view to releasing them into the environment to attempt to eradicate pests (GBIRd n.d.).

Since no GDOs have yet been released into the environment, it is worth examining some of the proposals to release GM insects – which have taken place, or are imminent – in order to compare the rhetoric of the relevant institutions with what happens in reality. This is particularly important in the case of Target Malaria, which plans to release GM mosquitoes in the next year, followed by gene drive mosquitoes in 5 to 10 years' time.

On its website, Oxitec describes its GM *Aedes aegypti* mosquitoes as "the solution" to the diseases spread by this species of mosquito (including dengue, Zika, chikungunya and yellow fever) (Oxitec n.d.a). In contrast, Wilke et al (2018, 5) note that the ecology of GM mosquitoes is not completely understood, and their supposed interaction with particular biomes and non-target species is mostly theoretical. That's just one of the reasons why environmental and ecological variations may alter the expected outcome of suppression strategies based on GM mosquito releases, which will possibly result in failure to suppress targeted mosquito vector populations, or in other surprises. Reis de Castro and Hendrickx state, "Even from a 'technical' viewpoint it is by no means clear when the mosquito technology can be said to work: does it mean diminishing the prevalence of dengue? To what extent? Does "working" mean suppressing the population of wild mosquitoes – if so, by how much, for how long? Further research will be necessary to see how the mosquitoes are made to work, under what sort of geographical and economic conditions, and with what types of political alliances" (Reis de Castro and Hendrickx 2013, 127).

To date, all Oxitec's open releases of GM mosquitoes have been experimental; there is no evidence of any reduction in the target diseases; and claims for successful suppression of mosquito populations have been highly exaggerated (GeneWatch UK 2018). Nevertheless, public engagement exercises undertaken by Oxitec take the claimed benefits of open releases of their GM mosquitoes as fully established and undisputed. For example, in Brazil, Oxitec's public engagement included a jingle claiming that Oxitec's GM mosquitoes are "the solution" to dengue, "Let him into your house, He's the solution, He fights dengue and won't bite anyone, Protect your health, He's the good mosquito" (Bevins 2012).

In 2018, the Environmental Health Minister in the Cayman Islands confirmed that trials of Oxitec's GM mosquitoes there did not work and would be abandoned (Cayman News Service 2018). Trials in Panama and Malaysia had already been abandoned by this time, and in Brazil, a totally new version of the technology was undergoing early trials. Thus, this claim that the GM mosquitoes that had already been released were a "solution" was not supported by any evidence.

Similarly, Oxitec's website describes its GM crop pests as "the solution" to pest control problems involving four different pest species affecting crops such as brassicas, soft and stone fruits, maize, rice, sugarcane, cotton and more than 250 kinds of fruits, nuts and vegetables (Oxitec n.d.b). However, Oxitec has not yet demonstrated that any of their Genetically Modified pests could suppress a wild pest population in the field. Further, the trait engineered into these GM pests is female-killing "late acting lethality", i.e. the female offspring of the release GM males die mainly at the late-larval or pupal stage (Fu et al. 2007, 354). This raises concerns about the damage they would do to crops during the repeated mass releases that would be needed to attempt to suppress a wild population (Benedict et al. 2010, 26); and about the contamination of crops with GM larvae (many of which may die inside the crop) (Reeves and Phillipson 2017). These issues are likely to limit the practical application of this technology in real-world situations, but are not mentioned in the company's publicity material.

Target Malaria's website does not claim it has an existing "solution", but does say it is aiming to develop one. It states: "Target Malaria is an innovative project aiming to reduce the population of malaria-transmitting mosquitoes in sub-Saharan Africa. By reducing the population of malaria mosquitoes, we aim to reduce the transmission of the disease" (Target Malaria, n.d.c) and "We aim to develop a technology that can be complementary to other mosquito control methods and which of-

fers a solution that is long term, cost-effective and sustainable as it tackles the problem at the source" (Target Malaria n.d.d). Nevertheless, Target Malaria's technology is excessively promoted considering it is something which does not yet exist in a form even close to being ready for experimental release, even in the lab. On the BBC in October 2018, one of the project's researchers stated that "The benefits that this technology can have in terms of human lives is massive" (BBC 2018), although the proposed open release of GM mosquitoes he is discussing is a small-scale release of a different technology, which the researchers expect to have no impact on malaria at all (ACB et al. 2018). A report published by the New Partnership for Africa's Development (NEPAD) of the African Union expresses near certainty about future benefits when it states "It will certainly take many years before actual outcomes are ready for field deployment, but potential benefits for African countries against malaria will almost certainly be extensive" (NEPAD 2018, 2). Even though they may include caveats about the technology, press articles include headlines such as "Here's the plan to end Malaria…" (Molteni 2018); "A swarm of mutant mosquitoes is out to eradicate malaria" (O'Mahoney 2018); and "A genetically modified organism could end malaria and save millions of lives — if we decide to use it" (Matthews 2018).

Target Malaria's proposal to release up to 10,000 GM mosquitoes over the coming year is a training exercise for the researchers; Target Malaria says that these GM mosquitoes will not be used for malaria control. This is because repeated large releases would be needed to seek to suppress the wild population of mosquitoes, which, even if successful, would be prohibitively expensive (Hayes et al. 2015, 7). Thus, there is no justification for making these releases in terms of "anticipated benefit" to public health. It is clear that the only benefit is to the researchers themselves.

A news report on the proposal to release GM mice on Nantucket describes the idea of genetically engineering mice that are immune to tick-borne diseases, such as Lyme disease, called "Mice against Ticks", and states: "the hope is to flood Nantucket with enough of these genetically engineered mice, that they would pass the immunity gene down to their offspring for multiple generations" (Boston 25 News 2017). However, the article also states that the researchers have only "identified the genes necessary" and does not mention if they actually have any evidence that the plan would work. A year later, another article asks "Will Nantucket vote to allow genetically altered mice to control Lyme disease?" (Mullin 2018). This could be taken to imply that mice containing traits that can control Lyme disease actually exist, and also suggests that their future ability to control disease is not in any doubt.

The GBIRd website asks: "Could we create a self-limiting gene-drive modified mouse that biases future generations to be male (or female) only, thereby achieving eradication by attrition? If so, should we do it? Under what conditions?" (GBIRd n.d.). Whilst GBIRd appears somewhat more cautious about making claims of benefit than the other projects discussed here, it nevertheless implies that once the technical challenges are overcome (the creation of the genetically engineered mice) this will inevitably lead to eradication of the population. Elsewhere on the same website a similar implication is made by stating "Researchers are exploring a technique of editing rodent genes in order to produce either all-male or all-female offspring, which, once released onto an island, would effectively self-eliminate the rodent population" (GBIRd 2018). Basic practicalities, such as how many GM mice would need to be released (perhaps many times the existing mouse population, in order to successfully mate with all the mice already there) and the damage the released GM mice would do on the island during the releases, are not discussed at all.

To date, public engagement exercises by Oxitec, Target Malaria and GBIRd have been led by these companies and research programmes, all of which have vested interests in promoting high expectations of future benefits and downplaying any risks. It is hard to see such engagement exercises as independent or unbiased. For credible public engagement to take place, uncertainty about what can be delivered needs to be openly acknowledged and unrealistic promises should be avoided. These issues are discussed further in Section 10.

5.5 Summary of findings regarding claims of benefits

Promises about the future benefits of new biotechnologies are often unrealistic, due to the unacknowledged complexity of real world biological, ecological and social systems. As Chapter 4, page 219 (Ethics and Governance) of this Report notes: "these desirable consequences and benefits in welfare only obtain if 1.) gene drives can be made dependably operational, 2.) they do not come with accompanying or hidden costs to human or environmental health, and 3.) they offer a real, long-term solution". In the case of GM mosquitoes without gene drive mechanisms it has been shown that claims of benefit, based on laboratory results and computer modelling, were not delivered in the field. In the case of gene drives, R&D is still in its infancy and far from any field trials. Many claims about future benefits of gene drives portrayed in media, scientific publications and patent applications seem farfetched. Public discussion is often limited to speculative health and conservation applications, with the aim of focusing on claimed benefits more likely to attract public support.

Framing public engagement exercises in a way that implies tremendous benefits are likely (or even inevitable), if and when open releases of gene drive organisms take place, is clearly problematic. For example, it limits the space for discussion of the usually poor success rates of so many biotechnological innovations thus far (Wallace 2010), the complexity of the approach and its dependence on numerous unverified assumptions. It also does not address the issue of the opportunity costs associated in investing in any approach that might not deliver the claimed outcomes. Further, over-hyped claims of future benefits may prevent concerns about negative impacts on human health from being included in the framing of the discussion. That is because, by definition, the still theoretical success of the gene drive organism in achieving its aim of disease reduction is assumed. It also prevents concerns about other impacts from being taken seriously because harm to ecosystems may be seen as less important than saving human lives.

Looking at biotechnology in medicine, Martin and Morrison (2006, 16) argue that in order for effective public policy to be developed, two things need to change: first, a more realistic set of expectations about the speed and scale of innovation needs to be adopted; and secondly, a different model, which views biomedical innovation as a slow and incremental process, should be used to inform public discussion and policy-making.

Similarly, McKelvey and Bohlin point out that decision-making in R&D has to be made under conditions of uncertainty about 'what will work' as well as about 'what will raise capital and what will sell'. If uncertainty is wide-spread, then the best course of action may be to invest in a set of diverse possible directions of technological development. They note that, "Certainly, biotechnology as an area of concern for basic science, small entrepreneurial firms and huge pharmaceutical companies has been one which holds out enormous promise - yet has also absorbed large amounts of resources with apparently few results in terms of direct industrial development" (McKelvey and Bohlin 2005, 98).

There is a danger that investors, policy makers and the public are being misled by unrealistic promises about what will be delivered through gene drive research and development. There may be significant opportunity costs if investments are diverted from more effective existing tools and R&D trajectories by these unrealistic promises.

6 The role of patents

As discussed above, promises about future benefits are an important means of securing research funding. Promises of potential future applications of new technological inventions or concepts are often voiced in intellectual property claims, the most stringent of which is the patent.

A patent gives its holder the right to exclude others from the reproduction, use, sale and distribution of his or her invention for a limited amount of time, generally 20 years (World Intellectual Property Organization [WIPO] n.d.). Requirements for patentability usually are: novelty, inventive step ('non-obviousness' in US patent law) and industrial applicability ('usefulness' in US patent law) (Art 52(1) European Patent Convention 2019, 27; 35 U.S. Code §§ 101-103, 2017).

The patent system is an artificial legal construct, established as a means of compensating inventors for their investments in R&D. The idea was that offering the possibility of gaining a reward would act as an incentive to create inventions and thereby foster innovation, economic growth and ultimately benefits to society. Today, however, the role of patents is controversial (see below).

In the next section, we give an overview of patents on gene drives and related technologies. We discuss what these patents cover, who the patents belong to and who they have been licensed to. Finally, we discuss whether patenting gene drive technology could be a means of regulating their use, as well as how patents on gene drives may influence innovation, research priorities and social benefits.

6.1 CRISPR-based patents

In 2014, Esvelt et al. were first to suggest using CRISPR/Cas9, a so-called genome editing technique, to build gene drive systems. This greatly boosted gene drive R&D as previous chapters of this Report have demonstrated. The CRISPR/Cas9 technology, which had been hailed as the "biggest biotech discovery of the century" (Regalado 2014), had started a flood of patent applications[4]. According to IPStudies, an IP consulting firm based in Switzerland, more than 2230 families of CRISPR-based patent applications had been filed by January 2018, 60% of which were filed by institutional applicants. The rest were filed by industrial applicants, individual inventors or were co-filings between industrial and institutional applicants (IPStudies 2018). The number of CRISPR-based patent applications increases monthly, with an average of 3 new patent publications per day.

The foundational CRISPR patents (Charpentier et al. 2013 and Zhang et al. 2014) have started a huge patent war between the institutional applicants and their researchers, Jennifer Doudna of the University of California, Berkeley and Emmanuelle Charpentier, then of Umeå University, Sweden, on the one hand, and Feng Zhang of the Broad Institute (affiliated with the Massachusetts Institute of Technology and Harvard University) on the other hand (see Box 1).

Box 1: War over CRISPR patents in the U.S.: UC Berkeley vs. Broad Institute

In 2012, Jennifer Doudna, University of California Berkeley and Emmanuelle Charpentier, then of Umeå University, Sweden, showed that CRISPR/Cas9, which is used by prokaryotes (bacteria and archae) as defence mechanisms against viral infections, can be reprogrammed to cut isolated DNA at a chosen site. On May 25, 2012, they filed a patent application for their invention in the US. A couple of months later, in December 2012, Feng Zhang of the Broad Institute and the Massachusetts Institute of Technology (MIT) in Cambridge also filed a patent application for the CRISPR/Cas9 technique in the US. Zhang's team reported that CRISPR/Cas9 also works in more

4 As of January 2019, the average pendency time (the time between filing of a patent application and the grant of the patent or abandonnement of the application, respectively) was approximately two years in the US. For individual patent applications, the pendency time might be much longer, especially if a an application is being appealed and needs a decision by the Board of Patent Appeals and Interferences (BPAI) (United States Patent and Trademark Office n.d.). With a pending patent application, the applicant can, however already begin to exploit their invention (Erickson Law Group n.d.).

complex living eukaryotic cells, including plant, mice and human cells that do not have an endogenous CRISPR system. Although filed later, Zhang's patent was granted in 2014, while the Doudna-Charpentier patent application remained under review. This led the UC Berkeley group to request an interference procedure with the US Patent and Trademark Office (USPTO). This procedure, unique to US patent law, is a means of examining whether the claims of two patents overlap and, if this is the case, who was the first to invent a commonly claimed invention. During the interference procedure, which started in January 2016, both parties filed hundreds of pages of documents with the court. The procedure moved beyond scientific argumentation and became unusually hostile, with allegations of impropriety and accusations of bias. The UC Berkeley team argued that Zhang's application to eukaryotic cells was obvious to a "person of ordinary skills" and hence lacks 'non-obviousness', a condition for a patentable invention. (Ledford 2016 a, b, c; Reardon, 2016; Sherkow 2017a)

The hearing, which received a lot of international attention, took place on 6 December 2016 at the USPTO. In February 2017, the US Patent Trial and Appeal Board (PTAB) ruled that there was no interference between the two inventions, which means that the Broad Institute will be able to keep its US patents. This ruling, which would give the Broad Institute control over the potentially most lucrative applications of CRISPR/Cas9 in plants, animals and humans, led to a rapid increase in the stock price of Editas Medicines, which has an exclusive licence from the Broad Institute to develop treatments for rare diseases using CRISPR, while the stock prices of its direct competitors Intellia Therapeutics and CRISPR Therapeutics, which have exclusive licence agreements to use UC Berkeley's patent application, fell by 10 and 15 percent, respectively (Regalado 2017; Ledford 2017).

UC Berkeley subsequently filed an appeal to the US Court of Appeals for the Federal Circuit, claiming "fundamental errors of law"; but on 10 September 2018 the US Court of Appeals upheld the previous decision by the USPTO. UC Berkeley could now still decide to appeal the decision to the US Supreme Court (Ledford 2018).

Although some were surprised about the hostile turn this patent fight has taken, a settlement was not to be expected, due to the huge commercial interests involved on both sides. The institutions behind the patents had already entered into a series of exclusive licence agreements with commercial companies founded by the institutions and one of their respective researchers. Zhang and Doudna founded Editas Medicine. Doudna, who has since cut ties with Editas Medicine, is involved with Caribou Bioscience and Intellia Therapeutics, while Charpentier has co-founded CRISPR Therapeutics with Rodger Novak and Shaun Foy (Ledford 2016a). These spinout companies had already further licenced the respective patents to other companies, including Bayer-Monsanto, DowDuPont and Novartis (Contreras and Sherkow 2017, 699) and invested millions of US Dollars in the patent fight. This system of surrogate licensing (see Box 2) of course may not be in the public interest. Editas Medicine, Intellia Therapeutics and CRISPR Therapeutics are publicly traded companies. Their duty is to maximise the profits of their shareholders and not to advance scientific knowledge in the public interest. Moreover, patent fights, where university turns against university, can complicate interinstitutional research agreements and impair the culture of scientific collaboration (Sherkow 2017b).

Box 2 University Intellectual Property Transfer

The 1980 adoption of the Bayh-Dole Act in the US allowed universities to own and commercialise patents arising from in-house inventions. Many other countries followed suit. This shift in policy reflected the growing acceptance of patenting academic research, along with the idea that social benefit could be created by licensing university patents to private firms, which would then develop commercially valuable products and services. It is now common for universities to seek to commercialise intellectual property by transferring their patent rights to private companies (sometimes co-founded by the inventors themselves), which then take on the role of further sublicensing and commercialising the invention. Contreras and Sherkow (2017) call these companies "surrogates for the institutions". They take on the role and responsibility of the patent owner, keeping a major share of the profits. The universities, often having a substantial equity interest in the surrogate company, still receive a substantial share of the profits, while minimising their risk. In 1988, Oxford University, for example, formed Isis Innovation (now called Oxford University Innovation), a wholly-owned subsidiary designed to help the universi-

ty exploit intellectual property. Intellectual property created at Oxford became generally assigned to Isis, which transferred the technology to industry through licensing agreements. In this "surrogate licensing model", research tools developed with public funding, instead of being licensed as widely as possible by universities operating in the public interest (as recommended inter alia by the US National Institutes of Health - NIH), are exclusively licensed to a number of "surrogate companies" that then control their further use. In addition to contradicting the conventional understanding of science as universally shared knowledge, this can have a negative impact on innovation, by decreasing competition (and information-sharing) in the respective fields (Contreras and Sherkow 2017; Tofano, Wiechers, and Cook-Deegan 2006, 54). This also gives a university a vested interest in promoting the technology, which might further undermine the supposed impartiality of science.

6.2 Gene Drive patents

In 2003, the first patent application describing a gene drive was published internationally (Burt 2003) The difference between national and international patent applications is described in Box 3. Therein, a method is described that has the intention of transforming a population or entire species, either for population suppression or for establishing a desired characteristic in that population. This is to be achieved by introducing a sequence-specific drive element, such as a gene with an increased inheritance ratio, e.g. a homing endonuclease gene (HEG), into the germline of an organism, thereby disrupting or knocking out a selected gene and subsequently introducing the then modified organism into the whole target population.

Box 3: National and international patent applications

The first step to secure a patent is to file a patent application. This can be done at the national patent offices in the respective countries where an inventor seeks a patent. If an inventor seeks protection in several countries, it may be more convenient to simultaneously request patent protection in multiple countries by filing the application at regional or international patent offices (WIPO n.d.). This way, filing several separate patent applications can be avoided. The European Patent Office (EPO) is a regional patent office with 38 member states. Once the patent has been granted by the EPO, it still has to be individually validated in the designated states. The new Unitary Patent system, which has yet to come into effect, would avoid individual validations (European Patent Office 2018). The Word Intellectual Property Organisation's (WIPO) Patent Cooperation Treaty (PCT), is an international patent treaty with more than 150 contracting states. The WIPO does not grant any patents, but rather forwards them to the competent patent office in the respective countries where a patent application is filed. Each state still autonomously decides whether or not to grant the patent within its borders. This is called the "national phase" (WIPO n.d.).

The first two letters of a patent publication number indicate the country or organisation in which the patent application was filed or granted. The prefix WO, for example, is short for WIPO and the prefix EP, for European Patent Office.

Long before the invention of CRISPR/Cas9 for genome editing, this patent application already described the idea of a two-component system to cut DNA at a specific target sequence and introduce the HEG at the cleavage site.

It also already described the various potential applications of gene drives, still being promised today: malaria control (either by mosquito population control or by conferring resistance to the malarial parasite); eradication or control of unwanted or colonising species which are detrimental to a previously-established ecosystem (for example rodents or goats); altering the balance of insects or microorganisms (for example those associated with food crops or livestock); or rendering pests susceptible to appropriate pesticides (for example insects, nematodes or fungi).

Its inventor, Professor Austin Burt, is now a member of the 'Gene Drives for Vector Control' group at Imperial College, which is one of the partner institutions of Target Malaria, and is Target Malaria's Principal Investigator. As well as patents on CRISPR technology or gene drives, academic institutions may also hold related patents on particular applications. Other members of the 'Gene Drives

for Vector Control' group at Imperial College, for example, have applied for patents to genetically modify insects, particularly malaria-transmitting anopheline mosquitoes (see Box 4). These are relatively old patent applications that may not apply to gene drive organisms, but they illustrate how GDOs developed in the future might also be patented, along with how academic scientists and institutions may already have (or may develop) commercial interests in particular technologies.

Box 4. Related patent applications from the 'Gene Drive for Vector Control' Group

In 2000, Crisanti et al. applied for a patent to genetically modify insects, particularly anopheline mosquitoes, by introducing foreign genes in the *Anopheles* genome. Therein, they provided a.) a method to delay the hardening process of the chorion, the rigid structure around the insect embryo, after oviposition so as to facilitate DNA injection; and b.) a DNA delivery vector capable of successful transposition in anopheline mosquitoes. They suggest either introducing a gene to control the transmission of malaria-causing parasites or producing sterile males intended to be released as a means of genetic control.

In 2004, Kafatos et al. applied to patent a method to render anopheline mosquitoes, in particular *Anopheles gambiae*, resistant to malaria-causing parasites.The method describes how to enhance or suppress mosquito proteins, that are either hostile or beneficial for parasite development, by application (feeding, spraying or injection) of a compound that interferes with the expression or activity of the protein. It further describes how to identify compounds that trigger an immune response in a mosquito of the genus *Anopheles* against *Plasmodium* (the parasite). For suppression of the protein expression, their suggestion is to use antisense-technology, or RNA interference (RNAi) in order to knock out the described genes.

With the discovery of the CRISPR/Cas9 technology, a dozen gene drive patent applications have followed, most of which either belong to Harvard University or the University of California (Table 1).

A key gene drive patent application, called "RNA-Guided Gene Drives" and filed by Harvard University (Esvelt and Smidler 2015), claims the ability to develop a method for targeted population suppression or extinction via the release of an RNA-guided genetic load drive into the targeted population, thus biasing the sex ratio of the population. The patent application describes the utility of this gene drive in the eradication of infectious diseases, the control of invasive species and the protection of threatened species, such as amphibians. However, the major part of the patent description is dedicated to "Agricultural Safety and Sustainability" and what they call "sensitising drives". Sensitising drives are gene drives meant to render the progeny sensitive to an external stimulus. This means that exposure of a weed or pest to a compound, for example a specific chemical, should result in a harmful reaction. The idea is to make pesticide-resistant weeds or pests susceptible to the original pesticide again - a major commercial 'rescue operation' for what have been failing markets for chemicals like glyphosate, due to the pests developing resistance. Subsequently, hundreds of weeds, crop pests and pesticides became covered by the patent, including glyphosate, 2,4-D and Bt toxins produced by CrylA.105, CrylAb, CrylF, Cry2Ab, Cry3Bbl, Cry34Abl, Cry35Abl, mCry3A, or VIP (Esvelt and Smidler 2015, 34-51). The same weeds, crop pests and pesticides are covered in a 2017 patent application, also by Harvard University (Esvelt and Min 2017, 42-60). In these ways, using and adapting the patenting system, academic science has been further integrated into the global agrichemical and GM industries. Along with other important domains, and with little democratic attention, gene drives have also become a driver of this transnational social and political change.

This shows that gene drives may be able to attract lucrative investors in the agricultural field of genetically modified (GM) crops. The most widely commercialised GM crops engineered to be resistant to herbicides, such as glyphosate and different insecticidal toxins derived from *Bacillus thuringiensis* (Bt), have suffered major setbacks with the development of glyphosate-resistant weeds and insect pests that are now resistant to Bt toxins (Bohnenblust 2016; Peralta and Palma 2017), something long predicted by those opposing this technology. Alternative GM crops, such as those resistant to the herbicides dicamba and 2,4-D, have led to huge problems with

Table 1: Gene Drive patent applications

WIPO Number	Publication Date	Applicants	Inventors	Title	
WO/2003/038104	5/8/03	Imperial College	Burt, A.	Methods for genetically modifying a target population of an organism	
WO/2015/105928	7/16/15	Harvard College	Esvelt, K.M., Smidler, A.L.	RNA-Guided Gene Drives	
WO/2016/073559	5/12/16	The Regents of the University of California	Bier, E., Gantz, V., Warren, W.L.	Method for Autocatalytic Genome Editing and Neutralizing Autocatalytic Genome Editing	
WO/2017/049266	3/23/17	The Regents of the University of California	Bier, E., Gantz, V., Hedrick, S., Warren, W.L.	Method for Autocatalytic Genome Editing and Neutralizing Autocatalytic Genome Editing And Compositions Thereof	
WO/2017/058839	4/6/17	Harvard College	Esvelt, K.M., Min, J.	Dependent Component Genome Editing Gene Drives	
WO/2017/132207	8/3/17	University of California	Akbari, O.S.	Use of *Medea* Elements for Biocontrol of *D. suzukii* Populations	
WO/2017/160689	9/21/17	University of Massachusetts	Sontheimer, E.J.	Anti-CRISPR Compounds and Methods of use	
WO/2017/196858	11/16/17	MIT, Havard College	Esvelt, K.M., Min, J., Noble, C.	Methods to Design and use Gene Drives	
WO/2018/035300	2/22/18	University of California	Bier, E., Gantz, V., James, A.A.	Split Trans-Complementing Gene-Drive System For Suppressing *Aedes Aegypti*	
WO/2018/049287	3/15/18	MIT, Harvard College	Esvelt, K.M., Min, J., Noble, C.	Methods and Compounds for Gene Insertion into Repeated Chromosome Regions for Multi-Locus Assortment and Daisyfield Drives	
WO/2018/053457	3/22/18	Joung, J.K.	Joung, J.K.	Methods of genetically alterning yeast to produce yeast variants	
WO/2018/071892	4/19/18	Joung, J.K., Gehrke, J.M.	Joung, J.K., Gehrke, J.M.	Epigenetically Regulated Site-Specific Nucleases	

herbicide drift when these crops are treated with their very toxic corresponding products, resulting in millions of acres of incidental crop and non-crop injuries in the US (Bohnenblust 2016; Bradley 2017; 2018). Moreover, multiple weed resistances to glyphosate, dicamba and 2,4-D are already seen today (Dellaferrera et al. 2018). Recently, hybridisation between two major agricultural pest insects (*H. armigera* and *H. zea*) has been confirmed, raising additional concerns about increased insecticide resistance problems in the future (Anderson et al. 2018).

Any technology that claims to be able to reverse these resistances is likely to attract the attention of the major biotech companies, many of which already have license agreements for using CRISPR/Cas9 (see above). In 1993, when applying for non-regula-

	State	Also published as
	International publication: A1 National phase entry: US, Canada, Australia, Japan Withdrawn: Japan (25.05.2006)	AU2002339086 (B2) CA2466129 (A1) US2005120395 (A1)
	International publication: A1 National phase entry: Japan, Canada, EPO Published: EPO (16.11.2016)	EP3092310 (A4) CA2936312 (A1) JP2017511685 (A) SG11201605550Q (A) WO2015105928 (A1) AU2015204784 (A1) CN106133141 (A) SG10201805815Y (A) US2016333376 (A1) WO2015105928 (A9)
	International publication: A1	US2018291382 (A1)
	International publication: A2 National phase entry: EPO Published: EPO (25.07.2018)	WO2017049266 (A3) CA2998894 (A1) EP3350315 (A2)
	International publication: A1	N/A
	International publication: A1	N/A
	International publication: A1	N/A
	International publication: A1	N/A
	International publication: A1	N/A
	International publication: A2	WO2018049287 (A3)
	International publication: A1	WO2018053457 (A9)
	International publication: A1	N/A

tion status of the first genetically modified Roundup Ready (glyphosate tolerant) soybeans, Monsanto claimed incorrectly that it was "highly unlikely that weed resistance to glyphosate will become a problem as a result of the commercialization of glyphosate-tolerant soybeans" (Monsanto 1993, 56). With the development of yet more genetically modified crops, allowing spraying of more and higher levels of herbicides, we face a form of herbicide intensification termed 'the transgenic treadmill' (Binimelis, Pengue, and Monterroso 2009, 9; Schütte et al. 2017, 7). In the case of gene drives, scientists now agree that resistance could eventually evolve again, but discard the whole problem by saying this technology could be used *repeatedly* to make weeds and pests susceptible again and again (Champer, Buchman, and Akbari 2016, 147). It seems evident that this would lead to a new level of treadmill,

whose purpose is not to prevent diseases or pests, but to maintain the prevalent chemically-dependent industrial agricultural system.

Another fundamental gene drive patent application, this one filed by the University of California and called "Method for Autocatalytic Genome Editing and Neutralizing Autocatalytic Genome Editing", mentions applications for combatting malaria, HIV and cancer and in reducing or eliminating immunogenicity, as well as in controlling agricultural pests and invasive species (Bier and Gantz 2016). It further includes hundreds of cancer types and model organisms, many of which are agricultural pests, thereby also covering potential lucrative applications in the health and agricultural sectors.

In 2017, MIT and Harvard University applied for a patent on daisy chain gene drives, a type of gene drive that is not yet functional, but would be "…designed to permit controlled, local gene drive activity." and claims to have "the ability to confine the gene drive organisms, such that they only affect local populations and do not risk global gene drive activities" (Esvelt, Min, and Noble 2017, 33). According to the patent, daisy chain gene drives may be used to reduce vector-borne and parasitic diseases, as well as to control or eliminate populations of agricultural pests or invasive species. Non-limiting examples of organisms which a daisy chain gene drive may be delivered to, or included in, according to the patent, are: "insects, fish, reptiles, amphibians, mammals, birds, protozoa, annelids, mollusks, echinoderms, flatworms, coelenterates, and arthropods, including arachnids, crustaceans, insects, and myriapods" In 2018, MIT and Harvard University applied for another patent on daisy chain gene drives, covering the same non-limiting examples of organisms (Esvelt, Min, and Noble 2017, 52; Esvelt, Min, and Noble 2018, 48). This kind of comprehensive patent ownership is not uncommon in patenting of genetic research. The fact is that most of the domains listed have never been tested even in a preliminary way for the effectiveness of the gene-drive; they have simply been imagined by the researchers as possible domains. This illustrates how institutions and academic researchers try to foresee and legally cover any potential future commercial exploitation of their invention.

The idea of using locally confined gene drives might seem more responsible, reducing ethical concerns about potentially eradicating entire species along with safety concerns about unintended and unforeseeable consequences. It means the prospect of developing daisy chain gene drives could increase public support for the technology. Along with funding, public understanding plays an important role when it comes to governance and regulation of new technologies (Mitchell et al. 2018, 3), so the development of "local gene drives" would also likely attract more private investment. A technology that potentially spreads to an entire population or species after an initial release is not as likely to develop a huge commercial market, hence the return on investment might be limited. With the possibility of spatially and temporally confining the spread of a gene drive organism, however, multiple subsequent releases at multiple locations are imaginable (Mitchell et al. 2018, 4). Going back to the theory of "sensitising drives", as explained above, a private company might be able to sell a package of a compound (such as a pesticide) and a corresponding gene drive organism (such as a crop pest) that has been rendered sensitive to said compound, each and every year to farmers around the world. These kinds of strategic and competitive business models, should in principle require democratic appraisal, since they have far-reaching and often unpredictable social, environmental, and economic consequences.

6.2.1 Regulation of Gene Drive patents

Esvelt has suggested that the patent system could be used to ensure gene drives are used ethically and responsibly. Those wanting to purchase a patent license would first have to disclose their proposed use to the patent holder before carrying out any experiments. The goal would be to ensure openness and also to limit licenses only to users ensuring ethical use (Regalado 2016c; Sherkow 2017b). Although this seems like a noble suggestion, this would mean that Esvelt himself and Harvard University, or any other scientist and their employ-

er-institution which had been granted a gene drive related patent, would be able to decide how gene drives should be used or *what constitutes an ethically justifiable purpose*. In so doing, they would take on the role of gene drive regulators, gaining legal control over not just the technology disclosed in their patent, but its distribution and use.

This would inevitably fragment the larger social regulation of the entire technology. A societal responsibility like gene drives (or any other technology) governance should not be placed in the hands of a research institution or individuals, most especially those who have a direct financial interest in its promotion. Those with vested interests in the technology cannot also be the ones overseeing its governance and use. How could it be ensured that the foundational gene drive patents, covering many potentially lucrative applications in the health and agricultural sector (see above), are not licensed to a few surrogates that are really part of larger companies, as has happened to the related CRISPR/Cas9 patents? In the end, society would have to put its trust in the patent holders alone to ensure that the technology is used (or not used) in the best public interest.

Instead, Parthasarathy (2018, 488) argues that transparency and political legitimacy would increase if government institutions, which are explicitly charged to represent the public interest, were to use patent systems to help regulate new technologies such as gene editing. The patent system would have to be linked to explicitly relevant laws for the purpose of regulation. In the US, this was already done in the Atomic Energy Act of 1946/1954, to reduce the development and commercialisation of atomic weaponry by private actors. This Act, for example, prohibits the patenting of any invention or discovery that would be "useful solely in the production of fissionable material or in the utilization of fissionable material or atomic energy for a military weapon" (Newman and Miller 1947, 750). If a patent for a production device could be obtained, the inventor would not be allowed to manufacture the device without a license from the Atomic Energy Commission, nor could they license its use to anyone except the government. If an intergovernmental regulatory framework for reviewing and awarding patents for their ethical and responsible use was set up, the patent system might indeed add another layer of protection from misuse of the technology. It cannot, however, be left to the patent system alone to regulate gene drives.

6.3 Social benefit implications of patents

The intent of the patent system is to increase innovation and enable the development of commercially valuable products and services, in order to create economic growth and ultimately social benefits. However, today the role patents play in fostering social benefits is ambiguous. As noted by the OECD, research and innovation thrive on collaboration and knowledge sharing (Gold et al. 2008, 16). Patent holders are required to publicly disclose the details of their inventions so that others can build on it by undertaking further research and development. At the same time, a patent, by definition, is the right to exclude others from commercially using the given invention. It has often been claimed that industry manipulates patent law to thwart rivals and block research, as well as to direct it away from humanitarian goals towards goals that maximise profits (Jenkins and Henderson 2008). In the health field, for example, despite increasing use of intellectual property patents, a decline in innovation has been observed (Gold et al. 2008, 7). As the example of CRISPR/Cas9 has shown, the commercial interests behind patents on biotechnological inventions often foster secrecy and hamper transparency and collaboration, thus interfering with overall innovation dynamics.

Kevin Esvelt, who openly opposes closed-door science, agrees that the current competitive approach to scientific enterprise doesn't promote open and transparent science: "It is a prisoner's dilemma. The benefits come from cooperation by everyone. But by participating you risk being exploited by people who steal your idea, get it working before you do, and claim the credit." (Esvelt 2016, 153). Gene drive research, however, would, according to Esvelt, offer a way out: "The field is new and small, and many of us have already worked together to publish a joint

recommendation calling for future experiments to use multiple stringent confinement strategies. Several groups already disclose proposed and ongoing gene-drive research and invite feedback, and active discussions between researchers and funders seek ways to ensure that everyone will be similarly forthcoming." (Esvelt 2016, 153). In 2016 he and his colleagues initiated the project "Responsive Science", intended to further this vision.

While the efforts of Esvelt and colleagues, to disclose their research ideas and foster open discussion (even before the experiments are performed), is very laudable, it is unfortunately questionable whether all gene drive researchers will follow Esvelt's call, as all he is doing is appealing to the individual scientists' sense of responsibility. He suggests no means of enforcing participation or controlling whether or not the rules he discusses are being followed. Furthermore; (1.) the appropriate rules would need lengthy negotiation amongst relevant parties; and (2.) those relevant parties would have to include institutions as well as individual scientists, and it is well-attested that institutions behave in ways which cannot be modelled from individual behaviour.

Patent rivalry between universities is not the only reason that scientists don't want to disclose their research ideas. Disclosing an idea to the public at an early stage may itself affect later patentability of related innovations. This in turn may decrease the likelihood of finding the funding that can translate the idea into reality (Fass et al. 2011, 11). Esvelt suggests that gene drives should be a non-profit technology (Esvelt 2018b), even if it would mean repercussions for his personal benefits from his patents. The same, however, cannot be expected from others, and it is questionable if everyone involved in gene drive R&D would agree (and could afford) gene drives to be a non-profit venture. Moreover, it has to be noted that the motive behind Esvelt's suggestion is unlikely to be free access to the technology (see Section 6.2.1. Regulation of gene drive patents) but rather public acceptance and the avoidance of a moratorium on gene drives. In a 2018 article titled "Gene drive should be a non-profit technology" Esvelt states: "When people know you will benefit financially from a proposal, they're less likely to trust your judgment", adding: "Gene drive and other ecotechnologies depend on popular support. Since they involve the genetic engineering of wild populations, that support is by no means guaranteed, especially if there is for-profit involvement." (Esvelt 2018b). However sincere his personal beliefs might be in terms of this technology bringing social benefits, such statements leave the impression that Esvelt's engagement for openness and transparency in science is as much a strategic choice to gain public acceptance, in order to move forward quickly, as it is a willingness to foster true public engagement. A lack of the latter in practice could delay or even lead to the rejection of the technology: "The primary danger posed by CRISPR-based gene drive is social. Given widespread scepticism of genetic engineering, any unauthorized release of a gene drive system could lead to a strong social backlash and serious damage to public trust in science and governance when society can least afford it. In addition to institutional damage, such backlash would almost certainly delay efforts to use gene drive to prevent vector-borne and parasitic diseases such as malaria and schistosomiasis, possibly resulting in millions of otherwise preventable deaths." (Esvelt 2018a). Furthermore, the issues described in this chapter also apply to non-profit enterprises, which have their own in-built social biases and assumptions, and which may also wield significant power over others.

Another important social issue highlighted by the increased use of patented technologies, one which has been less widely discussed, is the effect that patents have on research priorities. The role of patents is not straightforward and is often difficult to disentangle from the other factors influencing R&D investments and innovation. However, possible negative impacts of university patenting include diverting research resources (researchers' time and equipment) away from research questions that may not to be suited to the development of patents, but which may well offer potentially greater social benefits (Geuna and Nesta 2006, 799). As numbers of patent applications and income from intellectual property have become measures of university and industry success and funding, patentable inventions

will be given a higher priority over other types of research that might have greater social benefit. It is thus not only access to biological knowledge and discoveries that is controlled and shaped by the patent system, but also *what constitutes scientific knowledge itself* (Wallace and Mayer 2007).

With the rise of biotechnology, patents were legalised for living organisms for the first time in 1980 in the US (see Diamond v. Chakrabarty), and globalised in the 1995 Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement. The possibility of patenting genetically modified organisms in turn was a major incentive to further invest in genetic engineering, as it allowed patent owners to control and exploit genetic material that farmers previously freely replanted and exchanged amongst themselves[5]. Although it is clearly not the only factor driving research agendas, the commodification of genetic inventions via patent claims therefore plays a key role in the 'geneticisation' of both health and agriculture.

As mentioned, gene drive R&D is accompanied by promises of many beneficial applications. However, open releases of gene drive organisms have the potential of altering and interacting with ecosystems in new, complex, unpredictable and unforeseeable ways. Whether or not the deployment of gene drive organisms will in fact create social benefit one day is still very hypothetical. Nevertheless, gene drive technology hype and patents may help attract further investment in gene drive R&D and possibly divert resources from potentially more sustainable alternatives.

7 Fully informed consent

In this section, we consider issues related to the need for individuals to provide prior, fully informed consent to open releases of GDOs.

7.1 Fully informed consent for projects not involving medical research

For medical research such as releases of gene drive mosquitoes, fully informed consent is already an ethical requirement under the Helsinki Declaration (see Section 7.2). However, for other gene drive organisms, which are intended to alter ecosystems but not to impact on human health, the situation so far has been less clear. This changed in 2018 with the adoption of a decision by Parties to the Convention on Biological Diversity (CBD), as discussed in Chapter 5. This requires the consent of potentially affected indigenous peoples and local communities to be sought or obtained to the release of GDOs "where applicable in accordance with national circumstances and legislation". The CBD Decision is an important acknowledgement of the importance of consent to the release of any GDO; however, for medical experiments, any release will also have to comply with the more stringent and well-established requirements of the Helsinki Declaration, as discussed below.

7.2 Fully informed consent to medical research

In the case of releases of gene drive mosquitos with the goal of affecting tropical diseases such as dengue fever or malaria, the requirement for fully informed consent is enshrined in international principles for medical research.

The Declaration of Helsinki outlines the internationally agreed ethical principles for medical research involving human subjects (World Medical

5 The subsequent rise of a few agrochemical companies that today control a major share of the global seed and pesticide markets, and its impact on farmers' and consumers' choice, is still subject of controversy today. Others critique the patenting of life altogether (see for example the German and European initiatives "Kein Patent auf Leben!" and "NO PATENTS ON SEEDS!", respectively).

Association 2013). It includes the requirement that: "Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects" (Article 16).

The Declaration of Helsinki builds on the Nuremberg Code, adopted as a code of medical ethics to condemn the practices of doctors working for the Nazis (Fischer 2006). It also states that: "In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study…" (Article 26).

Thus, the Helsinki Declaration requires that research participants are adequately informed about the risks and anticipated benefits of the study. In theory, this allows potential participants to weigh up the potential risks and benefits, as part of the process of informed consent.

Resnik (2012) explores a hypothetical field trial of malaria-resistant GM *Anopheles* mosquitoes and highlights the fact that field trials should not be implemented unless research indicates that overall public health benefits are likely to be greater than public health risks (Resnik 2012, 5). He further notes that, "In a study taking place in a developing nation, it is likely that many of the subjects will be vulnerable, due to poverty and lack of access to health care" and notes that, "To protect these subjects, measures should be in place to ensure that consent is free from coercion and undue influence" (Resnik 2012, 7). Resnik also states that, "Individuals may be exploited if they are harmed in research when there is little expectation that they will benefit, or they do not provide consent" and that, "Exploitation of a community may occur when the community is placed at risk without the expectation of significant benefits" (Resnik 2012, 7).

Macer (2005) also considers ethical issues in relation to the release of genetically modified (GM) insects with the aim of controlling human disease. He notes that "Informed consent requires information to be provided, so disseminating information about the plans and progress of the project, and obtaining the consent of any person potentially affected by the release of transgenic insects, is important for the ethical conduct of research trials, whether or not national guidelines require this, or even exist" (Macer 2005, 653). Macer also highlights that if a study involves humans, oversight by an ethics committee or institutional review board (IRB) is also necessary (Macer 2005). He goes on to argue, "To consider the issue at a local level, as required for obtaining appropriate informed consent, it is essential that a local ethics committee (and/or IRB if associated with an institution) open to the communities involved is established" (Macer 2005, 654).

This raises issues about how these risks and benefits are determined and communicated, and how different value-judgements, unknowns and uncertainties are dealt with in this process. Aspects of these issues are covered by national and international agreements and regulations covering genetically modified organisms (GMOs). However, these regulations may be absent, contested, or not properly enforced. Below, we consider how risks have been dealt with to date during the process of obtaining consent for projects wishing to release GM mosquitoes (currently without gene drive). We highlight that in practice participants may not be fully informed by developers about the risks of new technologies and that power asymmetries may affect who has information, what choices people are able to make, and whose voices are heard. Hype about benefits will also substantially affect whether people are genuinely fully informed before they are asked for their consent.

7.3 Absence of adequate environmental risk assessments

The previous section highlighted the problems associated with the ethical requirement upon scientists to obtain fully informed consent from all potentially affected parties before they begin any environmental releases. For "fully informed" to be

a meaningful condition for the public, scientists involved also have to be fully informed about all possible harms that may result from their actions. This is a problematic normative condition. As Chapter 4 (Ethics and Governance) notes, risk assessments inherently involve making value-based judgements; for example, deciding what constitutes a hazard or an environmental protection goal, and what constitutes quality in safety science. This involves being explicit not only about imprecisions in knowledge of salient measures and relationships ("uncertainties"), but also about lack of knowledge ("ignorance"), and untested assumptions ("ignorance"), as well as about unanticipated contingencies (also ignorance, e.g. variable conditions in the environment which may affect validity of assumed extrapolations to broader conditions). Risk management decision-making also inevitably requires a determination of what constitutes an acceptable level of risk.

Both Oxitec's and Target Malaria's GM mosquitoes have been exported from European Union (EU) countries for open release into the environment elsewhere. Under EU law, the exporter should provide prior notification, including a publicly available environmental risk assessment that meets European standards, before exporting GM insect eggs for open release to foreign countries. This legal requirement arises because GM insect eggs are live, genetically modified organisms (living modified organisms or LMOs) covered by the Cartagena Protocol on Biosafety (CPB) to the Convention on Biological Diversity. The relevant legal requirements for export are implemented in the EU through the European Regulation (EC) 1946/2003 on transboundary movement of genetically modified organisms. This Regulation requires that the environmental risk assessment (ERA) provided by the exporter meets the EU standards on risk assessment contained in EU Directive 2001/18/EC. Regulation (EC) 1946/2003 is important because it requires the exporter to provide a comprehensive, publicly available risk assessment that meets EU standards for GMOs intended for release into the environment. The Precautionary Principle (discussed in Section 8) must be taken into account when applying this Regulation.

Avoidance of transboundary notifications has been a major issue with the commercial GM insect company Oxitec, which has never published a risk assessment which meets EU standards prior to undertaking any of its open releases of GM mosquitoes into the environment (GeneWatch UK 2014). Reeves et al. note that there were "significant omissions" (Reeves et al. 2012, 8) in the information made publically available prior to open releases of GM mosquitoes in the Cayman Islands and Malaysia, and that "Without the pre-release publication of complete risk assessment documents detailing all the potential hazards analyzed, it is often impossible to establish which have been considered (and by whom) and if any obvious hazards have been overlooked for rigorous consideration" (Reeves et al. 2012, 9). They also highlight that the Cayman Islands had no enacted legislation relating to living GM organisms at the time of the first open release of GM mosquitoes there (Reeves et al. 2012, 8).

Target Malaria has claimed to be holding itself to higher standards. However, it is currently arguing that it is not required to make a transboundary notification that includes such a risk assessment for its proposed release of male-sterile GM mosquitoes in Burkina Faso, because the GM mosquitoes were exported for an initial period of contained use (for which a notification is not required under EU law) before release (ACB et al. 2018). Instead, Target Malaria has commissioned its own risk assessment, without reference to the required standards, which omits some of the relevant issues, and relies heavily on 'expert elicitation' and unpublished data (Hayes et al. 2018).

In September 2018, Target Malaria announced that it had received regulatory approval for its first proposed open release of GM mosquitoes in Burkina Faso (Target Malaria 2018). However, there is no published environmental risk assessment (ERA) other than one published by Target Malaria itself, and there has been no public consultation, apart from "public engagement" activities conducted by Target Malaria, the organisation proposing the release. This is despite the fact that the Cartagena Protocol requires Parties, including Burkina Faso, to make available summaries of the risk assessments

generated by its regulatory process to the Biosafety Clearing House (paragraph 3(c) of Article 20), as well as to consult the public in the decision-making process (paragraph 2 of Article 23) (see also Chapter 5, Regulation).

According to the Helsinki Declaration, people must be fully informed about the potential risks of a study in order for their consent to meet ethical requirements. This cannot be the case until a comprehensive risk assessment has been published that meets the necessary standards and opened for public consultation. Because the idea of releasing GM insects into the environment is relatively new, best practice would be for specific guidance on how to do such risk assessments first be developed by the regulators, not the proponents, and for this guidance to be subject to public consultation, such as has happened in the EU (EFSA Panel on Genetically Modified Organisms 2013). Provided conflicts of interest can be avoided, this could help prevent the developer having too much influence over the risk assessment process, including how unknowns and uncertainties will be handled.

In addition, under the Cartagena Protocol, Parties are allowed to take into account socio-economic considerations that arise from the impact of GMOs on biological diversity when they make decisions about importing GMOs. Under national laws, socio-economic considerations or assessments may also be required as part of decision making on GMO applications

ERAs published to date for GM insects have not included any discussion of socio-economic aspects. The summary of the risk assessment commissioned for Target Malaria's proposed release of GM mosquitoes on Burkina Faso states, "The report is not a complete evaluation of all potential risks. Some potential risks, such as the risks to social endpoints identified in Burkina Faso's legislation, are not addressed in this analysis" (Hayes et al. 2018, 2). This sidesteps the question of where these missing social risks have been evaluated or how the public will be informed about any such assessment, as well as if they will be engaged in any decision-making (see Section 10). This issue will remain relevant for future proposed releases of GDOs (whether proposed by Target Malaria or others).

It should be noted that open releases of GDOs would challenge the regulatory system further, requiring updates and adaptations to GMO risk assessment methodologies as well as a precautionary approach (discussed in Section 8).

7.4 Power asymmetries

As noted above, power asymmetries may be particularly evident when technologies are transferred from wealthy to poor countries, and when the people affected may be vulnerable, not only because of their poverty, but because the state and related infrastructures are typically much weaker in poor countries.

In African countries, there have been a few studies of public and scientific attitudes to the release of GM mosquitoes which would potentially include gene drives. Preliminary research conducted in Burkina Faso concluded that "the community's acceptance of GMM [GM mosquito] release could be affected by the fact the citizens interviewed did not appear to completely understand either the possible negative aspects of GMMs in the environment or the detail of how GMMs operate" (De Freece et al. 2014, 265). In a small study of perspectives of people in Mali toward GM mosquitoes for malaria control, 62 participants said they would support a release of GM mosquitoes that satisfied their conditions, 14 said they would not support a release under any circumstances, and four were unsure (Marshall et al. 2010, 7). Conditions were wide-ranging and included requirements for evidence GM mosquitoes will not cause human health or environmental concerns and that there would be no costs to the community (Marshall et al. 2010). However, it is not at all clear how these conditions might be implemented and enforced.

Notably, Marshall et al. reports that, "The main concern expressed by participants in all groups, but particularly amongst those from rural areas, was that the strategy of releasing GM mosquitoes will not

work" (Marshall et al. 2010, 7). This is an important issue in view of the general over-optimism concerning the technology discussed above, as well as the untested claims of efficacy that are often made by GDO developers. To what extent can claims of efficacy (as well as risks) be contested in debate about new technologies? How can potential participants, who may lack resources and technical expertise, raise concerns about efficacy that are not dismissed by the scientists who have a vested interest (financial, or otherwise) in promoting such technologies? Finally, can people have any influence on research investments and the exploration or implementation of alternatives? These issues are discussed further in Section 10.

In some cases, power imbalances may occur not only between 'experts' and local people, but also between the relatively well-funded scientists promoting an open release of GDOs and local scientists or medical experts. Okorie et al. (2014) interviewed 164 scientists selected from academic and research institutions in Nigeria and found that a majority (83.5%) of the local scientists who participated in their study were sceptical about a potential release of GM mosquitoes in Nigeria. Further, 92.7% of these scientists would require contingency measures to be available to remove the GM mosquitoes "should a hazard become evident during the course of the release" (Okorie et al. 2014, 1).

Looking beyond debate about the benefits and risks of the experiment itself, Marshall et al. noted that some of their interviewees in Mali seemed to accept the proposed GM mosquito project for reasons unrelated to their actual feelings about the technology, in this instance "based on the expectation that they will get a hospital in return" (Marshall et al. 2010, 11). They also noted the limited participation of women in their study.

In the case of Target Malaria, concern about the process of informed consent is exacerbated by evidence that the company is paying 400 CFA francs (approx. 70 cents US) per hour to people collecting biting female mosquitoes from their own bodies (Flanagan 2018). Volunteers are required to sit for 6 hours in a room at night with the lower part of their leg exposed up to the knee, so that the mosquitos land and they can collect them with a suction tube (Target Malaria Burkina Faso and IRSS 2017). The use of a financial incentive to induce individuals to expose themselves to biting female mosquitoes, that is, potentially to contracting malaria, is ethically very questionable, and highlights a power imbalance between the researchers and research participants underpinned by great financial inequalities.

An independent report from Burkina Faso has detailed further concerns. It found that many people in the country are concerned about the potential impacts of Target Malaria's project and about the absence of risk assessment by the regulators, and are unaware of many of the details of the project, including where the funding for the project comes from (Fuhr 2018).

Target Malaria's lead funder, the Gates Foundation, is one of the largest on earth and extremely influential. Whilst its generosity has been widely praised (it spends more on global health every year than most countries), it has also been criticised for unknown efficacy, since the process is answerable only to the Gates family and therefore lacks accountability and transparency. This foundation has also been accused of what some regard as questionable priorities, in particular, too much emphasis on technology and technological fixes. It also supports strong intellectual property (IP) protections within these supposedly philanthropic projects. Finally, few people involved are willing to speak on the record about any concerns in these and other regards because they are being funded by the foundation (Belluz 2015). Emails released as a result of Freedom of Information requests and published as the *Gene Drive Files* reveal that a previously undisclosed gene drive "advocacy coalition" was run by a private PR firm, which received $1.6 million in funds from the Bill and Melinda Gates Foundation. The firm is on record at the UN for employing covert lobbying tactics to influence expert UN discussions (Gene Drive Files 2017c).

There is little public information regarding the consent process used by Target Malaria. However, NGOs and journalists have reported concerns about

other power imbalances, including from a woman highlighting her difficulties from within the community asked to give its consent, who told Le Monde "In any case, we do not have our say, it is the men who make the decisions here" (Dossou 2018; Douce 2018; Noisette 2018).

Power imbalances can also influence regulatory processes. In 2012, a group of NGOs published a report detailing how Oxitec had infiltrated decision-making processes around the world with a view to influencing regulations, guidelines and decision-making about the release of genetically modified insects (GeneWatch UK 2012). Subsequently, the European Ombudsman found that one of the experts involved in developing guidance for the risk assessment of GM insects in the EU had failed to declare relevant conflicts of interest (European Ombudsman 2015).

Thus, power imbalances may affect the regulatory framework and who is asked for their input to decisions, as well as influencing whose voices end up being heard and, ultimately, what decisions are taken.

8 Precautionary Principle

8.1 The need for a precautionary approach

A precautionary approach involves adopting a cautious attitude towards risk that takes pre-emptive measures to avoid harm (see Box 1 in Chapter 4: Ethics and Governance). It is an explicit commitment for all signatories to the UN Convention on Biological Diversity (CBD) and its Cartagena Protocol.

8.2 Brief history of the Precautionary Principle

Although the Precautionary Principle was originally anchored in the concept of prevention used in medicine, it has expanded its intrinsic notions of prevention into a general rule of public policy action and participation in matters that represent potential threats to health and the environment. According to Harremoës et al. (2001), writing on the history of the Precautionary Principle, the concept arises from the German *Vorsorgeprinzip* first introduced in 1974 by the German Clean Air Act. Since this date, the principle has been progressively integrated in political agendas and international agreements, expanding not just the scope and range of the principle, but also its names, which has resulted in a sometimes confusing discussion over terminology.

Wynne (2002, 469) argues that scientific risk discourse wrongly implies that risk analysis identifies all significant future consequences of the relevant actions. It thus ignores (or "deletes") ignorance and the unanticipated consequences – lack of control – lying beyond the reach of existing scientific knowledge. Wynne (2002, 465) argues that the dominant risk discourse also excludes many other questions, which he distils into three general types: 1.) other issues and interconnections, such as driving purposes, intended social benefits, and conditions (e.g. of ownership, implementation, investment and control, regulation and accountability); 2.) what is meant by 'the technology' as putative 'cause' of possible impacts; and 3.) are the consequences or questions even answerable, and if not, what then?

Stirling highlights that, "precaution is not simply about acting to stop something, but introduces instead a responsibility for more careful and explicit reasoning over what kinds of action might be appropriate" (Stirling 2016, 5). Further, "In particular (and unlike idealised notions of 'sound scientific' risk assessment), it embodies an awareness of the asymmetries and inequalities of the power relation-

ships that bear on processes of regulatory appraisal and help to shape the fabrics of the knowledges produced within them" (Stirling 2016, 5). Therefore, "the Precautionary Principle requires more explicit, scientifically rigorous and socially sophisticated attention to the implications of incomplete knowledge, than is routinely provided in the conventional regulatory assessment of 'risk'" (Stirling 2016, 6).

According to Harremoës et al. "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" (Harremoës et al. 2001, 192). Harremoës et al. describe twelve 'late lessons', based on an analysis of case studies, which highlight the importance of heeding 'early warnings' and taking a precautionary approach. Their case studies include examples of harm caused by X-rays; lead (and lead substitutes) in petrol; asbestos; poorly managed fisheries; 'mad cow' disease (BSE); radiation; and various chemical pollutants. The lessons drawn by the editors of the report are:

1. Acknowledge and respond to ignorance, as well as uncertainty and risk, in technology appraisal and public policymaking.

2. Provide adequate long-term environmental and health monitoring and research into early warnings.

3. Identify and work to reduce 'blind spots' and gaps in scientific knowledge.

4. Identify and reduce interdisciplinary obstacles to learning.

5. Ensure that real world conditions are adequately accounted for in regulatory appraisal.

6. Systematically scrutinise the claimed justifications and benefits alongside the potential risks.

7. Evaluate a range of alternative options for meeting needs alongside the option under appraisal, and promote more robust, diverse and adaptable technologies so as to minimise the costs of surprises and maximise the benefits of innovation.

8. Ensure use of 'lay' and local knowledge, as well as relevant specialist expertise in the appraisal.

9. Take full account of the assumptions and values of different social groups.

10. Maintain the regulatory independence of interested parties while retaining an inclusive approach to information and opinion gathering.

11. Identify and reduce institutional obstacles to learning and action.

12. Avoid 'paralysis by analysis' by acting to reduce potential harm when there are reasonable grounds for concern. (Harremoës et al. 2001, 168–169)

The most frequent argument coming from opponents to the application and expansion of the Precautionary Principle has been that it slows or even interrupts the innovation and development process. But as the editorial team from "Late lessons from early warnings: the precautionary principle 1896-2000" (Harremoës et al. 2001) has demonstrated, there is no empirical evidence to support such an argument. On the contrary, according to the editorial team and based on the fourteen case-studies that are the basis of their argument, the Precautionary Principle will only restrict innovation in some questionable technologies, while creating the space to foster innovation in other directions. These favoured technologies are often ones which may not be under the control of, or are otherwise not favourable towards, global industrial interests and their particular investments. This has demonstrated that curtailment of a particular option may actually serve to foster and intensify innovation, but in other areas (Harremoës et al. 2001, 182). The actual objection to applying the Precautionary Principle really seems to be that the technological pathways developed under it may not be the ones endorsed today by corporate and private interests. Stirling (2016) argues that precaution is about steering innovation,

not blocking it, as innovation can take many different pathways. He concludes "In the end, precaution is identified to be about escaping from technocratic capture under which sectoral interests use narrow risk assessment to force particular views of the world. What precaution offers to enable instead is more democratic choice under ever-present uncertainties, over the best directions to be taken by innovation in any given field" (Stirling 2016, 2).

8.3 Application of the Precautionary Principle to research

The dominant linear and reductionist approach to risk assessment is problematic, especially because of the many ambiguities, complexities and indeterminacies inherent in human knowledge. The twelve lessons above, highlighting problems which can occur due to the lack of application of a precautionary approach (Harremoës et al. 2001), have in fact demonstrated that science may be insufficiently reflexive and critical about the potential good and harm caused by its activities. The optimistic aura surrounding the promises of science and technology along with the excessive expectations that aura has fostered, has perhaps obscured the capacity to accept the fact that ignorance, uncertainty and risk are part of the scientific system. The current atmosphere accompanying any new technology (which is "hyped" in order to stimulate acceptance and funding), has created a distinction between how scientific uncertainty and change are accepted within the scientific community, compared with how they are downplayed outside it. These true descriptions of how science works tend to disappear when scientific researchers seek to provide society with unrealistic certainties in order to gain funding.

Stirling details how "various forms of the precautionary principle serve, in many specific ways, to help foster more transparent and deliberate democratic decision making concerning the steering of alternative directions for innovation" (Stirling 2016, 17). He concludes that, "By contrast with the technocratic procedures of risk assessment, precaution is about greater democracy under uncertainty" (Stirling 2016, 17).

The application of the Precautionary Principle at the level of project design may discourage some pathways of development, but it would provide researchers with the ethical and responsible principle of channelling alternative routes to scientific innovation and discovery, covering gaps in knowledge and fostering new discoveries. As a necessary stage to responsible technological development, it not only represents a strong commitment to the well-being of the population and systems affected, it also prevents the waste of resources on expensive interventions, lukewarm mitigation strategies and unnecessary and non-useful data gathering, that typically follow when technologies are adopted without due regard to the need to make precautionary decisions in a context of uncertainty. It promotes a scientific pathway that embraces complexity and uncertainty with more humility and less hubris.

The impact of the application of the Precautionary Principle on all technological research would not only favour science and policies regarding health and the environment. It has the potential of reinforcing democratic principles, by rebuilding trust between politicians, scientists and the public. When it comes to gene drives, this implies that alternative trajectories of innovation must be part of the debate, and that consideration of alternatives must occur not only at the point at which GDOs might be released into the environment, but also at very early stages, when research priorities are being set.

8.4 Precautionary Principle for GDOs

When GDOs are the subject of debate, the Precautionary Principle is often invoked, but rarely developed. An example may be drawn from the 2016 National Academies of Sciences, Engineering, and Medicine (NASEM) report "Gene Drives on the Horizon: Advancing Science, Navigation Uncertainty, and Aligning Research with Public Values".[6] Although the report mentions the Precautionary Principle a few

6 This report was requested by the National Institutes of Health and the Foundation for the National Institutes of Health to the Board on Life Sciences of the National Academies of Sciences, Engineering, and Medicine.

times, it gives more attention to its technical aspects rather than its ethical, philosophical and political dimensions. For example, it sometimes focuses on the principle as being useful at the stage of testing and environmental release, stating that uncertainties in the case of GDOs are structural to this phase of the technology development. In this matter, the experts contributing to the report promote the idea that a step-by-step assessment is necessary; however, they never question the necessity of developing such technologies in the first place, through applying the Precautionary Principle to research.

The authors also refer to the asymmetries among countries regarding the Precautionary Principle and the instruments available to regulate and govern GMOs. These may pose a barrier when it comes to national cooperation on research and assessment of GDOs, and also create asymmetries of power when it comes to definitions of ethical standards.

Beisel and Boëte note that regulation of GM mosquitoes with self-spreading genetics (such as GDOs), "is considered almost impossible, or at the very least extremely difficult" (Beisel and Boëte 2013, 50). Further, "GM mosquitoes and other public health measures to control malaria will not be able to coexist", because this strategy actually *relies on people fostering the survival and spread of the GM mosquitoes*, rather than avoiding and killing them as would normally be the case with other public health measures, such as using bed nets or removing breeding sites (Beisel and Boëte 2013, 53). Beisel and Boëte note that GM mosquito strategies are "particularly vulnerable to unforeseen effects and ecological uncertainties", (Beisel and Boëte 2013, 53) for example:

- it is unknown how (and how quickly) mosquito and parasite populations would react to the introduction of GM mosquitoes;
- it is unknown how many species would need to be transformed in order to interrupt the transmission of the malaria parasite;
- significant ecological uncertainties are inherent to the complex and shifting disease ecologies of malaria.

These concerns will also apply to other GDOs, not just mosquitoes, due to the intention that they spread and replicate in the environment. In effect, the open release of GDOs is intended to re-engineer whole ecosystems, and therefore the role of the Precautionary Principle is particularly important.

9 Who is liable if anything goes wrong?

Issues of liability are covered by the Nagoya-KL Supplementary Protocol on Liability and Redress, and, in addition, individual states have a responsibility under international law to not cause harm to the environment of another State. However, liability and redress is a critical if still deficient component in the regulatory toolbox. Deficiencies include the long term, irreversible nature of potential harm, and the difficulties in establishing proof of any damage and its source.

In releases of GM insects to date, one concern has been the use of in-country partners (by both Oxitec and Target Malaria) to make the applications to regulators, and the absence of transboundary notifications published by the exporter (see Section 7.3). Depending on whether the developer or the in-country partner is defined as the 'operator' in national law, this could mean that the in-country partner is held liable if anything goes wrong, allowing the developer (usually based in a rich country) to walk away and not take the responsibility or bear the costs of any future harm.

The difficulties in establishing liability may be exacerbated by gene drives spreading across national boundaries, with potentially long-term effects.

10 Public engagement

There is recognition by academics working in the field, such as Brossard et al. that "Deciding to use gene drives to control and suppress pests will involve more than a technical assessment of the risks involved, and responsible decision-making regarding their use will require concerted efforts from multiple actors" (Brossard et al. 2019, 1). They recognise that "technical expertise is not enough to address the complexities surrounding a scientific issue that has not only technical but also social, ethical, and legal dimensions" (Brossard et al. 2019, 1). They further note that "Editing pernicious genes to make a disease-causing mosquito, or a pathogen-carrying rodent, less harmful sounds like an appealing idea. But there are serious questions about the ethics of engineering a wild species and about potential environmental consequences that might change ecosystem dynamics or spread well beyond the specific targeted location" (Brossard et al. 2019, 2). Brossard et al. also argue that "Engagement about gene drives should aim to foster open, substantive dialogue between all interested and affected individuals in areas where the technology may be used" (Brossard et al. 2019, 4).

The history of Public Engagement of Science (PES) is vast and it has gone through several changes since it was first proposed by an official scientific/political body at the turn of the millennium (House of Lords Science and Technology Committee 2000). Today, PES is no longer just the ethical responsibility that scientists owe society; it is part of basic research design, expected to bring benefits to scientists' careers as well as to society. Some argue this is a win-win situation, with the optimistic claim that its theoretically two-way communication between publics and scientists generates mutual understanding and greater trust.

However, because the theory of PES is rooted in a process of sharing and mutual learning, any experience of engagement must be anchored on the premise that society (in its forms of organisation) has "ways of knowing" and also deep concerns that may differ substantially from those of science. In other words, society has methodological and epistemic resources that sometimes may diverge from those used by scientists.

10.1 Alternatives to a 'pathway for acceptance'?

For a long time, institutions have been defining the wrong questions and making the wrong assumptions when it comes to public engagement. Rather than seeing engagement as a democratic right, most of the initiatives taking place approach the provision of information to the public as primarily an attempt to create a system will does not generate controversy or resistance to scientific and technological outcomes. This means that the goal of public engagement as we know it is not democratic, but simply a 'pathway for acceptance', which does not allow for the option of rejecting a particular technology or approach and instead choosing alternative approaches.

This bias of public engagement in science is reflected in some of the initiatives already implemented. For example, it's not rare to find that the feedback from those engaged in deliberative forums often reflects feelings of disappointment, loss of time and feelings of impotence (PSx2 2008). One of the main reasons people experience these negative feelings regarding their engagement with science is that the apparatus for participation rarely reflects how most people would wish to approach the actual use of the technology. Others may even report exhaustion, especially when people are enrolled in a continuous process of participation that doesn't produce any achievable outcomes relevant to their own interests.

Stirling (2014) argues that if public engagement exercises around innovation, including gene drives, are to be credible and robust, they should not be restricted to issues of risk or safety alone, nor confined merely to the ways in which a new technology 'should' or is expected to work; nor should they assume that the technology will be introduced in any

case, whatever the outcome of the public engagement.

Stirling et al. (2018) discuss risk, participation and democracy in the governance of new synthetic biology and gene drive technologies. They argue (Stirling et al. 2018, 44) that genuine empowerment of all affected parties actually interested in making better choices differs from 'instrumental' participation, which is simply about engineering pre-existing aims (such as: fostering trust; providing justification; securing acceptance; and managing blame). Stirling et al. (2018, 44) therefore consider how regulatory assessment of gene drives can move from a purely risk-based analysis to diverse and more substantive processes of 'social appraisal'.

This same article also emphasises that appraisal should devote symmetrical attention to all practical alternatives and offer a balanced picture of associated pros and cons as seen by the affected stakeholders – particularly those having no commercial interest in the technology under consideration (Stirling et al. 2018, 46). Questions around benefit and harm must be directed to the potential pros and cons associated with a diverse array of alternative policy options. These pros and cons would highlight the importance of embedding risk-based assessment in a broader social appraisal that includes public participation. Real participation must recognise: a.) that some level of ignorance will always exist with a new technology; and b.) that a substantive social appraisal entails value-based judgements that probabilistic risk assessment techniques are not designed to address (Stirling et al. 2018, 48).

Leach et al. (2010) point out that technological fixes frequently fail to work and create further problems because they are most often modelled in labs or on computers, methodologies which do not reflect the complexity of real world situations. These authors argue in favour of offering a broader range of options at such participatory sessions, described as "multiple potential pathways to sustainability". Such an approach draws attention to the contrast between "dominant" and "alternative" narratives. For example, for infectious disease epidemics, the dominant narrative is that outbreaks are threatening humanity and need to be controlled through surveillance and technological solutions. An alternative narrative might be that "underlying causes need to be tackled, requiring a rethink of surveillance and diverse social, cultural, ecological and technological responses" (Leach et al. 2010, Table 7.3). According to Leach et al. (2010), that would lead to greater recognition of uncertainty and would empower approaches more rooted in local needs that feature more equitable, socially distributed outcomes. They list five key principles for appraisal for sustainability:

- Include a diversity of types of knowledge through participatory engagement;
- Extend scope and enable choice;
- Take a dynamic perspective, accept incomplete knowledge;
- Attend to rights, equity and power; and
- Be reflexive (Leach et al. 2010, Table 5.3).

The dominant versus alternative narrative is clearly visible in the case of GDOs, for example in proposals to release gene drive mosquitoes as a proposed technological solution to tackle malaria, as there are many other approaches that might work better with less risk. Leach et al.'s (2010) five key principles are therefore essential requirements for public engagement to be meaningful.

Ely et al. argue that technology assessment practices can serve to unjustifiably 'close down' debate, "failing adequately to address technical uncertainties and social ambiguities, reducing scope for democratic accountability and co-ordination across scales and contexts" (Ely et al. 2013, 1). They note that "existing efforts in technology development and wider innovation are typically most strongly steered by incumbent interests, which often do not match those of the most vulnerable groups, and frequently fail fully to account for social, technical and ecological complexities and uncertainties" (Ely et al. 2013, 1). They argue in favour of "broadening out" and "opening up" technology assessment. By

'broadening out', they mean including a variety of options, policies, methods of analysis, uncertainties, and so on (Ely et al. 2013, 2). By 'opening out', they mean communicating the results of the analysis more widely and in a way which allows for different interpretations, rather than giving a single answer (Ely et al. 2013, 2).

Campos et al. (2017, 14) describe how the multiple programmes of 'community engagement' undertaken during the open field releases of Oxitec's GM mosquitoes in Brazil served primarily to 'publicise' the releases, rather than to examine the fundamentally political choice about whether to pursue a biotechnological strategy of vector control, or whether to explore the conditions of public acceptability prior to a decision to deploy this technology. Campos et al. note that the processes of 'community engagement' promoted by the sponsors of Oxitec's GM mosquitoes in Brazil "neither encouraged inclusive deliberation nor gave rise to opportunities for responsiveness to public concerns on the part of innovation actors" and also note, "At the same time, the regulatory system never explicitly reviewed public expectations or concerns in its assessment of OX513A mosquitoes" (Campos et al. 2017, 3). Campos et al. argue that "the complex and conflict-ridden trajectory" of GM mosquitoes in Brazil "serves to highlight the role that political accountability must play in any effective implementation of the principles of Responsible Innovation" (Campos et al. 2017, 2). By political accountability, they mean "a set of mechanisms, institutional or otherwise, that render open to public scrutiny and debate the rationales that actors in positions of political authority draw on to support certain innovation trajectories", including, but not limited to, regulatory approval and community consent (Campos et al. 2017, 3).

Below, we consider some aspects of this problem.

10.1.1 Need for engagement in the definition of a problem and for 'broadening out' societal appraisal

Several aspects of today's current paradigm of engagement are responsible for the frustrations described above. One is the fact that participation intended to generate acceptance does not engage people in the first place in a clear definition of what the problem actually is for which their assessment is needed. For example, holding a public consultation, as part of gaining authorisation to market new genetically modified crops, may allow farmers to expose their concerns regarding the impact of these technologies in their production but it never asks the farmers what actual problems they're facing in the first place. Problems are, in public engagement of science and technology, defined *a priori* by the consultation, participation or deliberation spaces, and by the scientists and promoters who have already decided on what they are. The reason for this is that the hegemonic paradigm of participation or engagement sees citizens as objects and not as subjects of the discourse. As Wynne (2003) has described, in contemporary policy culture, it is problematically not ordinary public citizens, but scientific experts who are assumed to be the proper authors of "public meanings" (the accepted meaning of public issues, especially those involving 'science', for policy to manage).

This problem has led Civil Society Organisations to call for opportunities for participation to be provided from *the very beginning* of the process, which would then include the question of how funding for scientific research is allocated (PSx2 2008, 31). In the case of GDOs, this would mean opening up the question of research priorities to much earlier, more in-depth, discussions.

Unfortunately, most of the institutions that fund research promote only a limited forum for engagement. Discussion of what kinds of projects should be considered for a funding call is currently rarely open to the engagement of the affected public. There is a need to recognise that public engagement should be a fundamental part of the preliminary phases; that is, when the whole complex of funders,

innovation stakeholders and researchers engage in an exclusive and elite process in which they pose and develop a question for R&D.

Engaging society in debates about GDOs has many challenges, as does any initiative trying to include public engagement with scientific innovation. These challenges have been identified within the recurrent debates over the impact of new technologies with effects that are highly uncertain. One example, which is also stressed in the NASEM (2016) report, is: which groups should engage in the participatory initiatives of GDOs risk assessment? It is widely recognised that people affected by the technology have a strong interest in being able to join engagement initiatives; but the communities engaging in this participatory process are often vulnerable, that is, at serious disadvantages compared to the researchers and promoters. In the case of GDOs seeking public approval for release that promise to reduce or control an infectious disease, that vulnerability is constructed around the fact that they are the ones being affected by this disease. This fact may of course make such a public more liable to accept technologies that promise to eliminate the disease than those who are not affected. This may not mean they desire the technology, only that they are too vulnerable to oppose it.

Although the idea of public engagement in decision-making is accepted by most of the scientists and experts working in risk assessment with human communities, there is a fundamental bias in their vision of how this should work. They often assume that these communities are *inactive* regarding the disease concerned. This is often not true, which represents a challenge to mainstream strategies of engagement that mostly begin from the false premise that there are no local risk assessment strategies already being implemented, or that those in existence are based in ignorance and therefore do not serve to address the problem. When considering the engagement of communities, we should not only take into consideration the condition of the scientific research, we also need to engage in debates concerning value and power relations.

Discussing releases of GM mosquitoes intended to tackle dengue, Nading notes that, "Ethics that appeal to risk calculated in nested regulatory institutions, a standardizable body or an idealized 'nature', prevent us from asking, 'What if resources were put toward changing the conditions that make the environments of Grand Cayman, Bahia, Kuala Lampur and Key West (not to mention less research-ready spaces such as Managua and Manila) dengue-endemic in the first place?' In other words, these discourses divert our attention from the fact that dengue the disease, like the GM organism that would be its cure, is a product of uneven, though by no means unchanging, political and economic relations" (Nading 2015, 41).

When addressing the scientific questions regarding GDOs, rather than enquiring whether GDOs may cause unintended effects, we should ask ourselves at the earliest stages: 'How well do we know the diseases we are targeting? How well do we understand the complexity of the ecology of the target populations? Are these diseases *only* transmitted by certain vectors? Which disciplines do we need to engage in the development of such technologies?'

For example, according to the Target Malaria project, it seems that medicine and public health professionals are not included when these outreach teams are constituted. As we see from their website, the team mostly consists of biologists, geneticists and engineers, with a clear absence of health professionals. Such a team composition seems an odd choice, considering the promises made about these GDOs primarily concern improved human health. Furthermore, as is stressed in the NASEM (2016) report, communities also have their own 'ways of knowing' when it comes to these scientific questions, which means we should not only promote the exchange of knowledge, we should incorporate their knowledge in the apparatus of participation, the definition of the questions, the project design and its implementation and periodic review. We should also be prepared to fail; that means that engagement must not be conducted within the premise that the technology will be accepted, that it only needs some small modification and technical instruments for assessment to achieve that invariable goal. We

must be prepared to reject these technologies, not just in favour of alternatives that may already exist, but also in favour of alternative paths of development for the future.

10.1.2 The need for problem-led engagement

A related issue is the need for engagement to be problem-led, not technology-led. One of the major critiques of today's methods of scientific production of knowledge is that they are mostly oriented in order to serve their internal technological apparatus, rather than to seriously consider a problem or scientific challenge that needs to be addressed.

For example, the NASEM (2016) report reflects this problem. This report, which tried to "create a consensus to summarize the current understanding of the scientific discoveries regarding gene drives" (NASEM 2016, vii), not to mention its subtle contradictions, assumes that problems regarding the impacts that could conceivably be caused by gene drives are mainly to be solved by adapting new versions of the same technology. For example, it's often highlighted in the report that one possible solution regarding the impact of gene drives is to introduce *another* genetically modified mosquito (with the as yet non-existent "reversal drives"), even when the authors accept that these, even if eventually perfected, may create impacts of their own.

In contrast, problem-led research is based on posing fundamental questions about a given problem. If we accept uncritically that a technology is the best (or only) solution to complex phenomena such as famine or disease, we will be trapped in the current socio-technological apparatus. As Kloppenburg (2005) has argued, this bias generates a scientific contradiction. The contradiction is simple: the socio-technological bias of modern society (and consequently of modern science) is based on the desire to continuously revolutionise the means of production and consumption. Project applications for funding reflect this essentially economic goal.

Researchers have all faced that blank space in grant application forms, which requires an answer to questions such as: What is the novelty of your approach? Which new products does your research generate? What is the intrinsic value of your project? To these questions only a few will risk answering with "old", non-technological approaches (such as traditional, indigenous and local knowledge). Researchers tend to ignore them; they are no longer in fashion. The choices we are led to make by a technology-oriented approach makes us ignore tested methodologies built by our own communities. With time, and because research tends to move in the direction of innovation, some of this important knowledge is forgotten. This represents a creative form of destruction of memory and experience, opening a gap of open enquiry within the fabric of the scientific enterprise.

A broader approach would begin with different definitions of the problem that is being investigated (such as the challenge of tropical disease), especially to those problems involving social actors, and a serious consideration of all the alternatives that could be used or developed in order to tackle it, including social measures such as alleviating poverty or lack of access to clean water. In the context of GDOs, this means that public engagement should never begin with the promotion of a claimed technological 'solution'.

10.1.3 The need to avoid unrealistic promises

As noted above in Section 5, unrealistic promises distort public engagement in debates about new technologies. For credible public engagement to take place, uncertainty about what can be delivered needs to be openly acknowledged and unrealistic promises must be avoided.

If public engagement exercises are framed in a way that implies tremendous benefits are likely (or even inevitable) if open releases of GDOs are permitted, this limits the space for discussion of the complexity of such an approach and its dependence on numerous unverified assumptions. It also does not address the issue of the opportunity costs associated with investing in any approach that might not deliver

the claimed outcomes. Over-hyped claims of future benefits may also prevent some concerns from being included in the framing of the discussion (because, by definition, the gene drive organism is pre-supposed to be successful and therefore any harms associated with its failure are excluded from debate).

Addressing the issue of unrealistic promises also requires new approaches to the governance of science in order to regulate the 'political economy of promise' currently shaping scientific culture in the public interest. This has not even been posed as a problem to be addressed, let alone been subject to collective analysis and deliberation.

10.1.4 The need for inclusiveness and responsiveness

Civil Society Organisations have argued that the innovation process needs to be opened up so that all stakeholders have enough time to consider the implications of a new technology (PSx2 2008, 30-32). Everyone should be able to participate at some level and in some capacity; this would necessarily include Civil Society Organisations. Participation needs to be on an equal footing in order to address unequal power relations, and public concerns must be listened to and taken into account (i.e. the process must be responsive).

Due to issues with power imbalances, there is a particular need to include marginalised groups. Furthermore, 'inclusiveness' must not mean a simple invitation to speak, but a genuine opportunity to shape agendas, including research agendas, and to affect decisions. This should include *a right to refuse to take part in a particular project, and to propose and explore alternative approaches.*

The challenges of engagement in debates regarding GDOs are particularly great, due to this technology's potentially invasive, international and irreversible effects.

10.1.5 Role of scientists and 'counter-expertise'

Suppression of dissenting scientific voices has long been the norm in science (Martin 1999; Delborne 2016). The goal of this suppression is not just a defence of the rationality of the scientific system. It is equally a professional defence of the curtain of authority and power that separates science from society. That curtain makes sure that the roles for engagement are decided by the field of the "Us", that is, the protagonists for an innovation, and that the "Others" are the ones who need to adapt in order to participate.

Civil Society Organisations have argued that 'counter-expertise' plays an important role in exposing bias and enabling alternative perspectives to be heard (PSx2 2008, 31). However, there cannot be counter-expertise without funding and resources. Transparency and two-way exchanges of information, open-mindedness and genuine engagement are also essential for societal knowledge-development and learning. Debates both within and about science should involve different opinions/viewpoints and a plurality of expertise and recognition of other types of knowledge that take into account minority experiences and voices.

This means that another model of engagement is needed. Some alternatives have been initiated by groups of critical scholars in an interdisciplinary way (e.g. Nunes et al. 2014). These initiatives take into account many facets of society and of its communities and groups, including economic, social and cultural aspects. When a researcher approaches engagement from a critical and self-reflective perspective, mutual learning can take place; the movement of knowledge then becomes a flux and not a linear process. The tools and the apparatus for participation are both built on the people's forms of organisation and in their values and concerns. However, this effort requires time and resources.

11 Conclusions

In this chapter, we have considered the political economy of GDOs, including how research is patented and funded, and how funding concerns lead to unrealistic claims about what researchers can deliver. Gene drive R&D is still in its infancy and far from any field trials. Many claims about future benefits of gene drives portrayed in media, scientific publications and patent applications thus at best seem premature. Public discussion is often limited to speculative health and conservation applications, with the aim of focusing on those claimed benefits which appear more likely to attract public support.

We have explored how exaggerating effectiveness can lead to opportunity costs when alternative solutions are neglected, and how it can close down public debate about the best ways of developing salient knowledge collectively in order to tackle societal problems.

We then considered how issues such as obtaining prior informed consent have been undertaken by existing projects wishing to release genetically modified (GM) mosquitoes (currently without gene drive, but with some plans to include it in the future); and we noted serious limitations in these approaches. We discussed how power imbalances may affect the regulatory framework and who is asked for their input to decisions. We discussed liability and the Precautionary Principle and finally considered the issue of public engagement in decisions about research and development involving GDOs.

Public engagement has to take place at the very beginning of the process, when funders, innovation stakeholders and researchers define what a problem is and set R&D priorities. We conclude that social issues regarding GDOs can only be addressed by broadening the processes of public engagement with prevailing R&D and commercial interests, and by taking a properly precautionary approach. It is essential to acknowledge the extent of the ignorance and uncertainty embodied in the best of scientific understanding of the complexities of ecosystem and human health responses to the release of GDOs, and thus the unpredictability – and irreversibility – of the future effects of GDO releases. Alternative approaches to tackling problems must be part of public engagement with the scientific, regulatory and science policy debates, including questions about what kinds of research should be funded. Public debate should not be framed by unsubstantiated and unrealistic claims about what gene drives can deliver. Genuine empowerment of all affected parties in the interests of making better choices must not be conducted with the premise that the technology will be accepted and that it only needs some small modification and technical changes to achieve that goal. Society must be prepared to reject these technologies, not just in favour of alternatives that may already exist, but also in favour of alternative paths of development for the future.

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Chapter 4

Ethics and governance

Christopher Preston, Fern Wickson

1 Introduction

1.1 A broad range of ethical considerations

In a general sense, making an ethical assessment means trying to determine what is right and wrong in regard to a particular situation or set of conditions. Importantly, ethics is not simply about asserting an opinion. In ethical analysis, the use of reasoned justification and the provision of sound arguments is esse ntial.

The argumentation for why something is right or wrong can take various forms. Ethical arguments may consider things such as: a) how an action (e.g. the development and/or use of a particular technology) may or may not align with certain principles or (moral) laws; b) the consequences of an activity for different systems and actors; c) the underlying attitudes or virtues and vices being displayed; d) the impacts on social or environmental justice; or, e) the changes in relationships, cultural identities or ways of viewing the world and one's place within it. Ethical considerations may also involve the influence of a technology on culturally important considerations such as what is considered natural, the implications for future generations, consequences for animal welfare, and more.

Stating this broad range of considerations at the outset is important because there is a temptation for some to think that the ethical questions related to gene drives boil down simply to an assessment of the benefits and costs that the technology might have, or to assume that only benefits and costs for human beings are relevant. This is misleading, because to narrow down the ethical terrain to include only impacts for human beings or only health and environmental benefits and harms is a false simplification. As we will show in this chapter, ethical issues cover a much wider range of potential concerns, and these considerations are often interconnected. When parties to the United Nations Convention on Biological Diversity invited signatories to take into account "socio-economic, cultural and ethical considerations" related to biotechnology and synthetic biology, no prejudgement was made about what should count as an ethical consideration (UN Convention on Biological Diversity 2016). Therefore, it is important to remain sensitive and attentive to the broad range of considerations that represent the ecosystem of ethical concerns over gene drives.

A particular branch of ethics known as "environmental ethics" expands moral concerns to include elements of the non-human world. It asks questions about which entities (or processes) beyond human beings have moral value, what these moral values might be grounded in, and how extending moral values to aspects of the environment changes how we should act in the world. Environmental ethics also considers what constitutes a good life of co-habitation between humans and the broader community of life on Earth.

In asking these questions, environmental ethics tends to take issue with the view that only humans have moral worth. The field contains substantial debates about what types of entities and organisms are worthy of moral consideration in any ethical assessment, variously adding plants, animals, species, and even entire ecosystems to the mix of entities regarded as having value (Donovan and Adams 2000; Taylor 1981; Rolston III 1988). There are also lively debates about whether the moral value in need of protection resides in individual animals and ual animals and organisms, in populations or species as a whole, in elements of a genome, or even in the biogeophysical processes that sustain them

all (Dawkins 2006; Rolston III 2010; Kheel 2007). Environmental ethics also evaluates beliefs about human superiority that became common after the Enlightenment and the birth of modernity, and links them to the exploitation of nature that is characteristic of industrialization (Merchant 1980; Berman 1981).

Box 1: Ethical questions about gene drives in switzerland

New genetic engineering techniques and resulting applications such as gene drives are intensively discussed in Switzerland. The ethical issues arising from the application of biotechnology and genetic engineering in the animal, plant and environmental sectors are regarded as extending beyond human interests and concerns. In 1998, at a time when genetic engineering was generating controversy in Swiss politics and public conversations, Switzerland established its own ethics committee to deal with these issues, known today as the Federal Ethics Committee on Non-Human Biotechnology (ECNH).

An ethics committee that deals exclusively with the applications of biotechnology in the non-human field is unique in Europe. Generally, national ethics committees focus on human medical issues. A second specialty of the ECNH is its mandate to concretise the concept of the dignity of living beings. According to the Swiss Federal Constitution the dignity of living beings has to be taken into account when using them.

Recent topics dealt with by the ECNH include the new genetic engineering techniques and their application in plant breeding ("New plant breeding techniques - ethical considerations") and questions of risk surrounding the release of genetically modified plants in the environment ("Release of genetically modified plants – ethical requirements"). The committee has also recently addressed the more fundamental topic of "Precaution in the environmental field. Ethical requirements for the regulation of new biotechnologies".

Towards the end of 2017, the ECNH began working on a report on gene drives. In addition to questions regarding risk ethics and biosecurity, the moral status of the individuals, species, populations and biodiversity affected by gene drives is also considered.

With its reports and statements, the ECNH provides information at three levels. It advises the Federal Council and the administration on the preparation of legislation in the field of non-human biotechnology and genetic engineering, and makes proposals for future legislation. It advises the federal and cantonal authorities on the enforcement of federal regulations. Finally, it is tasked with informing the public and promoting dialogue on the benefits and risks of new technologies.

1.2 The importance of context for ethical assessment

Given the broad range of ethical concerns possible, it is important that any ethical assessment of new fields of technological development take into account the context in which they arise and will be used. Gene drive technologies have certainly not emerged in a vacuum. Gene drives follow from a specific line of scientific research and technical development set within a distinctive set of socio-economic and legal arrangements; they operate against the background of a particular political history, as well as having to face specific public health and environmental challenges.

This very new technology has arrived in the midst of decades of persistent and highly polarized debate about the environmental release of biotechnology in general. The history of this acrimonious debate includes suspicion about the underlying motives of biotechnological interventions into organisms; a lack of trust regarding the quality of existing scientific and regulatory frameworks; and significant concerns regarding concentrations of power and questions of ownership, control and justice. Emerging from this legacy of mistrust, anger, fear, and frustration (on all sides), gene drive technology is of course then immediately exposed to many of these pre-existing concerns. It is important that any assessment of the ethical issues associated with gene drives recognize this broader context and consider how the legacy of biotech in general shapes the discussion.

Gene drives are also arriving just as a new realization about the full extent of the deleterious effects of human impacts on earth is dawning. From

extensive habitat destruction and species extinctions, along with the spread of disease vectors and the loss of key nutrients like nitrogen and phosphorous in the soils, to rising sea levels, changing ocean currents and increasing greenhouse gas concentrations, the world is increasingly thought to be on the brink of a precarious future with 'no analogue' in history (Kammer 2017). The alleged arrival of the 'Anthropocene' or 'human-created' epoch is creating significant shifts in how people are thinking about nature and about humans' proper role within it (Crutzen and Stoermer 2000; Steffen, Crutzen, and McNeill 2007; Waters 2016).

Gene drives are one of a range of new technologies that are making new areas of environmental management possible for the first time. For example, climate engineering is creating the potential for deliberate manipulation of the solar radiation striking the surface of the earth (Shepherd 2009). Nanotechnology is permitting novel rearrangements of the structure of matter at the atomic and molecular scale (Drexler 2013). Synthetic biology is allowing the creation of hitherto unseen organisms through designer DNA (Hutchison et al. 2016). In an epoch full of new challenges, gene drives are emerging as one of a number of new technologies offering particularly radical ways of addressing a difficult future. However, the ethics of gene drives, along with all these other emerging radical technologies, are deeply contested.

Unanswered questions about just how much to step up human management of the natural world, in order to secure human and environmental benefits, are on many people's minds (Marris 2011; Asafu-Adjaye et al. 2015; Preston 2018). What is clear about the range of powerful technologies emerging in the Anthropocene is they have the potential to scramble many familiar ethical categories. This type of techno-moral change (Swierstra, Stemerding, and Boenink 2009) means that the future may not be characterized by the same ethical contours as the past. A Nuffield Council report expresses this as the idea that gene drives are "transformative technology, one that both displaces current ways of doing things and subtly changes the nature of what is done" (Nuffield Council on Bioethics 2016, 31). Deeply contested cultural perspectives on these puzzling changes are also more visible now than ever before through a range of new media.

What makes ethical analysis so central to the consideration of gene drives is that a key argument for pursuing them is also an ethical one. Gene drive technologies are being developed in large part due to the perception they might offer enormous benefits for human health challenges, for example malaria, Zika virus, and dengue fever (Nuffield Council on Bioethics 2016; National Academies of Science, Engineering and Medicide [NASEM] 2016; Matthews 2018). They are also being presented as offering hope in the face of difficult ecological challenges, such as the management of invasive species on island ecosystems. Furthermore, they are being touted as potential tools for helping to address perennial agricultural challenges, such as pernicious weeds and virulent insect pests. Real solutions to these kinds of pressing health and environmental problems would clearly provide large and highly desirable benefits, which means the moral and ethical stakes are therefore undoubtedly high.

Powerful as these potential benefits appear, almost everyone in the discussion of gene drives admits that the most important of the moral questions they present are not all resolved. The number of scientific uncertainties gene drives create, the radical type of intervention into ecology and evolution they represent, and the social and economic disruption they might generate, all suggest gene drives may not confer their proclaimed benefits without posing a serious threat to a number of equally important human and environmental values. The potential for very significant disruptions and harms and the fact that this is accompanied by equally significant levels of scientific uncertainty mean that there have been loud calls for precaution and regulation.

With enthusiastic researchers and a hungry media having a tendency to over-sell the potential benefits of every transformative technology (see Chapter 3 for a discussion of hyped promises), a broader examination of the ethical questions gene drives raise is essential. As these ethical discussions occur, they must be tied directly to the scientific

research and technological developments now occurring. This means that ethical issues must be considered not only in connection with any future deployment of a gene drive in nature, but also in terms of how the technology is being imagined, financed and developed. Furthermore, as recognised in international agreements such as the Rio Declaration, sound environmental decision-making and sustainable development also require that such analyses be inclusive, participatory and sensitive to the views of indigenous peoples (Principles 10 and 22). Incorporating this kind of inclusive ethical reflection is increasingly recognized as a requirement for responsible forms of research and innovation (Stilgoe, Owen, and Macnaghten 2013).

1.3 The approach of this chapter

This chapter focuses on providing a general overview of the wide range of ethical issues connected to gene drives. This range has been organized into three broad categories or ways of thinking: a.) the impacts the technology can have for human and environmental health and justice, b.) the character of the technological intervention itself, and c.) the intentions and worldviews driving the technology forward. Organizing the ethical issues according to the overarching categories of "Impacts," "Interventions" and "Intentions" is an attempt to draw awareness to three different arenas of ethical concern and to highlight the breadth of issues at stake.

It is, however, important to note that the ethics of gene drives cannot, in the end, be neatly packaged into separate silos. The acceptability of any one impact, for example, will depend on both the intention behind the pathway and on the kind of interventions any particular worldview permits. Worldviews, values, principles, intentions and beliefs are interconnected - continually informing, shaping, reinforcing and remaking each other in action. This means that there are shifting and productive tensions across the categories presented and that they interact in a dynamic and reciprocating ecosystem. In the presentation of our categories of ethical issues, we therefore also try to make visible where there is an overlap between the different factors in order to illustrate both the breadth and the complexity of the ethical issues gene drives create.

A key message contained in this chapter is that the scope of ethical issues associated with gene drives is much wider – and therefore the ethical bar for their release into wild populations much higher – than some of their advocates admit. Furthermore, the chapter makes the case that the state of the art in gene drive science and the current state of regulatory preparedness suggest that the technology is a long way from reaching this bar. To meet the goals of sustainable development in a way that is consistent with a precautionary approach (Rio Declaration Principle 15), (see Box 2) this powerful and controversial technology requires not just addressing the numerous still-unanswered technical questions, but also a much more active commitment to broad ethical analyses that must be performed in a timely and participatory manner. The chapter therefore concludes by pointing towards some essential features of good governance for gene drives if they are to be developed in a manner that is sustainable, responsible, safe and ethical.

2 Impacts

Gene drives are designed to have considerable physical impacts on humans, animals, and ecosystems. Like other powerful technologies, gene drives will not just affect the total amount of harm or welfare present in the world; they are likely to impact how these costs and benefits are distributed. Furthermore, the distribution of these impacts is not just relevant for today. It will bear on future generations of humans as well as future generations of non-human organisms. A full ethical consideration of the impacts of gene drives will therefore need to consider questions of justice alongside con-

siderations of total welfare and harm. It will have to consider both questions of just distribution (e.g. how will the benefits and burdens be distributed?) and questions of just process (e.g. who has decision-making authority over gene drive development and deployment?). All this must be done while remaining sensitive to intergenerational and interspecies concerns. We consider each of these different types of impact in the discussion below.

2.1 Impacts on human and environmental welfare

As discussed in Chapter 2, perhaps the most vocal argument made in support of gene drives involves the benefits they may bring to human health and well-being. In 2017, according to the World Health Organization, approximately 435,000 people died of malaria worldwide, with 90% of these deaths in Africa and more than two-thirds of them involving children under the age of five (World Health Organization 2018). If a gene drive could cause a mosquito population to crash (through engineering sterility or a bias in sex ratio) or if it could interrupt transmission of the parasite that causes malaria, then a great deal of human suffering could potentially be prevented. The elimination of these deaths and the suffering they involve is, to humans, highly morally desirable. If gene drives could also crack difficult agricultural or conservation problems, the resulting benefits might also be significant.

Considerations of this kind fit squarely into consequentialist modes of ethical reasoning and cost/benefit frameworks of analysis. The first set of complicating factors faced by these arguments are perhaps the obvious ones. These desirable consequences and benefits in welfare will only be obtained if: 1) gene drives can be made dependably operational, 2) they do not come with accompanying or hidden costs to human or environmental health, and 3) they offer a real, long-term solution. At present, there are no guarantees for even one of these points.

The US National Academy of Sciences opened their comprehensive report Gene Drives on the Horizon with the claim that "gene-drive modified organisms hold promise for addressing difficult to solve, persistent challenges, such as the eradication of vector-borne diseases and the conservation of threatened and endangered species" (NASEM 2016, 1). Almost immediately after this claim, however, they declared that "considerable gaps in knowledge about potential off-target (within the organism) and non-target (in other species or the environment) effects" of the CRISPR/Cas9 tool remain (NASEM 2016, 1).

In a similar fashion, the UK's Nuffield Council's report, Genome Editing: An Ethical Review, pointed to the same potential benefits of the use of gene drive technologies, including "eradication of insect pests and disease vectors, reduction of invasive species and management of ecosystems" (Nuffield Council on Bioethics 2016, 76). Very shortly afterwards, they too pointed towards important elements of uncertainty that must be taken into account, including "the sensitivity of natural ecologies, concern for the welfare of animals, risk of unpredictable ecosystem effects and ecological catastrophe" (Nuffield Council on Bioethics 2016, 76).

Both of these major reports are honest about the fact that the research community is at a very early stage of understanding the full range of effects of gene drives. The fact that gene drives involve deletions, insertions and suppressions of complicated genetic codes, whose influence on organismal phenotypes – given the multiplicity of possible genetic backgrounds – is not yet fully understood, creates one dimension of uncertainty (Wolf and Ellegren 2017) (see also Chapter 1). The fact they are designed to spread widely throughout open systems, rather than to remain within the bounded system of a laboratory or the semi-bounded system of an agricultural setting, creates another. The potential for harm from gene drives, combined with high levels of scientific uncertainty, triggers calls for the application of a precautionary approach in the development and application of this technology.

Box 2: A precautionary approach

A precautionary approach involves adopting a cautious attitude towards risk. This includes taking decisions or actions that aim to minimize or avoid potential harm even before it is sure that such harm will occur. It has been cited in a wide range of regulatory policies and is often emphasized in arenas where objectives of industrial development and environmental protection intersect.

A precautionary approach can also adopt the position that when there is scientific uncertainty about the possibility of harmful effects arising from a particular development, policy-makers can legitimately lean on the side of caution. One authoritative statement of the approach declares: "When an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically" (Wingspread Statement 1998). This means the potential for harm does not have to be proven with absolute certainty before pre-emptive measures may be taken to avoid it.

Versions of the precautionary approach appear in the World Charter for Nature, the Montreal Protocol, the Rio Declaration, the Kyoto Protocol, the United Nations Convention on Biodiversity, the Cartagena Protocol on Biosafety, the Swiss Gene Technology Act and other international agreements. A legally binding Precautionary Principle is also part of statutory law in several areas of European Union regulatory policy.

Despite its appearance in so many international texts, the precautionary approach is challenging to implement in practice. Different understandings of what constitutes a relevant harm and exactly how to assess risk demonstrate the presence of interpretive flexibility. This opens the application of stringent pre-emptive measures to political contestation. Questions typically arise about how following a precautionary approach may create its own risks and how strictly the approach should be followed if economic costs are high.

Despite these challenges, many people feel that a precautionary approach has both strong intuitive plausibility and also legal legitimacy in the case of powerful global technologies such as gene drives, especially given their potential to have impacts on unprecedented scales.

Useful genome editing requires knowing which gene or genes to edit to cause a particular effect. Understanding the relationship between genes and the ability of an organism to succeed in a particular environment is plagued with difficulty (Barrett and Hoekstra 2011). One of the mistaken dogmas in molecular biology is that genotypes map onto phenotypes in a one-to-one, causal relationship (Lewontin 1991; Sultan 2000; Pigliucci 2001; Morris 2012). Many of the associations between genotype and phenotype that have previously been claimed to exist cannot be replicated (Chanock et al. 2007). The Nuffield Council study of genetic editing conceded that many variations in phenotype "have no determinate association with genetic characteristics" (Nuffield Council on Bioethics 2016, 7). Epistatic effects mean that desired changes in phenotype will often depend on the presence or absence of any number of additional genes in the background. The U.S. National Academy of Sciences recommends, at the very least, that the "examination of the fitness consequences of introduced genetic material requires measurement of its effects across multiple genetic backgrounds" (NASEM 2016, 35). This sort of complicated work remains in its infancy.

Uncertainties about the direct effects of altering genes are constantly being revealed. The first laboratory experiment on the use of a gene drive in mammals was partially successful, but it came with some considerable surprises (Grunwald et al. 2018). The gene drive designed to change the coat color of mice only worked on females. The genomes of the male mice for some reason did not respond with the required homology-directed repair. The timing of the edit in the germline cells, the authors of the study propose, may be important to its success or failure. Development geneticist Paul Thomas described the results as a "reality check" for gene drive enthusiasts (Callaway 2018). While gene drives for rodent populations may be possible, the techniques are not sufficiently understood at present in the lab, let alone in an operational context.

2.2 Creating only the desired effect on phenotype

The use of CRISPR/Cas9 systems is commonly lauded as the key that unlocks the possibility for effective gene drives (Nuffield Council on Bioethics 2016; NASEM 2016; Oye et al. 2014). Unlike other gene editing techniques, such as Zinc Finger Nucleases and TALENs, CRISPR/Cas9 is said to be cheap, accurate, and efficient.

Evidence is starting to emerge, however, that the CRISPR mechanism for editing genomes may not be as reliable as initially thought. CRISPR/Cas9 edits have been found to cause "large deletions and more complex genomic rearrangements at the targeted sites", as well as completely unintended "lesions distal to the cut site" (Kosicki, Tomberg, and Bradley 2018, 1)(See also Shin et al. 2017; Mou et al. 2017). Allen Bradley, a co-author on the first study, wrote "we found that changes in the DNA have been seriously underestimated before now. It is important that anyone thinking of using this technology for gene therapy [in humans] proceeds with caution, and looks very carefully to check for possible harmful effects" (Sanger Communications Team 2018). Although the concern expressed by Bradley is directed not at gene drives but at germ line editing, the same considerations would apply to editing non-human organisms with CRISPR when attempting to develop gene drives.

Other considerations also provide reasons for caution. Pleiotropism is the phenomenon by which one gene can be responsible for several phenotypic effects. Researchers using CRISPR/Cas9 in an attempt to change the pigmentation of a butterfly's wing recently found that the edits changed both the color and the structure of the scales on the wing (Matsuoka and Monteiro 2018, 60). One phenotypic change quickly became two, with the potential for additional changes also present. If a gene drive can change an organism in more than just the intended way, the technology may be considerably less manageable than anticipated.

2.3 uncertainties created by the complexity of ecosystems

At the same time that gene editing creates uncertainties for the phenotype of the organism being edited, driving an edit through a whole population living within a wild ecosystem generates many other uncertainties. When gene drives are used to create effects across such a population, "a complex molecular system will be introduced into complex ecological systems, potentially setting off a cascade of population dynamics and evolutionary processes that could have numerous reverberating effects" (NASEM 2016, 86). Ecologists are sensitized to the power of ecological cascades. Australian cane toads and Yellowstone wolves are living exemplars of how well-meaning interventions into ecological systems have unanticipated and wide-ranging effects.

Gene drives may also not spread in the intended ways. The NASEM report draws attention to the fact that there are "considerable gaps in knowledge regarding the implications of gene drives for an organism's fitness, gene flow in and among populations, and the dispersal of individuals, and how factors such as mating behavior, population sub-structure, and generation time might influence a gene drive's effectiveness" (NASEM 2016, 42). These gaps create the possibility that undesirable ecosystem effects will follow, threatening both ecosystem values and, indirectly, the numerous human values which may depend on them. Article 26 of the Cartegena Protocol draws attention to the particular relevance of such threats to the lives of traditional and indigenous peoples.

The ecological uncertainties surrounding the effects of gene drives are considerable. One concern involves the possible spread to non-target conspecifics. A pernicious species in one location may be a desirable native in another (e.g. possums in New Zealand vs Australia). The potential inability to limit the spread of a gene drive to only the target population creates reason for caution. After recognizing how far a drive could spread outside of the target population, molecular biologist and evolutionary engineer Kevin Esvelt conceded that his earlier endorsement of the use of gene drives as a conserva-

tion tool now looked like "an embarrassing mistake" (Zimmer 2017). He offered a general warning for future attempts at ecosystem-scale management, stating that "invasiveness and conservation don't mix" (Esvelt and Gemmell 2017). Techniques such as "reversal drives," "precision drives," and "daisy drives", that would limit the invasiveness of a gene drive, are still at an early stage of development and come with the same uncertainties as the technology they are attempting to manage.

Another ecological concern involves the possibility of gene drives spreading accidentally to the wrong places through horizontal gene transfer. Although a gene drive is designed to move 'vertically' between generations of sexually reproducing organisms, genetic material is known also to move horizontally. This type of lateral genetic transfer can take place between different species or even between different biological domains (archaea, bacteria, eukaryotes) (Brown 2003). While the risk is currently little understood, a horizontal gene transfer could potentially move a gene drive mechanism from the target species to a non-target species or even genus. The U.S. National Academy of Sciences, the Norwegian Biotechnology Advisory Board and a draft report of the International Union for the Conservation of Nature, all highlight horizontal gene transfer as a potential risk factor for gene drives (NASEM 2016; Bioteknologirådet 2017). This low likelihood but very high consequence scenario would be an unacceptable outcome of gene drive deployment.

These risks of unintended gene drive spread appear in a range of applications. If gene drives are used to target weeds in agriculture, for example, can researchers be confident that only the pernicious species will be affected? The NASEM report uses the example of the weed Amaranthus palmeri as a candidate for a suppression drive within the southern United States. Other members of the Amaranthus genus in North and South America, however, are grown as food staples, and in China as pig feed. If the weed species with the gene drive hybridizes with the food staple, the suppression drive may wipe out the agriculturally important crop (NASEM 2016, 57-58).

Concerns about hybridization are not limited to agricultural arenas. Mosquitoes, now actively being researched as targets for gene drives could hybridize with closely related species, creating unintended and potentially deleterious effects. Accidentally eliminating not just the ones responsible for disease transmission, but all mosquitoes in a region, would certainly be ecologically undesirable. A similar concern exists with Rattus species in Australia, where ecologically harmful non-native species live in proximity to half a dozen or more species of native rats (Moro et al. 2018). Hybridization is a worrying and largely unstudied potential impact of gene drives.

Even if a gene drive works in exactly the manner intended, ecological concerns still linger. Rapid and dramatic reductions in the population of any species will typically have ecological consequences. Of course, when a gene drive is used to suppress the population of an invasive or dangerous species, this is precisely the point. Numerous variables would go into determining just how much of an ecological impact the suppression of a targeted species might have. Removal of an invasive species through a suppression drive could never perfectly reverse the negative effects the invader has caused, while removal of a native species (e.g. a parasite-carrying insect) could have unforeseen consequences. Due to the complexity of ecological relationships, some of the impacts may be hard to predict. Another species acting as a disease vector could move in to the newly unoccupied niche. The targeted species (or parasite) could evolve resistance to the gene drive and become an even greater problem. Numbers of a targeted population could rebound aggressively after temporary suppression, something that could be devastating if immunity to the disease within a vulnerable human population had been lost during the period of suppression.

The uncertainties for both organism and environment described above may, in some cases, be reduced through concerted research in population genetics, evolutionary biology, ecosystem dynamics and ecology. The current state of play, however, is that research on the environmental effects is struggling to keep up with the lab-based work on the molecular mechanism itself (NASEM 2016, 42).

Even if these other fields catch up, uncertainties will remain and more modelling is unlikely to prove capable of adequately addressing them all. Researchers in the Centre for Ecological and Evolutionary Synthesis (CEES) at the University of Oslo suggest that modelling the ecological impacts of gene drives involves so much guesswork over the values of the relevant variables that "it cannot be used in risk assessment in a meaningful way" (Biotecknologirådet 2017, 7-8).

While field-testing gene drives for their ecosystemic effects has been hailed as necessary to remove such uncertainties, this process is also fraught with difficulty. Even limited-scale field tests will be risky due to the built-in mechanisms designed to spread gene drives through a wild population of organisms (Noble et al. 2018). Small-scale field tests would also not necessarily provide the required information to understand large scale, ecosystem impacts. Indeed, such knowledge may not become available until "several years or even decades after deployment" (Kuzma and Rawls 2016, 288). This means subjecting people to an unprecedented global experiment without any assurance of its success or even its usefulness. These types of uncertainties make a compelling risk or cost/benefit assessment of gene drives virtually impossible to accomplish with enough confidence and granularity to be reliable.

In a situation like this, where a sound scientific knowledge base is lacking, making an ethical evaluation of gene drives through assessing the possibility for harmful consequences clearly faces significant challenges. However, an assessment of impacts also requires deciding what constitutes a hazard or harm; this will always be based not on science, but on social and environmental values. Values will often be contested and require democratic processes of engagement to resolve (Wickson 2014). Determining what constitutes an acceptable level of risk also varies significantly with the characteristics of the risk in question, as well as with social and psychological factors (Slovic 1999; Kasperson et al. 2003). Furthermore, deciding what constitutes quality in safety science, including what are appropriate methods and interpretations of the available knowledge, will likewise involve value-based decisions (Wickson and Wynne 2012a, 2012b). All of this means that in terms of assessing impacts, there are ethical questions not only about ratio of benefit to risk involved, but also about how calculations of risk are framed, researched and interpreted.

In the case of the potential eradication of diseases that come with a high human cost, the potential benefits of a successful gene drive application may be judged by some to be so high that they outweigh any uncertainties about ecological and evolutionary costs. For example, Min and others propose, perhaps rashly, that "no known human-caused ecological effect approaches the toll in human lives and suffering inflicted by malaria" (Min et al. 2018, S51). Some advocates also think it possible to overemphasize the worries over misapplications and unintended effects. They remind skeptics that ecosystems are constantly adapting to change and that nature can be remarkably resilient (E. Marris 2011; Pearce 2015). Enthusiasts might point out that when the *Aedes aegypti* mosquito was virtually eliminated from Central and Southern America in the 1960s, after decades of continuous pesticide application, that there was little evidence of a cascade of harmful ecological effects. It is hard to tell, however, if this conclusion was premature. It is possible that not enough time had passed or studies been completed in order to determine the full impacts of the suppression. The conclusion may be based more on hope than on science.

Discussions about gene drives seem to be falling within what Alfred Nordmann calls "speculative ethics", in which "an imagined future overwhelms the present" (Nordmann 2007, 32). Future promises made about gene drives, for example concerning malaria, can make them look morally irresistible, while other scenarios of ecological collapse make them appear morally abhorrent. Nordmann warns about misleading characterizations of distant hypothetical futures that only serve "to distract us from comparatively mundane, yet no less important and far more pressing issues" (Nordmann 2007, 43). One such characterization is arguably that the technology can act as a "silver bullet" that will solve some of the serious problems we are facing (Webber, Raghu, and Edwards 2015). A more sober assessment

of present uncertainties already in play provides a reminder that all bullets can pose a threat.

In light of the entangled questions of science and values and the deep uncertainties in the available evidence, an ethical assessment of the impacts of gene drives encourages a precautionary approach. It points towards the need for both sound scientific assessment of potential risks and honesty about the current state of knowledge. Currently, far too little is known about how gene drives will impact organisms and the environments in which they reside to make confident predictions about the impacts they would have on existing social, cultural and ecological values.

2.4 Impacts on justice

Let us imagine that all the risks and uncertainties detailed above were magically resolved and gene drives could be deployed with entirely predictable impacts on all organisms and ecosystems. If gene drives could help some of the world's poorest people by decreasing their exposure to dangerous diseases, then a powerful ethical argument in their favor might be their potential to promote global justice. The technology would be deemed ethically desirable because it could relieve some of the world's poorest people from a large amount of unnecessary suffering.

While this argument is persuasive on its surface, it should be remembered that many of the children dying of malaria in Africa could be saved by medications and preventative measures already widely available in developed countries. The unequal distribution of wealth across the globe responsible for this vulnerability is already a grave distributional injustice. Attempting to avoid this ongoing injustice by trying to develop a technological work-around may not be the right way to scrape the ethical conscience clean (see also the Section 4.3 below).

Although powerful new technologies such as gene drives may, under the right circumstances, provide the opportunity to promote global justice by increasing the well-being of the poor, this proposition currently remains entirely speculative. Technologies have the potential to rearrange social relations in ways that undemocratically concentrate power and skew the availability of benefits (Preston and Wickson 2016). Genome editing technologies, says the Nuffield Council, can impact social, intergenerational, and global justice, which they characterize as "the fair distribution of advantages or opportunities among different groups in a society, between one generation and the next or between nations, particularly the nations of the Global North and those of the Global South" (Nuffield Council on Bioethics 2016, 29).They insist that powerful new technologies with the potential to affect welfare must do so "without discriminating unfairly among people" (Nuffield Council on Bioethics 2016, 29).

A first consideration relevant to justice is to recognize that gene drives would not be chosen by individual citizens. They would be deployed after some national or regional level decision. In this regard, gene drives are like climate engineering in their ability "to impact many lives without requiring mass adoption in the marketplace" (Min et al. 2018, S51). There is the potential for this to raise "troubling ethical issues" (Min et al. 2018, S51). The fact that gene drives are mostly being developed in the richer countries and may initially be deployed in the poorer ones brings several justice considerations to the foreground. Some of these issues are matters of fair distribution. Others are matters of fair procedure. The full context of gene drive development and deployment will need to be scrutinized for justice-based concerns if they are to avoid inadvertently promoting the injustices that important efforts like the Sustainable Development Goals are trying to curtail. This includes considerations such as: who has the power to shape the technological development; who decides about its deployment; whose stories are being heard in decision-making processes; whose history is being taken into account; which generations and species count in the assessments; who profits from any potential successes; and who bears the burdens of any failure.

2.5 Who shapes the technological development?

Any harms to environment or health that result if gene drive organisms create unanticipated problems would likely be borne by those least prepared (in terms of wealth, health care infrastructure, disaster response preparedness, etc.) to suffer them. It would be easy for those developing a technology from the safety of a rich country to discount the risk of impacts born by others. Nnimmo Bassey of the Health of Mother Earth Foundation in Nigeria has expressed concern that Africa is on the point of being used as a "testing ground for a technology that has not been proven" (Stein 2018). Of course, public values could also cut the other way. It is possible that those desperate to escape an immediate public health or conservation-related harm may have a higher tolerance for risk than those already insulated from it, even if this higher tolerance may be a product of ethically dubious prior treatment (Gardiner 2013; Carr and Yung 2018).

To ensure justice around gene drives, developers and decision-makers must be particularly attentive to matters of fair procedure. As pointed out above, risk analysis is never entirely a matter of science. It is also a matter of social context and public values. Fiorino makes it clear how "studies of lay judgments about technological hazards reveal a sensitivity to social and political values that expert's models would not acknowledge" (Fiorino 1990, 227). These values depend on culture, history, past experiences and other social and political factors. To their credit, some of the most prominent advocates of gene drives have acknowledged they are proposing a technology which morally requires "transparency, public discussion, and evaluation" (Esvelt et al. 2014, 16). Continuous public engagement from within the socio-ecological context in which a gene drive would be deployed is a moral necessity in any process to fund, research, develop or release gene drive organisms (Oye et al. 2014) (see also Section 5 below).

2.6 Who decides about deployment?

If a gene drive mechanism were to be deployed in the field for public health reasons, it looks probable that its first deployment would be in some part of Africa, to suppress *Anopheles gambiae*, the species of mosquito most responsible for malaria transmission on that continent. Researchers recognize that a decision to deploy must rest with those who have both the most to gain and the most to lose. This means putting the decision about whether to go ahead with deployment into the hands of a joint governance arrangement within African countries. The African Union's New Partnership for Africa's Development (NEPAD) may be such an arrangement (Matthews 2018). The African Union, however, is made up of fifty-four countries, not all of which are host to the same mosquito species and not all of which might see gene drives the same way. This is particularly problematic given the way gene drive technologies are inherently transboundary.

While insect populations can be "clumpy", with high densities in some areas and gaps between populations in others, a gene drive may travel to any place where *Anopheles gambiae* (or other target species) live. A self-propagating CRISPR-based gene drive system is "equivalent to creating a new, highly invasive species: both will likely spread to any ecosystem in which they are viable, possibly causing ecological change" (Esvelt and Gemmell 2017, 2). Responsible gene drive advocates point out that "moving forward without the permission of every other country harboring the target species would be highly irresponsible" (Esvelt and Gemmell 2017, 3). Regulatory approval, affirm Min et al. "must be obtained from every country that would be affected by an eventual deployment" (Min et al. 2018, S52). For actions that would affect indigenous peoples, the principle of "free, prior and informed consent" is an essential pre-requisite, affirmed by the United Nations Declaration on the Rights of Indigenous Peoples (UNDRIP), the UN Convention on Biological Diversity and the International Labour Organization Convention. It is unclear how or whether such permissions could be obtained.

Box 3: Free, prior, and informed consent

Free, prior and informed consent (FPIC) is a condition of procedural justice affirmed in a number of international declarations and treaties.

Procedural justice is a type of justice requiring that policies with direct effects on a particular population are not implemented without the full agreement of those impacted.

'Free' requires that the population is in no way coerced politically, economically, or physically into accepting the policy. This is in direct recognition of the historical marginalization, oppression and exploitation of indigenous peoples. 'Prior' demands that the affected population must be consulted before the policy comes into force rather than after it has been implemented. 'Informed' demands that the consenting party has a full understanding of the effects of the policy before they offer consent.

FPIC has a particularly important application in the case of indigenous peoples who tend to have especially long and intimate relationships with the landscape and are not always adequately represented in government decision-making. Patterns of collective ownership amongst indigenous populations can bring unique demands for securing the ethical use of land and resources. As a consequence, the idea of free, prior and informed consent features prominently in the United Nations Declaration on the Rights of Indigenous Peoples adopted in September 2007.

Importantly, 'consent' is a higher threshold than 'consultation.' The right to self-determination is today seen as a fundamental condition of legitimate political governance and is present in Article 1 of the United Nations Charter. FPIC consequently goes some way towards ensuring self-determination for indigenous populations.

In 2017, the report of the Ad Hoc Technical Expert Group (AHTEG) on Synthetic Biology under the Convention on Biological Diversity wove together the Precautionary Principle (See Box 2) with the need for FPIC. "Given the current uncertainties regarding engineered gene drives, 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."

2.7 Whose history is taken into account?

Putting power for decisions regarding deployment in the hands of those with the most at stake is an important first step, but it does not resolve all the justice questions. Another concern for global justice is the power dynamics created by historical circumstances. A technology developed in the wealthy countries for the benefit of Africans will inevitably come with baggage attached. Thompson points out how "it is highly reasonable for those who have been exploited on the basis of race or gender to regard techno-scientific projects with initial suspicion" (Thompson 2018, S166).

Social science research on a different emerging technology, solar radiation management, makes it clear how relevant this concern is. A Kenyan respondent to a study on affected populations' perceptions of climate engineering asked:

> Where would the power be in terms of who decides what to do? In the past, countries with not as much wealth and the indigenous populations always get put on the back burner and don't get to decide these things. Would that be the same case? (Carr and Yung 2018, 127).

An indigenous resident of the Alaskan Arctic expressed a similar worry:

> With what we've experienced already in terms of our past history and outside influences dictating more than local people are dictating, it gets to be being a bit more protective in the sense of, is this the right thing? How much risk are we going to be subjecting ourselves to? (Carr and Yung 2018, 127)

Inhabitants of African nations who have suffered malarial outbreaks for generations would rightfully be concerned about how treatments for the disease and preventative steps commonly available in the wealthier countries have never made it to where they are most needed. They might reasonably doubt whether offers of help through a new technology are motivated by the right reasons; and they might suspect the persistence of colonial forms of relation-

ship. They might also have a good historical basis for wondering whether the promise of a technological fix lying a number of years in the future might simply be a tactic to divert attention from other types of assistance, which might be of more immediate help.

2.8 Who profits?

These concerns about decision-making power across international boundaries may appear to be diminished by the philanthropic origin of much of this work on gene drives for malaria (e.g. by Target Malaria). Outside of the case of malaria, the larger picture of gene drives is not so reassuring. Amid the enthusiastic development of gene drives for use in agriculture against insects and invasive weeds, many early patents include lists of herbicides and pesticides for which recently evolved tolerances (now inhibiting the effective use of these chemical substances) could potentially be reversed by a gene drive. This would allow chemical companies to recapture the market for those currently failing substances. The pitfalls of creating a gene drive that so ostensibly benefits certain actors raises questions about how "commercial interests could potentially derail precautionary governance" (Thomas 2016).

The Nuffield Council also notes how the quest for funding has the potential to skew research into gene drives. In their view, the presence of intellectual property rights and the background context of stock market speculation "are likely to play a significant part in shaping the dynamics of scientific research and technological innovation" (Nuffield Council on Bioethics 2016, 17). This substantially increases the likelihood of the technology contributing to, rather than diminishing, injustices.

2.9 Which generations are considered?

Intergenerational justice demands that the needs and interests of future generations are considered morally relevant for the actions of the current generation. The geographical extent of the change created by a gene drive intervention and the potential longevity of a trait placed in the germline of an organism means that the impacts of gene drives on ecology and evolution will almost certainly be felt by future generations.

Kuzma and Rawls identify three questions surrounding gene drives most relevant to intergenerational justice:

(1) How would the deployment likely affect the ability of future generations to use the natural world to ensure its own health and well-being?

(2) How would the deployment affect the ability of future generations to apply their own values to enjoy or appreciate the natural world?

(3) How reversible is the deployment so that future generations could apply their own values to restore their options for use or nonuse decisions? (Kuzma and Rawls 2016)

Even though present generations have the right to make changes to the environment for reasons of self-preservation, they also have a moral obligation to leave to future generations a world that is in no worse a state than the one they found. The time lag for the full unfolding of the ecosystem effects of a gene drive and the unlikelihood of complete reversibility mean that the obligation between present and future generations will be uncertain when any decision to deploy is made.

Kuzma and Rawls also suggest that future generations should have the option to enjoy unmodified versions of species. They worry that later generations will have been deprived of the 'wildness' of species altered by today's gene drives (see Sections 3.1 and 3.2 below). But in an argument that may cut in favor of the use of gene drives, they also point out that a drive directed towards preserving an endangered species and the values it offers to future generations might be desirable, when other options for preserving it have been exhausted (Kuzma and Rawls 2016, 292). At the very least, considerations of intergenerational equity imply "there is a strong argument to be made for consulting with the generations that are to inherit the world altered through

this technology" (Kuzma and Rawls 2016, 295). They suggest bringing younger people into the discussion of gene drives.

2.10 Interspecies justice

The justice issues mentioned thus far have all concerned the fair treatment of current and future humans. Many positions in environmental ethics, however, insist that justice between humans and the non-human (or more-than-human) world should also be considered. This might involve justice towards individual organisms, towards species, or towards ecosystems as a whole. While these positions require arguments for the moral consideration of these entities that won't be developed here, it is clear that a technology that deliberately impacts the biological functioning of a particular population of organisms raises legitimate questions about whether humans are treating the non-human world as they should (see Sections 3.1 and 4.2 below). Consenting to be subjected to the effects of a gene drive is obviously not possible for a non-human species, so considerations of interspecies justice need to move beyond an assurance of free, prior, and informed consent. In addition to questions raised by the possibility of impairing biological function and persistence of both target and non-target organisms, depending on the species involved, there may also be unanswered questions about animal welfare and suffering.

Impacts on justice are an important consideration for the ethics of gene drives. Being sensitive to justice issues requires clear and internationally agreed legal frameworks to clarify responsibilities in the case of failure, damage and trans-boundary movement. The Nagoya-Kuala Lumpur Supplementary Protocol on Liability and Redress (under the Cartagena Protocol on Biosafety) could be one such instrument. However, careful and consistent engagement with the affected public is also essential. The NASEM report suggests the outcomes of this engagement "may be as crucial as the scientific outcomes to decisions about whether to release a gene-drive modified organism into the environment" (NASEM 2016, 141). Such engagement is not just an exercise in lecturing lay publics about the alleged benefits of the technology; nor is it a matter of offering the public a simplified up or down vote on whether to proceed. Deliberative public processes around gene drives must be historically informed, contextually relevant, and highly sensitive to important power differentials. The public has a right to shape the path of a technology as powerful as gene drives. It also has a right to say "no" to a proposed deployment.

3 Intervention

The ethical considerations discussed so far resonate strongly with consequentialist types of thinking. If gene drives are deployed, what will their consequences be for human and environmental welfare, and how might gene drives affect procedural, distributive, intergenerational and interspecies justice? The assumption in the ethical considerations up to this point has been that gene drives have the capacity to cause significant impacts – both positive and negative – on present and future humans and non-humans.

A different kind of ethical lens turns away from the impacts which might follow from a gene drive and looks instead to cultural norms or rules to determine whether they might be acceptable. We might think of these as assessments of gene drives that emphasise the principles they might contravene, precedents they might set, or changes to valued ideas they might cause. In these kinds of arguments, questions are raised about the character of the intervention that a gene drive represents. Is this the kind of thing human society should be doing? Is it acceptable on principle? Are there norms of decent behaviour that gene drives would transgress?

When using this lens, costs and benefits are relegated to secondary importance. This is based on the assumption that there are some things it might be desirable to do – or not do – regardless of consequences. In this section we discuss ethical concerns oriented towards how the use of gene drives impacts principles of noninterference, preserving naturalness, and extinction on demand, and how their use would affect hands-off ecological management.

3.1 Noninterference

A principle of noninterference has been prominent in environmental ethics since the field began. Henry David Thoreau was an early proponent of the idea that "a man [sic] is rich in proportion to the amount of things he can afford to let alone" (Thoreau 1906). The value of wild places for another early thinker, John Muir, lay in the fact that they were "…part[s] of the world that had not been shaped by human hand" (Elliot 1982, 90). Rachel Carson had similar values in mind when she lamented the modern exercise of human power: "Only within the moment of time represented by the present century has one species -- man -- acquired significant power to alter the nature of the world" (Carson 1962, 5). Each of these early environmental thinkers found important value in how the world has been shaped during geological and evolutionary history, independent of human action.

Human interference with the operation of the surrounding environment has become progressively more widespread since these early environmentalists were writing. Nevertheless, the principle of noninterference has continued to remain prominent across wide swathes of environmental thought. In a ground-breaking article in 1973 often credited with marking the beginning of modern environmental ethics, Richard Routley stated the foundational belief that "some worthwhile parts of earth's surface should be preserved from substantial human interference" (Routley 1973, 205). According to this line of thinking, Earth's formative processes occupy a special place in the scheme of things. When designating the Grand Canyon as a National Monument in 1908 Theodore Roosevelt declared, "Leave it as it is. You cannot improve on it. The ages have been at work on it, and man [sic] can only mar it." Entities existing and evolving independently of humans are deemed morally important precisely on the basis of their independence.

The idea of nature's intrinsic value (i.e. value in and of itself, beyond its usefulness for humanity), which appears in the preamble to the Convention on Biological Diversity and in the UN's Earth Charter, hinges in large part on the fact that valuable parts of nature are the product of forces operating independently of humans. While it is impossible for humans to live on this planet without intervening and interfering with non-human processes in some shape or form, the presumption in this type of thinking is that human actions need to be controlled in such a way that certain entities and formative processes of the Earth are left largely intact and on their own terms, free from human manipulation and re-direction. A Swiss Federal Ethics Committee on non-human biotechnology expressed this presumption as it applies to plants when concluding "we require justification to disturb plants' lives", on the basis that plants possess their own "dignity" (Swiss Federal Ethics Committee 2008, 17).

Gene drives represent a direct intention to shape organisms and influence evolutionary processes in radically new ways. The evolutionary process, with its long-established mechanisms for genetic inheritance, would no longer be left alone. Using gene drives means engineering evolution to move in a direction chosen by humanity to meet our own objectives. The Nuffield Council claim this amounts to "expedit[ing] the expression of human preferences over the composition of the biosphere" (Nuffield Council on Bioethics 2016, 81). The concern is that this type of intervention into key formative processes is unethical because it is in violation of principles valuing the independence and autonomy (or capacity for self-direction) of nature.

Some find arguments resting on the presumption of noninterference unconvincing, arguing that humanity has directed the evolution of species either intentionally or unintentionally for thousands of years, through the domestication of animals and

plants, habitat change and destruction, climate change, nuclear radiation, and other significant global impacts. The argument continues that this existing track record means that interference with biological processes cannot be wrong in and of itself.

One way to respond to this point is to ask whether environmental ethics means anything at all, if every type of human interference with the natural world is permissible. Isn't environmental thinking, in some measure, about determining proper forms of restraint? Furthermore, not everything that has been considered acceptable in the past is necessarily morally right (slavery being a classic example of this).

Another way to respond is to illustrate how gene drives intervene in natural processes in ways that are qualitatively different from anything that has come before. For example, there is a basic difference in the way gene drives target whole populations rather than individuals or how they interfere with evolutionary mechanisms and inheritance patterns. It is a deeper type of intervention into the natural world to intentionally redirect key processes. This type of intervention may therefore be more morally significant than any that have preceded it and may represent entry into a new type of synthetic age (Preston 2018).

3.2 Maintaining naturalness

The suggestion that noninterference is a morally important principle in environmental ethics has a corollary. Noninterference is viewed as desirable because it protects something of value. The thing of value noninterference protects is 'naturalness'. Another type of ethical concern oriented around the type of intervention gene drives represent therefore focuses on the way the technology threatens what is deemed to be 'natural'.

Like the principle of noninterference, the goal of preserving 'the natural' or 'naturalness' has played a significant role in environmental thought. Bill McKibben is perhaps the most well-known author expressing a concern that humans might be causing the "end of nature", in his eyes, through human-caused climate change (McKibben 1989). Given the prominence of the idea of naturalness in debates over other forms of biotechnology (Evans 1997) as well as over similarly powerful emerging technologies such as climate engineering (Corner et al. 2013; Corner and Pidgeon 2015), concerns about naturalness are likely to feature prominently in the ethics of gene drives.

The two most widely-read analyses of the ethics of gene drives confirm this. The NASEM report states that arguments based on the value of nature and naturalness are "likely to be very important in the public's response to gene drive technologies and in decisions about how those technologies should be developed and used" (NASEM 2016, 75). The Nuffield Council also acknowledges how the idea of "respect for the natural world" is a significant moral and societal consideration (Nuffield Council on Bioethics 2016, 76). The Swiss Federal Ethics Committee concluded along these lines that "Genetic modification of plants should….always involve consideration of conserving and safeguarding the natural" (Swiss Federal Ethics Committee 2008, 20).

Critics respond to this concern about retaining natural processes by pointing out that the category of 'the natural' is so vague and slippery as to be unhelpful. Helen Siipi, for example, has identified more than a dozen different ways that the idea of naturalness is used in environmental and bioethical discourse (Siipi 2008), which creates uncertainty about whether people mean the same thing when using this word. The complicated range of meanings identified by Siipi represents an extension of John Stuart Mill's observation that the category of the natural is highly ambiguous (Mill 1874). On the one hand, it can include everything that takes place on the earth that is not supernatural, including all the products of human works. On the other, it can encompass everything that takes place on earth, with the noted exclusion of human works. Neither of these, Mill observed, are very helpful for guiding policy. Even though there are powerful contemporary accounts of naturalness that are not subject to the Siipi/Mill critique (Lie 2016), worries about the

utility of the idea of naturalness might be especially pertinent in the Anthropocene epoch, now that human-created changes to the planet appear to be ubiquitous.

Box 4: Are humans part of "nature"?

The environmental movement that emerged in western countries in the late nineteenth century has often assumed that the value of wild nature is dependent on an absence of signs of human influence. This generally means keeping human impacts outside of protected natural areas as much as possible. Both the United States Wilderness Act (1964), and the definition of wilderness developed for the European Community's Natura 2000 (2013), view human activities as importantly disruptive when they occur in protected areas. The US Wilderness Act, for example, allows humans to visit wilderness areas but not remain and it forbids any signs of permanent change.

Indigenous people across the world tend not to assume this same separation between humans and the natural world. The concept of "iwígara," for example, used by the Rarámuri of Mexico's Sierra Madres mountains, expresses "the total interconnectedness and integration of all life in the Sierra Madres, physical and spiritual." The people consider themselves accordingly "an integral part of the life and place in which they live" (Salmón 2000, 1328).

Because of their different starting point on the proper human-nature relationship, worldviews of this latter type may not contain the same worries about "noninterference" and "naturalness" as some western views. At the same time, it is often the case that indigenous worldviews embody a deep respect for the surroundings into which a culture is integrated, imposing limits on the type of exploitation of those surroundings permitted. The Rarámuri, says Salmón, "understand that they were placed here as caretakers of their land, but also to aid in the health of the Creator, who works hard each day to provide for the land and its inhabitants" (Salmón 2000, 1329).

This means that although concerns with naturalness and noninterference are more likely to be expressed by those defining humans as separate from nature, even those defining humanity as a part of nature can propose restrictions on the types of intervention into the living world that are permissible based on ethical considerations.

The discounting of the relevance of a concept of naturalness, due to the pervasiveness of global change, is, however, misleading. Although hungry polar bears, heat-stressed hedgehogs and proliferating pine bark beetles are all impacted by human generated change, these changes have not been deliberately shaped or intentionally designed in order to achieve human ends. Intentionally modifying an organism to achieve human ends adds a degree of unnaturalness that unintentionally impacting it does not. When humanity starts to intentionally design biological life, something important has changed. The biosphere is being transformed into the technosphere. For environmentalists who believe that "value exists in nature to the extent that it avoids modification by human technology" (e.g. Katz 1992, 265), this will be a real problem.

A particularly notable aspect of gene-driven organisms is that they would not only exist in the types of human-managed environments that domesticated animals and genetically modified crops do. They would also spread through wild environments. This matters, because wild species have hitherto (by definition) been ones whose lives are lived beyond the bounds of intentional human control (Delborne et al. 2018). With the use of gene drives, there is not only direct human intervention into the operational code of other organisms; their use also entails expanding the laboratory of experimentation beyond agricultural fields into the whole of the wild world.

Emphasising the differences between intentionally modified organisms and others is not reserved for philosophical discussions alone. Property law also subscribes to the idea that deliberately altered organisms are in a separate class. According to many legal regimes, intentional changes introduced into the complex operating systems of self-maintaining and self-reproducing living systems are considered one of the features that may transform them from a natural organism into a human invention, eligible for patent protection (World Intellectual Property Organization 2018). In other words, artifactual organisms can be owned and subject to monopoly intellectual property rights. Increasingly, so too can intentionally-made copies of genes. Doing some-

thing intentionally is the action that makes a real difference in law.

Despite the feeling amongst some commentators that the Anthropocene has diluted the ideas of 'nature' and 'the natural' (Hobbs et al. 2010; Purdy 2015), naturalness remains a powerful category in public and policy discourse around emerging technologies. The continued existence of natural systems independent of human design remains widely valued for both human-focused and non-human-focused reasons. The former can include the way in which they enable humanity to feel emotions such as wonder, awe and humility in the face of the emergence of something greater than ourselves. The latter can be based on the fact that these systems are part of a sacred creation, or are simply worthy of respect due to their own striving for self-maintenance and continuance. Whether gene drive advocates believe in the idea of naturalness or not, the concept's deep roots in environmental history means that, in certain contexts, it is likely to animate a significant portion of the ethical debate. It is therefore important that any comprehensive ethical analysis of gene drive technology considers what the technology does to naturalness.

3.3 Driving extinction

Another concern about gene drives as a type of intervention lies in how some of them are designed expressly to counter inherent and characteristic biological tendencies. That is, gene drives designed to create sterility, or to bias the sex ratio between males and females in a population, work against the biological interest present in all organisms to survive and reproduce. At an individual level, it may be morally problematic to manipulate an individual organism in such a way as to undermine its basic interests in survival and reproduction. At a population or species level, driving a whole collection of organisms towards extinction may be of even more moral concern.

Environmental philosopher Holmes Rolston III describes human-caused extinctions as "super-killings" (Rolston III 2012). The loss of a species is the loss not just of a life but of a form of life. If evolution as a whole drives speciation, creates complexity and diversifies life, the intention to reduce the fitness of organisms and drive certain populations towards extinction points in the opposite direction. The underlying aim is not to support the flourishing and expansion of life, but to directly curtail and impede a species that has been deemed problematic and to do this at the genetic level. This makes an engineered suppression drive an anathema to the evolutionary process. While proponents may point to the existence of gene drive mechanisms in nature to defend the technology, their function in nature has never been to drive a population towards extinction. When purposed towards this goal, new ethical issues arise.

In Section 3.1 on "Noninterference" above, it was claimed that gene drives demonstrate a particularly invasive way of interfering with the biological world. What is apparent now is that certain applications of gene drives are not simply invasive, they are invasive in a particularly pernicious way. They intentionally disrupt the central creative mechanisms of the living world. The Norwegian Biotechnology Advisory Board's statement on gene drives describes the technology as being in the business of "overriding evolution" (Bioteknologirådet 2017). Technicians not only intervene in the evolutionary unfolding of organisms, rewriting their DNA in pursuit of human goals, but they do so by deliberately distorting Mendelian principles of inheritance and Darwinian principles of survival (Delborne et al. 2018; Preston 2018).

The ability to push a chosen trait through a population and undermine its fitness directly contravenes how the process of evolution works. Doing this in a wild population, rather than one intended to operate in the highly constructed environment of a lab or a farmer's field, is also a novel development. This new technique for undermining a key creative capacity of living things is a significant basis of ethical concern (Midgley 2000). While not applying to all uses of gene drives, population suppression and elimination represents one of the key objectives for early developments of the technology. It is therefore

also one of the central ethical concerns of this new way of intervening in the world.

3.4 Re-wilding as a resurgent environmental value

As indicated earlier in this section, it is common in contemporary environmental discourse to suggest the arrival of the Anthropocene epoch has upended some of the long-held premises about wildness and naturalness in environmental ethics. By doubting the untouched character of any remaining landscapes, some might say the arrival of the Anthropocene makes the principles of noninterference, preserving naturalness, or respecting historic Mendelian and Darwinian forces obsolete (Crutzen 2002; Minteer 2012). With every part of the world reflecting the human signature, why worry about noninterference or protecting how biology used to work in the past?

If these suppositions are true, a new management philosophy may be appropriate. The Anthropocene may be destined to become a more hands-on epoch. A whole different set of management strategies and interventions, including gene drives, may now be permitted. Humans might, in fact, be under a new obligation to intervene into an irredeemably manipulated natural order, for both their own and for environmental goods. This is a position that a number of today's "Anthropocene" or "Eco-modernist" thinkers embrace (Asafu-Adjaye et al. 2015; Marris 2011).

There are, however, powerful countervailing trends pointing in the opposite direction. Conceding that there has been human influence on a landscape provides no license to continue that interference, and certainly not to step up human management of natural processes. A growing international movement towards the 'rewilding' of landscapes, previously impacted by agriculture but now available for other uses, is pushing back in the opposite direction. A recent call by environmental scientists and conservationists to dedicate half of the earth to independent natural processes suggests that the desire to grant nature the opportunity to function independently of human design is alive and well (Wilson 2016; Locke 2013). Advocates of rewilding and proponents of 'Half Earth' believe the answer to the challenges presented by global change is not to intervene further, but to seek ways to step back in some regions and let independent natural processes re-emerge.

According to Rewilding Europe, one of the organizations at the forefront of this movement in the EU, rewilding "is about letting nature take care of itself, enabling natural processes to shape land and sea, repair damaged ecosystems and restore degraded landscapes" (Rewilding Europe 2018). Rivers regaining their floodplains in the Netherlands, agricultural fields returning to scrub in the UK, abandoned military bases being reforested in Germany and reintroducing lynx to the Iberian Peninsula are all examples of choices made by humans to withdraw. In a rapidly proliferating literature on the theoretical underpinnings of rewilding, Andrea Gammon (2018) finds a strong unifying thread emphasizing the value of freeing non-human lives and processes from human designs. Amongst a cluster of uses of the term, Gammon identifies two common themes of "decreas[ing] the degree of intervention and human management of ecology" and encouraging the presence of "non-human autonomy" (Gammon 2018, 340-341).

In numerous projects, with proven ecological benefits carried out by practitioners of traditional ecological knowledge – as well as modern scientific ecologists – in Asia, Africa, Europe, and the Americas, rewilding has reestablished the core values of "autonomy, spontaneity, self-organization, absence of human control" in ecosystems (Corlett 2016, 455). George Monbiot, a UK-based rewilding advocate, describes rewilding as the call to "permit ecological processes to resume" (Monbiot 2013, 8). A growing number of international projects are directed at "the pursuit of 'autonomy' for nonhuman subjects and processes" (DeSilvey and Bartolini 2018). Pushing an engineered gene drive through a wild population of organisms would be at odds with these popular and effective directions in contemporary conservation.

The vigorousness of today's rewilding movement and the growing re-commitment to autonomous natural processes raises questions about the use of gene drives to promote conservation goals. Rather than object on the grounds of potential unforeseen impacts, this argument objects on the grounds that the sort of intervention into nature displayed by gene drives is inappropriate. A commitment to promote the autonomy of the non-human, to decrease human management and intervention, and to adopt a hands-off approach to the natural world, has a resurgent moral and environmental legitimacy. This suggests, contrary to some advocates of stepped-up environmental management, that gene drives are not an inevitable consequence of an Anthropocene epoch.

4 Intention

The last major lens chosen for assessing the ethics of gene drives looks at what might be characterized as the intentions behind their advance. Rather than look at the specific impacts that might follow from their deployment or worry about the particular principles or management practices a gene drive might embody, this approach focuses on the type of thinking, attitude, or worldview underlying and informing the technology. In other words, in this section it is how the technology embodies particular ways of viewing – and being in – the world that is under ethical scrutiny.

One of the most obvious ways to engage the "intention" question may be to consider whether gene drive organisms could be deployed with malevolent or hostile intent. This may be a genuine worry for the future, confirmed by both the academic literature (Gurwitz 2014; Oye et al. 2014) and by the funding of the 'safe genes' program by DARPA (DARPA 2018) (see Chapters 2 and 3 on Social issues and Applications). While 'dual-use' deserves consideration, the speculative nature of even the most basic field applications of gene drives means that it may not yet be an appropriate time to speak to these concerns. The kind of concern with intention that we address here operates at a deeper or more overarching level than overtly hostile applications of gene drive technology, but, we believe, is just as important to consider as part of the landscape of ethical concerns.

By probing the implicit types of thinking and attitude in the underlying intentions of even benevolent uses of gene drives, this approach is less likely to dictate specific permissions or prohibitions in the same way as the other lenses might do. However, this approach can beneficially combine broader discussions about the good life and desirable directions for human development, with a more specific focus on technological innovation. An ethical analysis focused on the attitudes and beliefs motivating a technological development engages with considerations of questions such as: What is the good life? What types of characteristics should we be cultivating as people? How should we relate to both human and more-than-human others? Such questions take ethical assessments beyond narrow concerns with the impacts of gene drive technology or a rigid application of particular principles. Focusing on intention opens the discussion up for engagement with a much broader range of questions concerning what it means to live ethically on this planet, and how views on this relate to the technology in question.

4.1 Control and domination

One of the arguments levelled against the use of powerful emerging technologies to address social or environmental issues is that they are accompanied by a Promethean attitude towards mastery and control of the natural world. Concerns about humanity "playing God" have been widespread in debates about biotechnology and synthetic biology since their beginnings (Dabrock 2009; Kirkham 2006). As Kirkham puts it, the idea of "playing God" expresses "a concern for the virtue of, and doubt about the intentions of, the agents whose acts are

described in these terms" (Kirkham 2006, 177). The complaint indicates disagreements over the purposes of technology and understandings of "the place of humanity within nature" (Kirkham 2006, 183). It also represents an ethical concern about humanity holding an overreaching and overconfident belief in its grasp of natural phenomena, along with an overinflated image of its role in determining the fate of other organisms and ecosystem processes. The type of intention embodied by gene drives is vulnerable to this type of criticism.

Arguably, the issue here is the presence of a certain type of worldview, one that some suggest is a deeply flawed basis for human action. Those opposing this worldview typically take aim at its mechanistic and reductionistic way of approaching the living world, as well as the masculinist way in which these are employed in a quest for power and control. The targeted views purport to use rational powers to understand how the different parts of nature work, with the ultimate aim of controlling them and placing them in the service of (what is always assumed to be superior) human goals. This attitude is thought to be a core characteristic of the patriarchal era following the scientific revolution, as well as a defining feature of the industrial age (Merchant 1980; Griffin 1978).

In a polemic against some forms of biotechnology, Mary Midgley warns about the dangers of these attitudes when accompanied by today's more powerful technological tools. "We now know that eighteenth century mechanists were mistaken in supposing the world to be made of clockwork", she says. "A twentieth-century repetition of their overconfidence does not seem likely to prove any more lasting" (Midgley 2000, 8). For Midgley and other contemporary critics of reductionism and mechanism, biotechnology raises serious questions "about where our world pictures come from" (Midgley 2000, 8).

These critiques of reductionism and mechanism seem to apply readily to gene drives. Gene synthesis and gene editing are often characterized as an attempt to apply engineering principles to biology. Yet the limitations of this type of thinking for understanding genomes have been continually acknowledged as the field of genetics has evolved – prompting the revision of core initial understandings, such as the 'central dogma' and notions of 'junk DNA'. Recent findings about off-site impacts of CRISPR/Cas9 gene editing in other parts of the genome again suggest that there are serious dangers to treating genomes in a reductionistic manner (Kosicki, Tomberg, and Bradley 2018; Mou et al. 2017). As immensely complex systems, there are very likely to be inherent limits to how much genomes can be broken down, reassembled, tinkered with, re-designed, engineered and precisely controlled.

Not only is reductionism technologically inappropriate for genomes, it may also be ethically inappropriate. Reductionism is often accompanied by an attempt to instrumentalize the living world. The attitudes and orientations behind instrumentalist views are seen by some as the driving forces behind the environmental crisis (Berman 1981; Horkheimer and Adorno 2002). Continuing to employ reductionist views to transform natural systems into instruments for human ends risks perpetrating the same mistakes. It is quite appropriate to point out that gene drives perfectly illustrate this flawed way of viewing the world; and, as powerful new technologies capable of re-designing evolution, introduce the potential for damage on a much grander scale. For those holding concerns about attitudes of domination and control, it is how the technology embodies particular ways of viewing (and being in) the world that is ethically problematic. To counter these instrumentalizing attitudes, some contemporary commentators advocate for "relational worldviews" to take their place.

4.2 Relational worldviews

To exist in the world is to exist in relationships. No organism can choose otherwise. Cafaro and Sandler remind us that "[O]ne simply cannot opt out of a relationship with the natural world…but whereas a relationship with nature is given, the nature of that relationship is not" (Sandler and Cafaro 2005, 1). How we approach those relationships is where ethics enters the picture.

There are numerous different philosophical orientations advocating for relational worldviews. While diverse in their details, all such orientations place emphasis on the importance of prioritizing the relationships between different things, rather than simply thinking of entities in isolation. Relational worldviews take issue with approaches in which parts are perceived as causally primary and independent of each other. In relational worldviews, all organisms and processes are understood to be working through a multitude of networks of interconnections and feedback loops. Imagining them in isolation from their relationships leads to a flawed understanding of what they are and how they work.

For those holding a relational rather than a mechanistic view of the world, efforts to isolate genetic information and transpose it into completely different genomic, cellular, organismal and ecological environments will not lead to it operating in predictable ways. Genes do not exist in some kind of essential form, but rather are an expression arising through particular interactions between various elements within a system. Altering the relational context will therefore inevitably lead to different results. When the relational network is changed, so is the entity itself.

Relational approaches to nature are clearly in evidence in the scientific fields important to the application of such technologies, such as ecology and quantum physics. They are also found in a number of indigenous worldviews and Eastern philosophies (Pascual et al. 2017; Verbos and Humphries 2014, see Box 4). In areas of ethics and innovation governance, relational worldviews are found in such fields as deep ecology and feminist philosophy, as well in social studies of science and technology (STS). It is to these latter three that we briefly now turn to further illustrate how relational worldviews affect the ethical assessment of new technologies such as gene drives.

Deep ecology has been described as seeking "fundamental change in the dominant worldview and social structure of modernity" (Katz, Light, and Rothenberg 2000, 1). Early proponents of deep ecology sought to demarcate it from what they termed "shallow environmentalism (or ecology)", by claiming to focus in much more detail on the underlying causes (rather than symptoms) of environmental decline. These causes were thought to be the prevailing attitudes towards the natural world and our relationship to it (Naess 1973). The deep questioning process that is an essential part of the deep ecology approach confronts "our basic values and lifestyles and reflects on our fundamental relationships with nature and who we are" (Næss, Drengson, and Devall 2010, 26-27). To overcome environmental challenges, deep ecologists suggest it is crucial that human societies embrace a relational worldview.

Drawing inspiration from the science of ecology but also from philosophical thinkers such as Spinoza, as well as from Gandhi and Eastern schools of thought such as Buddhism, deep ecology views all of life on Earth as inherently interconnected. Within this worldview, there are no firm boundaries in the field of existence. Entities are co-constructed through networks of interrelations (Fox 1995; Næss, Drengson, and Devall 2010).

Deep ecology offers a position that directly counters the reductionist and technocratic worldview, in which nature is seen through the metaphor of a machine and technological fixes are relied upon to solve all environmental problems (Drengson and Drengson 1989) (see also Section 4.3 below). When our environmental crises are understood as stemming from a particular way of viewing the world, technological solutions stemming from that same worldview may be deemed not only technically flawed, but also ethically wrong. "Trying to control the whole of nature is futile and wrong" (Næss, Drengson, and Devall 2010, 27).

Like deep ecology, many versions of feminist philosophy also embrace a relational worldview. For feminists, the will towards domination of another person or process is a masculinist impulse that has created a wide swathe of problems (Tong 2013; Collins 1990). For ecofeminists, such as Val Plumwood, Karen Warren and Carolyn Merchant, the problems associated with masculinist agendas of domination extend their consequences beyond

women to include the life-giving world, which has also historically been understood and portrayed in most human societies in feminine terms, e.g. as 'Mother Nature' or Pachamama. The ecological crisis is presented as a product of "our mistaken belief that we can successfully dominate Nature" (Hallen 1995, 199). Ecofeminists make the point that the logic of domination is environmentally destructive wherever it is found (Warren 1990; Plumwood 1993).

The intention towards control and domination is highlighted by feminist philosophers of science as a problem embedded deeply within the scientific method. Susan Griffin, Evelyn Fox Keller, Carolyn Merchant, Sandra Harding, and many others have pointed out serious problems arising from the ideology of detachment and domination permeating modern science. This ideology crystalized in the 17th and 18th centuries during the Scientific and Industrial Revolutions, when thinkers such as Francis Bacon and René Descartes encouraged using rationality and a commitment to absolute objectivity to bring nature under the mastery and control of man (Griffin 1978; Keller 1983; Keller 1995; Merchant 1980; Harding 1991; Bleier 1986).

Keller has illustrated how this 'masculinist' ideology works to shape the selection of scientific agendas, goals, methods and explanations. In her biography of the Nobel Prize-winning geneticist Barbara McClintock, she emphasises the limitations McClintock encountered when relying on detached observation and reasoning alone. Seeing herself in relationship with her object of study was crucial to McClintock's groundbreaking work on "jumping genes." This meant developing what McClintock called a "feeling for the organism" (Keller 1983). McClintock performed her science from a relational understanding of phenomena, seeking scientific knowledge through a thorough absorption in, and identification with, her material. The objects she studied were never viewed in isolation from the context in which they existed.

Reversing the Baconian approach, McClintock thought that the goal of science is "not the power to manipulate, but empowerment, the power to understand, the power to appreciate, the power to humble" (Hallen 1995, 209). From a feminist perspective which emphasises a relational view, gene drive science and technology is problematic not only because of its reductionistic approach to genomes and its mistaken assumptions about predictability, but also because of the faulty approach to the wider foundation of science and type of understanding that it represents.

Science and Technology Studies (STS) is the third field championing a relational understanding of the world. STS has developed around a core set of interests in the interrelations and forces of co-production operating between the spheres of 'science' and 'society.' The field examines how science and society, including its facts and values, permeate, shape and co-produce one another (Jasanoff et al. 1995). This has, for example, included demonstrating how economic and political factors shape scientific research and regulation, so much so that science cannot claim to be independent of them.

STS scholars have a special interest in scrutinizing how particular views and approaches come to dominate and shape science and innovation, and especially what interests are served, who benefits and who gets to decide on the trajectories of development (See Section 2.4 above). Within this field, there is also a growing interest in describing how worldviews get enacted in the practices of science and technology and what alternative modes of relationship are offered by different views (Lynch 2013; Mol 2013). The STS lens reveals how worldviews, politics and technology can enter tight, self-reinforcing circles. STS scholars put the spotlight on these reinforcing relationships and break them open to ensure there is room for alternate visions (Stirling 2018).

STS approaches allow biotechnological practices to be questioned both in terms of the worldviews they emerge from and the worlds they enact. An objection to gene drives from an STS perspective might be rooted in a rejection of the reductionistic and non-relational worldview informing the technological trajectory of gene drives, and/or the instrumentalizing of nature that the pursuit of this trajec-

tory tries to build (Wickson 2015). It could also draw attention to the monetary, social and political interests propelling the research forward (Stirling 2018). Concerns about how gene drives express relations between humans and nature, between developed and developing worlds, and between technological and social solutions to challenging conservation and public health problems, all come to the fore. Concerns are also raised about the intention to control other organisms, the lack of respect for diverse perspectives and forms of agency, and the continued operation of a hubristic rather than caring attitude towards the natural world (Stirling 2018).

Despite some differences, deep ecologists, feminist philosophers, and STS scholars share a common concern about the failure to take relational context into account. For the specific case of gene drives, concerns about not sufficiently considering relational context operate at various layers. This includes the relational context within a genome all the way out to the interactions constituting the cell, the organism, the ecosystem and broader socio-political systems. Not accounting for context within the genome, organism or ecosystem is seen by all these disciplines as undermining the possibility for sound understandings and predictable/stable forms of control. Not considering the social and political context can also neglect important questions about the underlying interests at play. To the extent that genetics as a science, biotechnology as a field, or gene drives as a specific example, stem from either: a) an approach to knowledge insufficiently sensitive to the importance of context or b) an approach to the natural world that seeks to assert control, then ethical critiques are likely to be raised by anyone holding relational worldviews.

4.3 Technological fixes

Because of their emphasis on the importance of context, disciplines holding relational worldviews would also tend to express concern with the idea of gene drives as a technical fix to a complex socio-ecological problem. The term 'technical fix' was coined in the 1960s by Alvin Weinberg to describe the process of transforming a social and behavioral problem into a technical or mechanical one (Weinberg 1967). In the right circumstances, an engineering solution can be cheaper and easier to implement than a large-scale behavioral change, lending great appeal to this idea of a technical fix.

Despite this advantage, there are several reasons to object to certain kinds of technical fixes. One of them is the worry that by solving one aspect of a problem, a technical fix can introduce new problems that weren't there before. This is particularly likely when technologies are developed in a way that is not sufficiently sensitive to context and the network of interrelations involved in complex natural systems. A technical fix can therefore appear as a type of 'quasi-solution.' Chlorofluorocarbons, for example, looked like they were going to help solve the problem of reliable food preservation when employed in refrigerators, but it turned out that they were also capable of destroying the ozone layer. Nuclear power plants generate electrical energy but also generate radioactive waste. Anti-lock brakes stopped some drivers from skidding but encouraged others to drive faster. Technologies that look good in prospect can often create headaches as great or worse than those they tried to fix.

A different concern is that the technical fix might solve the wrong problem. Sometimes there might be underlying behaviours that need fixing, and the technical 'solution' can distract attention away from these challenges. Energy efficiency measures, for example, may temporarily reduce energy consumption. But efficiency measures can also lead to an increase in energy use and continuation of problematic wasteful behaviours. By using gene drives to suppress a particular population of agricultural pests, agricultural systems that employ biodiverse-poor monocultures may be allowed to further expand and destroy biodiversity-rich habitats. By providing the promise of a technical fix to one problem, one may allow underlying problems to continue or even be exacerbated.

A third concern (related to the second) is that technical fixes can sometimes encourage societies to become reliant upon researchers and engineers in ways that can be dangerous in the long run. Rath-

er than viewing problems and challenges through social and behavioral lenses, the promise of a technical fix can lead to the idea that most of society can disengage from certain problems and hand them over to the experts. One worry about this approach, says Jeremy Baskin, is that it can set societies on a trajectory that is "deeply authoritarian and de-politicizing" (Baskin 2015, 22). When all social and political problems start to look like technical ones, disengagement of the public and a blind obedience to those who promise solutions may result. The turn towards technology and away from politics seems particularly likely in cultures drawn in by the "technological sublime" (Nye 1994).

Technical specialists also demand time and resources to come up with workable solutions. These investments can be significant, even if they ultimately do not lead to effective applications. In many cases, despite initial appearances, the social and behavioral options may turn out to provide far more efficient, reliable, and long-lasting solutions to the problems.

Resisting the technological fix can also encourage local solutions rather than ones depending on expertise located elsewhere. (See Section 2.4 for why this is important). Sleeping under insecticide-treated bed nets, making prophylactic malaria treatments much more widely available, systematically eliminating sources of standing water that serve as breeding sites, all these local solutions are less technical and less risky interventions for malaria control than engineering genes. Often the local solution can be more quickly deployed, is less expensive, and is also more open to direct citizen engagement. An ethical assessment of gene drives demands consideration of the non-technical alternative strategies, including such holistic approaches as improving access to primary healthcare and education or providing better housing with plumbed water and sanitation systems. To put this another way, a technical fix should not be characterized as plan A or B if it really deserves to be plan Z (Fragnière and Gardiner 2016).

The tendency to see the world through the lens of the technical fix is widespread in many of the worldviews of domination and control which today are being challenged by relational approaches. The more mechanistically and reductively one views the world, the more likely one is to see all problems as technical problems, solvable through better engineering. Similarly, the more interventionist one's tendencies are, the more appealing is the technical fix. Widespread talk of a new epoch of the Anthropocene has tended to legitimate these reductionist and interventionist approaches. Paul Crutzen, for example, has called upon scientists and engineers to see the Anthropocene as a calling for them "to guide society towards environmentally sustainable management" (Crutzen 2002, 23).

In deciding on the most appropriate path, it matters how the problem is framed. It makes a difference, for example, whether the problem of malaria is understood as stemming primarily from the presence of a certain species of mosquito, the existence of standing bodies of water where mosquitoes can breed, a mosquito's ability to harbor a certain parasite, the human susceptibility to a certain parasite, or the maldistribution of health care resources across human populations. In a similar fashion, it makes a difference whether agricultural challenges are perceived primarily as the need to increase yields or involve other multifactorial goals (including soil fertility, water retention and nitrogen fixing). It also makes a difference whether agricultural problems are framed as the presence of too many insects and weeds, or the use of monocultural cropping systems that invite vulnerability to such pests.

Like many of the issues raised in the "Intentions" section, the ethical concern with embracing the technical fix is not a concern with a technology in and of itself. It is a concern with the worldview or mindset in play. The underlying problem may be being formulated in entirely the wrong way. The range of available alternatives may not be being adequately considered. Resources may also be being misdirected into promises that cannot be delivered. The underlying political and social input may be neglected. A full ethical evaluation of gene drives must look behind the technology towards the attitudes and intentions that are promoting it.

4.4 Intentions & virtues

Looking into the backstory of the ethics of gene drives by considering underlying attitudes and intentions that may be lurking there makes it now possible to draw an important connection with the language of virtue theory. According to a virtue-based approach to ethical assessment, the problem may not simply be a matter of a faulty worldview or a misplaced trust in the technical fix. The problem may also be a failure to display appropriate virtues in the human relationships to each other and to nature. Specifically, the problem may be seen as the types of unvirtuous attitudes (such as arrogance, hubris, greed, and self-interest) that have been characteristic of how modern industrial societies have conducted their relations with nature.

Virtue ethics is an ancient approach to moral reasoning that has experienced a revival in recent decades (MacIntyre 1981; Foot 1978). The field of environmental or ecological virtue ethics has also emerged out of this revival as an alternative approach to navigating human/nature relations (Wensveen 2000; Sandler and Cafaro 2005; Cafaro 2001). Environmental virtue ethics asks about the attitudes and habits of behavior that good planetary citizens should cultivate. A virtue approach prompts discussion about what it is to be a person of goodwill in society, as well as what it means to be a good ecological citizen in today's world.

Reflecting Aristotle's belief that ethics is not a precise subject, virtue ethics tends to be more plural and contextual than other approaches to ethics that have been dominant in modern environmental policy-making. Nevertheless, advocates of environmental virtue ethics argue that its characterization of environmental problems and approaches resonates well with popular thinking and is exactly the type of framework that may be needed to handle the complex and diverse challenges of global environmental degradation. As Sandler points out, given the great variety of human relationships with the natural environment and the diversity of our current environmental problems, it is surprising to find that the most prominent environmental ethics approaches advocate positions or solutions meant to be singularly correct and universally applicable (Sandler 2007).

The environmental virtue approach coheres with the relational approaches in worldviews described above, in that it states that context matters and relations are of primary concern. Environmental virtue theorists believe technologies should be scrutinized not only for the impacts they may cause or for the 'lines in the sand' they might cross, but also for the attitudes and intentions they embody. Virtue theorists try to determine the approach that would be taken by people of good character. This means questions should be asked, for example, about whether humanity is approaching the natural world from a position of compassion, cooperation and care, or whether their actions aim to conquer, control, or coerce. Are human actions motivated by feelings of generosity, humility and respect, or greed, hubris, and intolerance?

The underlying attitudes and character traits expressed in the human/nature paradigm are a key issue for virtue theorists; how these play out in our interactions with non-human beings is central to environmental virtue ethics. Cultivating virtue means cultivating appropriate attitudes, states of mind and dispositions in morally challenging situations. According to this position, better environmental practices and policies are going to require better habits and "a substantial shift in our dispositions towards the environment" (Sandler and Cafaro 2005, 3).

In terms of the use of gene drives, this approach may include concerns that the pursuit of the technology is reinforcing undesirable human character traits and attitudes towards the natural world. For example, the desire to manipulate genomes is arguably the expression of a desire to impose one's own will upon others. A willingness to alter a whole population's right to its own evolutionary unfolding evokes forced sterilization programs, which, when used on humans, are regarded as immoral. Making the lives of others subservient to one's own goals, especially when based on a false sense of superiority, echoes the practice of slavery. While these parallels might sound too vivid, they highlight how

and why underlying attitudes can matter for ethical assessment.

There are various ways in which environmental virtues may be developed. These include examining the character traits of exemplary individuals, extending the virtues already recognized in interpersonal relations, and selecting traits that enable an organism or community to flourish or live well in the world. As an example of this final strategy, Rosalind Hursthouse (1999) has proposed that an organism can be understood as flourishing if its parts and operations "are contributing, in the way characteristic of such a member of such a species, to (1.) individual survival through the characteristic life span of such a member of such a species and (2.) continuance of the species" (198). The deployment of a gene drive specifically designed to suppress a population clearly challenges this kind of requirement for environmental virtue.

Like feminist theorists and many STS scholars, virtue ethicists are also unwilling to let a single form of knowledge production dominate the discourse, advocating for "cultivating scientific knowledge, while appreciating its limits" (Cafaro 2001). In common with the other relational worldviews described above, the language of environmental virtue ethics also seeks a better integration of emotion and reason in moral judgment about technological futures. It particularly asks for more attention to be paid to the narrative contexts in which particular decisions are being made, along with the affective dimensions of these contexts. "The cultivation of virtues," says Van Wensveen, "allows and encourages us to integrate emotions, thoughts and actions" (Van Wensveen 2008, 8).

Box 5: Many ways of knowing

Various relational worldviews point to the problems associated with seeing science as the only legitimate way to generate knowledge about the world.

Indigenous and local knowledge systems (ILK) are now increasingly recognized, under international agreements such as the Convention on Biological Diversity, as legitimate and important to include in environmental policy-making. Significant efforts are also underway in understanding and developing synergies between science and ILK in, for example, the work of the Intergovernmental Platform on Biodiversity and Ecosystem Services (IPBES).

Challenges to the sufficiency of the detached form of reasoning used in science have also been expressed by deep ecology and feminist philosophy. Deep ecology has argued for the importance of lived experience as a mode of accessing knowledge of the world, in part due to the way it integrates the rational and emotional levels of reality. Feminist scholars have also developed concepts of 'connected' and 'situated' rather than 'separated knowledge' and together with STS scholars have emphasised the importance of understanding how knowledge is always located within and stems from a particular set of conditions and beliefs.

The Swiss Federal Ethics Committee on Non-Human Biotechnology has indicated the importance of recognizing different approaches to knowledge by pointing out that, when assessing risk, "attention must be paid to promoting and cultivating diversity of perspectives and cross-sectional competences" (Swiss Federal Ethics Committee 2018, 24). Acknowledging the limitations of science and the value of more experiential forms of knowledge have important ramifications for how the ethical issues related to gene drives will be framed and assessed.

A virtue-based approach as a guide for action is particularly accommodating for situations like gene drives, where we do not yet know everything we need to know and where agreed principles for action may be lacking. This is because seeking virtue can offer a framework for action that is not set or fixed from the outset. It instead offers a dynamic approach that is always developing in connection with evolving realities. This feature makes it a particularly useful ethical lens to adopt for gene drives, where the technology, the knowledge of its impacts, and the contexts of application are all still developing. When complete knowledge of consequences and clear principles are lacking, focusing on cultivating desirable character traits can be a useful way of guiding decision-making. Given the current state of knowledge concerning gene drives and the complexity of the interactions between genome, organism, and environment, a virtue theorist will likely

argue that a sense of caution and an appreciation of complexity are appropriate habits of mind to adopt.

This observation can be expanded outwards into a broader point. When the question is how to credibly govern fields of emerging sciences and technologies in which the facts are uncertain, values are in dispute, the stakes are high and decisions urgent (Funtowicz and Ravetz 1994), emphasis should be placed on developing the virtue of 'responsibility' in research and innovation. In the final section of this chapter, we outline a range of values and virtues that are important to cultivate if we are to govern emerging technologies responsibly. We also briefly point to how these guidelines might be applied in the case of gene drives.

5 Governance

The survey of the range of ethical considerations provided in this chapter makes it clear that evaluating a technology as powerful as a gene drive requires much more than a quick cost-benefit analysis focusing exclusively on human needs and interests. In addition to adding their potential impacts on animals and on future generations of humans, a comprehensive ethical evaluation will attend to the justice dimensions of gene drive development and deployment; the environmental principles and practices they might support or contravene; the understanding of organisms, ecosystems and human-nature relations they promote; the worldviews they support; and the virtues and vices that produce them.

These various lenses reveal a diverse ethical landscape that admittedly is difficult to navigate. Considerations that range from concrete (if unpredictable) consequences, to historically developed background attitudes and cultural beliefs, as well as to shifting principles of environmental management, all combine to create a swirling ecosystem of values within which ethicists and technologists must try to orient themselves. Some of these values flow directly from particular worldviews. Others are only loosely associated with each other through a complex and distributed web of relations. Sketching the different elements of this ethical ecosystem would not be helpful if it did not lead to some conclusions about how to proceed. However, proceeding does not necessarily mean taking a position concerning which ethical lenses may be most appropriate, or adopting a particular conclusion about whether the use of gene drives for particular applications is ethical or not. The sketch of the ethical ecosystem we have provided can also be used as a basis for determining what is important for good governance of gene drive research and innovation.

Governance of science and technology refers to all of the different ways in which the directions of research and innovation are decided, shaped and guided. This includes the daily work of individual researchers, research organizations and funding bodies, as well as what happens within the media, public discourse, and governmental authorities. These guiding practices should embody principles that 1.) reflect larger societal values and norms and 2.) are appropriate for the character of the technology in question. Given the wide range of questions over impacts, interventions, and intentions articulated above, it is clear that the development of gene drives needs to be conducted in a manner that is transparent, inclusive, thoughtful, and respectful of difference. This is aligned with a broader commitment that has emerged in recent years to govern emerging technologies democratically and responsibly (Stilgoe, Owen, and Macnaghten 2013; Wickson & Carew 2014).

In what follows, we draw on work connected to 'responsible research and innovation', and in particular look to a specific articulation of this approach as related to agricultural biotechnologies, in order to outline what have been described as "essential features of responsible governance" (Hartley et al. 2016, 1). We briefly sketch what these features for

advancing responsible forms of biotechnology development are, and how they might be applied to gene drives. In so doing, we hope to indicate the direction to take to achieve credible and ethically appropriate governance of gene drive research, innovation and deployment.

5.1 Commitment to openness

Gene drive advocate Kevin Esvelt makes a good start towards a commitment to openness when he insists that "complete transparency" is a moral requirement for a technology this powerful (Specter 2017). "For both moral and practical reasons," he adds, "gene drive is most likely to succeed if all the research is done openly." However, for responsible governance, a true commitment to openness requires going further. Although it is of course an important element, advocates should not only be open about the work that they are doing; to facilitate responsible and ethical governance of gene drive technology, honesty and humility concerning the scope and quality of the available scientific knowledge, particularly on questions of impacts and risks, is also essential. Furthermore, openness and honesty need to extend outwards to include sober assessments of the true likelihood of the claimed risk/benefits, the comprehensive assessments of the range of ethical concerns (e.g., including those beyond physical risks), and the range of available alternatives. Clear descriptions of any potential conflicts of interest must also be required, as well as honest statements from researchers and funders about what is motivating investment in the field.

Transparency and honesty regarding the underlying motivations for the technology's development and use becomes particularly important when the research is being heavily invested in by organisations such as DARPA (the Defense Advanced Research Projects Agency of the US), who are specifically aiming to "develop game-changing military capabilities" (DARPA 2018). Without a wider scope for what should be expected in terms of openness, the involvement of organizations such as DARPA in research surrounding the technology will always raise suspicion and concern. Therefore, to adequately address ethical issues, transparency about what researchers are doing will be a necessary but insufficient condition for good governance, which requires a commitment to openness with a much wider scope than the general understanding of the term.

5.2 Recognition of underlying values and assumptions

Good governance demands that actors specifically reflect on how values and assumptions shape and inform their work. This includes how values and assumptions are influencing gene drive research, development, communication, risk assessment, and risk management. Recognizing underlying values and assumptions in gene drive innovation systems is important if we are to understand and critically question how desirable futures are being imagined, and by whom, as well as how problems and solutions are framed, along with how risk-based science and assessment are actually being performed. Acknowledging the significance of the underlying value assumptions of different actors would particularly allow for divergent worldviews to be brought into the open, rather than being obscured by an overly narrow debate about human and environmental risk.

While risk regulation is important, the wide range of ethical considerations outlined above makes it clear that risk does not exhaust the ethical dimensions of gene drive organisms. Treating governance as more than simply controlling immediate, physical risk broadens the discussion and directs attention towards wide-ranging concerns associated with the intentional use of gene drives, rather than only with the unintended risks that may result. Such an opening up enables more transparent decision-making and more effective dialogue between innovators, risk assessors, risk managers, policy makers, and affected publics. If dialogue between different actors with different agendas is going to be fruitful, it is vital that any divergence in underlying values and assumptions is made clear, and is also permitted to be a legitimate part of the conversation. Otherwise there will always be a danger that underlying value differences are never directly acknowledged

or addressed; they therefore become hidden or masked within a debate that is ostensibly about risk but is actually about a clash in value systems. Indeed, in this sense, recognizing underlying values and assumptions and commitment to openness are complimentary and mutually reinforcing features of good governance and ethical innovation.

5.3 Involvement of a broad range of knowledges and actors

The acknowledgement that good governance is not only about risk regulation makes it more likely that decision-making will include a plurality of perspectives, worldviews, and types of knowledge drawn from a broad range of actors. This means perspectives must be gathered from different scientific disciplines and from different rights- and stakeholders. If the debate about gene drives is confined to a narrow technical assessment of risks, thus privileging scientific and technical experts, it significantly limits who can legitimately participate in decision-making processes. It is clear that democratic and justice demands will often require the involvement of a wider range of actors. For example, the participation of indigenous people, or farmers who hold rights over the land, territories and resources that may be affected, will be essential to include if gene drives are ever to be deployed. Furthermore, if applications are to be used in health or agricultural spheres, patients, consumers and workers in these arenas would have a legitimate right to be consulted and involved in decision-making.

Beyond consultations around deployment, there are also arguments to be made that opening up research and technology assessment processes more broadly may have significant benefits (Stirling 2008). This can be in instrumental terms, such as the way involving and accounting for diverse perspectives from the beginning may enable the technology to be more socially acceptable or robust. However, there can also be substantive benefits from including a diverse range of views and experiences into research and assessment processes. Such an inclusive approach can help ensure that a thorough and comprehensive approach to the issue is being taken, and that all potential knowledge sources are incorporated into the final decision-making process. Including diverse actors and views also makes the innovation process more democratic. Opening up the governance of gene drives to include a wide range of knowledge sources and perspectives, through the now well-established practices of public participation, citizen engagement and deliberative decision-making, will be the best approach to ensuring that the full range of relevant considerations are incorporated and addressed (see also Chapter 3 for more information on this). This inclusive approach will also be an essential feature for creating more ethically defensible decisions.

5.4 Consideration of a range of alternatives

Ethical governance of gene drives should not just openly and inclusively consider gene drives themselves but should also consider the range of alternative ways of formulating and framing the problems the use of the technology claims to address. These alternate framings of the problems will encourage discussion of a range of alternative approaches to solving them. In the case of gene drives, this will include all the alternative ways available for understanding and addressing the problems, for example, of disease or invasive species control. Many of these alternatives may carry fewer risks, may be more actionable in the short-term, more sensitive to local needs and resources and/or may better align with a diverse range of worldviews. All of these will be important factors to consider for practices of good governance and ethical decision-making.

At present, the lure of the technical fix means that policies to address global challenges can often focus on problems treated in isolation from each other rather than seen within their broader socio-political and ecological context. In today's world, there is also a desire to generate economic returns for any investment in solution development. As a result, there is a tendency to call almost exclusively on science and technology to devise suitable solutions, since this method is most easily monetized. Adopting such an approach can quickly

lead to a slippery slope for gene drive technology. That is, once it begins to be seen and employed as a technical solution to social and ecological challenges, the question inevitably arises as to how and where boundaries to its use would be drawn. Under what conditions would it become inappropriate to employ this technological solution? The slippery slope idea suggests that once you accept and start to employ a technology, like gene drives, as a technological solution for some problems, it becomes very difficult to establish and maintain boundaries against its use in other areas.

A more transparent and inclusive conversation that pays serious attention to the values and worldviews of different stakeholders is, however, more likely to uncover and explore alternative understandings of the problem and the available solutions at hand. Thinking more broadly in terms of "innovation governance" (i.e. how to govern and guide the innovation process as a whole) rather than "risk governance" (i.e. how to govern the potential physical impacts of any given technology) will also place technical solutions in their proper context as only one of many different ways to conceptualise and address a particular problem (Felt et al. 2007). Such thinking opens the way for an explicit consideration of the range of available alternatives, and also makes more likely the development of solutions capable of addressing multiple challenges simultaneously. Good governance therefore requires that we do not necessarily begin with the technology as a given, focusing only on handling its potential impacts. Rather, it becomes important to consider the various ways available for understanding the problem that is driving the technology's development, as well as all of the potential solutions that may be available for addressing it by other means.

5.5 Response preparedness

In order to achieve good governance of a powerful technology, it is not enough to just do all of the work described in the preceding section. There also needs to be a willingness to respond to what is revealed and to act in concert with these findings. For all of the essential features of responsible innovation to function effectively, innovators, safety researchers and decision-makers need to be prepared to consider and respond to societal needs and ethical concerns, as well as to technological or scientific desires. There also needs to be a willingness to respond to diverse views and values, and to take action on the basis of any assessments made, including those on the available alternatives. The inherent limitations of scientific knowledge and our inability to fully predict and control gene drive technologies in dynamic natural systems places further emphasis on the need for preparedness and a willingness to respond if we are to achieve ethical governance of any powerful technology.

A prepared response in matters of societal concern, diverse views and values, and changing socio-ecological conditions is important not only for ensuring the democratic accountability of gene drive technology in liberal democracies, but also as a means of enhancing adaptability, resilience, and perhaps reversibility, in all innovation and policy systems in the face of change. For the specific case of gene drives, the question of reversibility is complex but key for ethical decision-making. If there is no potential of recalling a technology or reversing any negative impacts it may have, the ability to respond will be severely curtailed. When response preparedness is recognized as an essential feature of good governance, innovation processes are compelled to take seriously questions about how the technology may be contained, controlled, recalled, or reversed. Indeed, it may not be considered ethical to go ahead with any release until such features are in place.

6 Conclusion

Gene drives are a prime example of one of a range of powerful technologies emerging today that demand a particularly broad and inclusive type of ethical scrutiny. This chapter of the report has sought to highlight the broad range of ethical concerns to which gene drives gives rise. Being responsible about technological innovation means taking all dimensions of these ethical considerations seriously: not dismissing the concerns of those who urge caution, and not getting caught up within a single optimistic narrative about the desirability or inevitability of a particular technology.

The immediate appeal of a highly technological solution to a complex and serious problem cannot be denied. However, the overview of ethical issues presented in this chapter highlights how a more sober approach involves stepping back from the excitement generated by what might be possible if the technology succeeds, towards what may happen if it does not. It takes the time to consider the technology within its broader social and historical context, to reflect with humility about what we know (and can hope to know) about complex systems; and it encourages open and participatory engagement with the widest possible range of perspectives and stake- and rightsholders. If gene drive advocates wish to obtain a clear social license, it will be essential that they take all ethical concerns into account and follow responsible practices of governance. We hope that the overview presented in this chapter may help in the navigation of this thorny landscape.

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Chapter 5

Legal and regulatory issues

Lim Li Ching and Lim Li Lin

1 The need for specific and effective laws and regulation

A gene drive system is designed to purposefully spread genetic modifications through populations, with species-wide and ecosystem level impacts, as well as to persist, which points to the likely irreversibility of those impacts (Heitmann et al. 2016, 174). Even if releases are halted, spread of the genetic modifications, which may have unanticipated adverse effects, will almost certainly continue. Thus, the very characteristics that make organisms containing engineered gene drives or gene drive organisms (GDOs) attractive for development also require specific consideration of the risks unique to this technology. Gene drives that are designed to suppress populations could potentially result in population or species extinction, making this subset of particular concern.

While GDOs are also genetically modified organisms (GMOs), for which our collective experience is largely confined to agricultural crops in cultivated systems, with gene drive organisms there are novel conceptual and biological differences that pose particular challenges for regulation (Simon et al. 2018). The depth of this new technological intervention capability is such that "humanity has no experience engineering systems anticipated to evolve outside of our control" (Esvelt and Gemmell 2017, 5).

Some of the features of GDOs that distinguish them from GMOs include their purposeful spread and persistence. With GMOs, the intention, at least, has always been to prevent spread of the modified genes and to confine their effects, with gene flow or contamination, for example, being one of the major issues to consider in a risk assessment and to mitigate through risk management. However, with GDOs, spread and persistence are their *raison d'être*, posing different legal and regulatory challenges. Moreover, GDOs will now deliberately move beyond cultivated fields, into wild populations and ecosystems. The complexity of the systems that could be affected and the impacts that could be realized increases scientific uncertainty manifold, requiring more precautionary approaches to regulation than already required with GMOs.

Working gene drives using the CRISPR/Cas[1] genome-editing platform have been recently demonstrated in several organisms in laboratory settings, only in 2015 (see Chapter 1). The pairing of gene drives with CRISPR/Cas has, however, accelerated the pace of gene drive development considerably. Potentially far-reaching applications are in the pipeline, backed by huge financial investments, to which the United States' Defense Advanced Research Project Agency (DARPA) and the Bill and Melinda Gates Foundation are the biggest contributors. This means that there is real urgency in creating mechanisms to ensure that there is effective regulation of this technology in place before any release of GDOs into the environment.

It is important to set out governance and regulatory arrangements well in advance so that would-be developers are informed of the requirements they must meet. Meanwhile, time must be taken to achieve consensus among different countries as to how to apply new regulatory standards (Sustainability Council of New Zealand 2018, 7-8). The time to consider the legal and regulatory regime for gene drives and GDOs is therefore now.

1 'CRISPR' is short for 'clustered regularly interspaced palindromic repeats'. 'Cas' is short for 'CRISPR-associated'.

While there exist biosafety regulations for research, development and use of GMOs, also termed living modified organisms (LMOs[2]), and GDOs are undisputedly covered by these laws, there is still an urgent need for specific strict regulation of these new entities, GDOs, that goes beyond existing biosafety regulations and that must take into account their unique features and effects. The US National Academies of Sciences, Engineering, and Medicine concluded that current US regulatory practices for assessing risks or potential environmental effects of field experiments or planned releases for GMOs are inadequate for gene drives (NASEM 2016, 170-171). The change in the spectrum of organisms and environments that will be affected by the application of gene drives therefore necessitates new approaches for risk assessment and governance (Simon et al. 2018).

A regulatory regime for gene drives and GDOs must consider worst-case scenarios in order to be able to adequately deal with and to anticipate the full spectrum of possible adverse effects. While not all gene drives are global in nature, the advent of CRISPR-based gene drives, which have the potential to spread 'globally' – i.e. to all populations of the target species that are connected by gene flow – and also to be invasive in certain contexts, certainly makes this a realistic concern. Mathematical models based on empirical data show that even the least effective gene drive systems are highly invasive; release of a small number of GDOs often causes invasion into the local population, subsequently followed by the invasion of additional populations that are connected by gene flow (Noble et al. 2017). "The bottom line is that making a standard, self-propagating CRISPR-based gene drive system is likely equivalent to creating a new, highly invasive species: both will likely spread to any ecosystem in which they are viable, possibly causing ecological change" (Esvelt and Gemmell 2017, 2).

In addition, while there have been some mitigating proposals that claim to be able to restrict the spread of gene drive systems (for example, so-called 'local' or 'self-limiting' drives (Esvelt and Gemmell 2017, 4-5)), these remain largely theoretical and currently have not been demonstrated to work. Such drives are complexifiers that may also carry their own risks, due to greater difficulty in their creation and the many ecological dependencies in their function. (See Chapter 1 for a technical discussion on these issues). Therefore, a legal and regulatory regime for gene drives and GDOs has to be designed to deal with the maximum implications of the technology, that is, it has to be prepared to regulate global gene drives and their potential impacts. This chapter focuses largely on global gene drives and the resulting GDOs, in order to discuss their effective regulation.

Box 1: 'Global', 'standard' and 'local' gene drives – a question of semantics

Min et al. (2018) classify 'global' gene drives as 'standard' gene drives. These drives are likely to spread to all populations of a target species connected by gene flow. 'Local' gene drives are those that can spread to regional populations but cannot spread to all populations connected by gene flow.

These classifications are an example of the semantics at play. 'Global' gene drives of course convey the idea that such a gene drive system, once released, has the potential to spread globally, at least in so far as the target population is concerned. This is one of the major concerns and regulatory challenge raised by organisms containing gene drives. In addition, the use of the term 'global' usefully calls attention to the need for internationally agreed rules for the governance of gene drives and GDOs.

Changing the language to 'standard' gene drives, while helpfully conveying the fact that these are the prevalent gene drives that are currently being researched, detracts from the notion of potential transboundary spread globally. 'Standard' also conveys the positive idea of usual correctness or acceptability and quality. In addition, the use of the term 'standard' may provide a sense of false security, leading to an assumption that there are already some authoritative standards in place for gene drive or GDO governance, which is not the case yet.

2 In this chapter, we generally use the term 'genetically modified organism' (GMO), unless we refer specifically to the Convention on Biological Diversity, the Cartagena Protocol on Biosafety, the Nagoya – Kuala Lumpur Supplementary Protocol on Liability and Redress, or the International Plant Protection Convention, which all use the term 'living modified organism' (LMO).

The name 'local' gene drives, on the other hand, suggests that these types of gene drives will have limited or restricted impacts and can be confined geographically or to the immediate area of release. It should be pointed out that these various 'local' drives are at present theoretical, and it cannot be assumed *a priori* that they will work reliably, in all situations, or that they will not themselves carry their own risks.

Proposals for self-regulation by scientists, such as the development of guidance documents for best practices by those involved in research, are clearly not enough to ensure adequate oversight and governance of a technology as powerful as gene drives. An example of how self-regulation has failed with a closely related genetic technology is the recent controversy over the birth of genome-edited twins, announced in November 2018. The scientist responsible was widely condemned for conducting such an experiment without due regard for ethical or safety considerations, bringing attention to the fact that there are no international rules specifically governing this new field. The World Health Organization (WHO) later belatedly announced the establishment of a WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing (WHO, n.d.).

While such 'rules of the road' (Adelman et al. 2017), described in some detail in this chapter, can certainly play a role, and existing guidance developed for GMOs could be updated to take into account the particular characteristics of GDOs, these will have to be rooted in a legal and regulatory system that is specific and responsive to all the particular challenges raised by gene drives and GDOs. Given that GDOs have the potential to cause serious harm to the environment, a public good, it would not be appropriate to place regulation and decision-making about the technology solely in the hands of private actors (Sustainability Council of New Zealand 2018, 20). As such, a legally binding regime is needed.

Governance and regulation of gene drives and GDOs must be international in nature because of the potential for transboundary spread of GDOs. Because "ecosystems are connected in myriad ways", even a small number of GDOs introduced in one country is very likely to have ramifications well beyond its borders (Esvelt and Gemmell 2017, 5). As such, the Ad Hoc Technical Expert Group (AHTEG) on Synthetic Biology, established under the Convention on Biological Diversity (CBD), recognised that "a precautionary approach and cooperation with *all countries and stakeholders that could be affected*... 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" (AHTEG on Synthetic Biology 2017, paragraph 25, emphasis added).

The need for international governance is also recognised by the US National Academies of Sciences, Engineering, and Medicine, which called for "clearly defined global regulatory frameworks, policies, and best practice standards for implementation" (NASEM 2016, 171-172). Decisions about the application of the technology require international cooperation, which means that the establishment of an international regulatory framework for gene drives and GDOs is necessary (Norwegian Biotechnology Advisory Board 2017, 15).

At the same time, while a significant number of countries are party to the Cartagena Protocol on Biosafety and thus would likely also have national biosafety laws or regulations governing the use of GMOs or LMOs (which would apply to GDOs), these national laws and regulations are not explicit or specific to GDOs as a special category of GMOs/LMOs. National laws, however, are likely to be shaped by international developments and can be developed, or amended, if national biosafety laws already exist, to specifically take into account gene drives and GDOs. Countries may also provide for more stringent GDO regulation, as is their sovereign right, within the context of their international obligations.

This chapter is concerned with the legal and regulatory aspects relevant to gene drives and GDOs, and primarily focuses on biosafety assessment and decision-making. There are many other relevant aspects as well, including the issue of 'biopiracy' and

access and benefit-sharing of genetic resources, governed by the CBD's Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization, which are beyond the scope of this chapter.

It must be acknowledged that discussion of decision-making in the context of biosafety is often a narrower focus, and usually does not involve asking the broader, important questions which do not always fit within this framework, and which include: Who defines the problem? What are the options for solutions? Which are more sustainable, and why? Where should research and investment be directed? Who decides all this, and how? These are fundamental issues that should rightly be addressed before embarking on activities that require biosafety assessment, rather than at the biosafety decision-making stage.

Many of these issues are discussed elsewhere in this publication, in particular in Chapters 3 and 4. However, the reality of the situation now is that research on GDOs in the laboratory is on-going, and deliberate releases into the environment are planned. Currently, there are no legally binding international rules and standards that are adequate to regulate these activities. This must be urgently addressed.

At the same time, legal and regulatory processes alone, while necessary, are not sufficient to confront the multiple challenges posed by gene drives and GDOs. A deep and broad global and cross-societal discussion and action on this is urgently needed. What is clear is that "this conversation should not be confined to scientists, regulators, politicians, or any single nation, no matter how strong its legislative frameworks, environmental risk management, and biosecurity networks" (Esvelt and Gemmell 2017, 5). There is urgent need to engage all citizens, especially farmers, indigenous peoples and local communities, and those who could be affected by this far-reaching technology and its impacts. This should also not just be a one-off exercise, but should rather be an on-going feature of the approach to governance of gene drives and GDOs.

This chapter will conduct a review of the international and other legal and regulatory instruments and processes that are and will be relevant to gene drives and GDOs, in so far as they address biosafety issues, and will address whether they are equipped to enforce their decisions. A particular focus will be on the CBD and its Protocols, as GDOs fall under their scope, and as they are already addressing GDOs in their substantive work. A 'Limitations' section located after each description will enumerate the problems a dependence on one or another (or even all) of the existing instruments would entail. The gaps in the existing international regime will be assessed. The specific issues raised by the characteristics of GDOs will be discussed, together with what needs to be done to address them. This chapter also considers what elements are necessary in a legal and regulatory regime that is suited to the challenges posed by gene drives and GDOs, including the urgent need to take the time to remedy any serious legal and regulatory gaps *before* any release of GDOs is even contemplated.

2 Review of relevant international and other legal and regulatory instruments and processes

2.1 The Convention on Biological Diversity and its Protocols

Substantial work has already taken place under the Convention on Biological Diversity (CBD) on synthetic biology and this work will continue in the coming years. The discussions on synthetic biology include the issue of 'organisms containing engineered gene drives'. At the same time, the use of terms under both the CBD and its Cartagena Protocol on Biosafety clearly define organisms which contain engineered gene drives as living modified organisms (LMOs), the subject of the Cartagena Protocol and its Nagoya – Kuala Lumpur Supplementary Protocol on Liability and Redress. Discussions under the Cartagena Protocol have begun to specifically address GDOs, via its work on risk assessment.

Additionally, another protocol to the CBD, the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization, deals with the fair and equitable sharing of benefits arising from the utilisation of genetic resources. This treaty was negotiated to address the issue of misappropriation of genetic resources, and discussions are underway on 'digital sequence information' on genetic resources. The Nagoya Protocol may well apply to GDOs if the genetic resources (and possibly, the information related to the resources) used are sourced from provider Parties; but this chapter will not discuss these issues, as our focus is on the regulations and governance needed to ensure the safety and suitability of gene drives in terms of their environmental, health and socio-economic effects.

As multilateral environmental agreements dealing with the protection of biological diversity, the CBD and its Protocols, in particular the Cartagena Protocol and the Nagoya – Kuala Lumpur Supplementary Protocol, are therefore well placed to be the main reference point in international law for GDOs.

2.1.1 Convention on biological diversity

Scope, objectives and key provisions

The CBD is an international, legally binding environmental treaty that was adopted at the Rio Earth Summit in 1992 and entered into force the following year. It has near-universal membership, as the United States (US) is the only non-Party country. Its objectives are the conservation of biological diversity, the sustainable use of its components and the fair and equitable sharing of benefits arising out of the utilization of genetic resources.

As a multilateral environmental agreement, it has helped to shape global thinking and action on biological diversity. At the same time, it has fallen short of its objectives and lacks the concrete and coherent implementation and strict compliance measures that are needed to address the biodiversity crisis. Often, it is a combination of civil society action, media attention and public opinion that has played a critical role in highlighting and promoting adherence to the CBD rules and targets. Much is also dependent on national implementation and enforcement through policies and laws. Other specific limitations of the CBD are discussed later in this section.

Article 7(c) of the CBD puts in place an obligation for Parties to identify processes and categories of activities which have or are likely to have significant adverse impacts on the conservation and sustainable use of biological diversity, and to monitor their effects. It can be argued that this would include re-

search in contained use, field trials and release of GDOs, since all these activities could result, whether unintentionally or intentionally, in impacts on biological diversity.

Article 14(a) further obliges Parties to conduct environmental impact assessments for activities that are likely to have significant impacts on biological diversity, with a view to avoiding or minimising such effects. A release of a GDO would clearly fall under these broad obligations. For example, some gene drive systems that are designed to suppress populations can potentially cause those and related populations to go extinct. Others that spread modified characteristics through the population may result in adverse and unexpected impacts on biological diversity.

Furthermore, Articles 14(c), 14(d) and 14 (e) address the situations where activities are likely to significantly adversely affect, or pose imminent or grave danger or damage to, the biological diversity of other States. In the first instance, the responsible Parties have to meet obligations for notification, exchange of information and consultation on activities under a Party's jurisdiction or control. Immediate notification to potentially affected States and initiation of action to prevent or minimise any imminent danger or damage is also required. National arrangements are needed for emergency responses to activities or events that present a grave and imminent danger to biological diversity, supplemented by international cooperation and joint contingency plans. As the release of some GDOs can easily result in the unintentional crossing of national borders, especially when the populations concerned are spread over different countries, these provisions are thus especially relevant.

Paragraph 2 of Article 14 further obliges Parties to examine the issue of liability and redress, "including restoration and compensation", for damage that is caused to biological diversity.

The importance of Article 14 in relation to GDOs has been reiterated in several decisions on synthetic biology, in particular the most recent decision from the Conference of the Parties (COP) (see later section on 'Decision on gene drive organisms at CBD COP 14 (November 2018)').

Relevance to gene drive organisms

The specific biosafety provisions regarding "living modified organisms resulting from biotechnology" are in Articles 8(g), 19(3) and 19(4) of the CBD. A GDO is a LMO, according to the definitions under both the CBD and its Cartagena Protocol on Biosafety.

Article 8(g) refers to LMOs resulting from biotechnology that are likely to have adverse environmental impacts that could affect the conservation and sustainable use of biological diversity, taking also into account possible risks to human health. Parties are required, as far as possible and as appropriate, to establish or maintain means to regulate, manage or control these risks at a national level.

Article 19(3) was the enabling provision that gave rise to the Cartagena Protocol on Biosafety, because it obliges Parties to consider the need for and modalities of a protocol in the field of the safe transfer, handling and use of LMOs.

Article 19(4) obliges Parties to provide any available information about the use and safety regulations required to handle LMOs, as well as any available information on the potential adverse impact of the specific organisms concerned, to a Party into which these LMOs are to be introduced.

Taken together, these three provisions broadly oblige Parties to establish or maintain means to regulate, manage or control risks of LMOs at a national level, to ensure safe transfer, handling and use, and to provide available information about usage, safety regulations and potential adverse impacts. The Cartagena Protocol puts into operation these obligations, which are then implemented at the national level.

For example, Parties such as the European Union and its member states have in place comprehensive biosafety legislation, requiring prior risk assessment before any LMO is deliberately released

into the environment or placed on the market as food or animal feed. Biosafety laws, however, have not always proven to be effective. For example, China had to deal with a significant incident of illegal sale and planting of a genetically modified (GM) rice variety only approved for field trials and not for human consumption (Zi 2005).

Ad Hoc Technical Expert Group on Synthetic Biology

The issue of organisms containing engineered gene drives has been discussed at the CBD under the topic of 'synthetic biology'. Parties to the CBD established the AHTEG on Synthetic Biology in 2014. The 2017 report of the AHTEG discusses organisms containing engineered gene drives extensively (AHTEG on Synthetic Biology 2017). The relevant points from the report are summarised below:

a. For some developments, such as engineered gene drives, there might be a need to consider more thoroughly the potential benefits and adverse effects at the ecosystem level. (paragraph 17)

b. These considerations could be particularly relevant and urgent for GDOs because of the impacts they might have on biological diversity, as well as on the knowledge, innovations and practices of indigenous peoples and local communities, particularly if released into the environment. Uncertainties related to the efficacy and safety of engineered gene drive systems, as well as the relative risks that could be posed by the different applications, were noted. Additional research and guidance are needed before any GDO could be considered for release into the environment, including into lands and territories of indigenous peoples and local communities. The AHTEG noted the potential for unintended transboundary movements and geographic spread of GDOs released into the environment. "Given the current uncertainties… 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 GDOs, including experimental releases, in order to avoid potential significant and irreversible adverse effects to biodiversity." (paragraph 25)

c. Updates and adaptations to LMO risk assessment methodologies might be needed to account for the lack of experience with the introduction of GDOs. (paragraph 41)

d. Existing risk assessment considerations and methodologies might not be sufficient or adequate to assess and evaluate the risks that might arise from GDOs, due to limited experience and the complexity of the potential impacts on the environment. The development or further development of guidelines on risk assessment of GDOs would be useful. It was noted that the step of release into the environment is irreversible and, therefore, a precautionary approach might be warranted. (paragraphs 44 and 45)

e. Best practices for effective containment of LMOs should be adapted and applied for GDOs. It was noted 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. Internationally agreed standards for effective containment of GDOs might be useful in order to avoid accidental releases from laboratory facilities. (paragraph 51)

The AHTEG recommendations in point (b) above are particularly relevant as GDOs may well be released in indigenous lands and territories. Research proposals that envisage future experiments with GDOs have been made for Hawaii, New Zealand, Australia and West Africa (see Chapter 2), which include areas that indigenous peoples have traditionally owned, occupied or otherwise used or acquired.

The AHTEG recommendations in point (e) above are pertinent for contained use considerations (see Sections 2.4 and 4.1), especially because there are proposals to begin release of GDOs on islands, as

they supposedly offer a 'confined' environment. For example, the suitability of islands in Uganda as field trial sites for gene drive mosquitoes is being investigated (Lukindu et al. 2018).

Decision on gene drive organisms at CBD COP 14 (November 2018)

At COP 14, Parties to the CBD laid down strict and precautionary conditions for any introduction of organisms containing engineered gene drives into the environment, including for experimental releases and for research and development purposes.

The CBD's Subsidiary Body on Scientific, Technical and Technological Advice (SBSTTA) had met earlier in 2018, and had reached agreement on most of its recommendations on synthetic biology, including the need to apply a precautionary approach to organisms containing engineered gene drives.

However, language asking Parties and other Governments to "refrain from" the release, including experimental release, of such organisms could not be agreed upon. Some Parties wanted a moratorium on environmental releases of organisms containing engineered gene drives, but others were opposed.

After protracted negotiations, a final compromise on the paragraph addressing organisms containing engineered gene drives was agreed upon (Decision 14/19, paragraph 11):

> Calls upon Parties and other Governments, taking into account the current uncertainties regarding engineered gene drives, to apply a precautionary approach*, in accordance with the objectives of the Convention, and also calls upon Parties and other Governments to only consider introducing organisms containing engineered gene drives into the environment, including for experimental releases and research and development purposes, when:
>
> a. Scientifically sound case-by-case risk assessments have been carried out;
>
> b. Risk management measures are in place to avoid or minimise potential adverse effects, as appropriate;
>
> c. Where appropriate, the "prior and informed consent", the "free, prior and informed consent" or "approval and involvement"* of potentially affected indigenous peoples and local communities is sought or obtained, where applicable in accordance with national circumstances and legislation;
>
> [* denotes two footnotes, discussed below]

These conditions should therefore be met when Parties and other Governments are considering the release of organisms containing engineered gene drives into the environment, including for field trial and research purposes.

Both the decisions on synthetic biology and that on risk assessment and risk management under the Cartagena Protocol on Biosafety further stipulate that before GDOs are considered for release into the environment, specific guidance may be useful, to support case-by-case risk assessment. The Parties to the Cartagena Protocol will consider, in 2020, whether additional guidance materials on risk assessment is needed for such organisms.

Therefore, it would also be prudent and responsible for Parties and other Governments to wait until such international guidance specific to the obligations in the Cartagena Protocol is available, before considering any introduction of GDOs into the environment.

Precautionary approach

In addition, a footnote to the words 'precautionary approach' recalls a series of inter-related decisions by the CBD Parties (XIII/17, XII/24 and XI/11), which set out further important principles. The decisions urged Parties and invited other Governments to take a precautionary approach to synthetic biology and to do the following, as spelt out in Decision XII/24 (paragraph 3) and summarised below:

a. establish effective risk assessment and management procedures and/or regulatory systems to regulate environmental release, consistent with Article 3 of the Convention (which reiterates the principle in international law that States have a responsibility to ensure that activities within their jurisdiction or control do not cause damage to the environment of other States; an issue of particular concern with GDOs, given the high potential for spread and transboundary movement);

b. approve field trials only after appropriate risk assessments have been carried out in accordance with national, regional and/or international frameworks;

c. carry out scientific assessments with regard to potential effects on the conservation and sustainable use of biodiversity, taking into account risks to human health and addressing also other issues such as food security and socio-economic considerations with the full participation of indigenous and local communities;

d. encourage provision of funding for research into risk assessment methodologies and promotion of interdisciplinary research that includes related socio-economic considerations; and

e. cooperate in the development and/or strengthening of human resources and institutional capacities, including on methodologies for risk assessments, taking into account the needs of developing countries for financial resources, access to and transfer of technology, establishing or strengthening regulatory frameworks and for risk management.

Decision XIII/17 additionally noted that the above elements "can also apply to some living modified organisms containing gene drives" (paragraph 2).

The precautionary approach is itself to be taken "in accordance with the preamble of the Convention and with Article 14" (Decision XI/11, paragraph 4).

The preamble of the CBD notes that, "where there is a threat of significant reduction or loss of biological diversity, lack of full scientific certainty should not be used as a reason for postponing measures to avoid or minimise such a threat". This provides Parties the right to take precautionary measures, including bans and moratoria, even in a situation where scientific knowledge is lacking.

Article 14 of the CBD meanwhile sets out principles applying to impact assessment and intended to minimise adverse effects, spelling out elements such as environmental impact assessment and allowing for public participation in such procedures; dealing with the consequences of extra-territorial impacts by promoting reciprocity, notification, exchange of information and consultation; immediate notification as well as action to prevent imminent or grave danger or damage beyond national jurisdiction; and emergency responses and international cooperation for joint contingency plans when there is a grave and imminent danger to biological diversity. Furthermore, the issue of liability and redress, including restoration and compensation for damage to biodiversity, is to be examined.

All these elements are particularly pertinent to GDOs, and are now part of the package of precautionary conditions that should apply to such organisms, when their introduction into the environment, including for experimental releases and research and development purposes, is being considered.

"Prior and informed consent", "free, prior and informed consent" or "approval and involvement"

An additional footnote in the COP 14 decision (14/19), on "prior and informed consent", "free, prior and informed consent" or "approval and involvement", refers to the COP decision (XIII/18) that adopted the Mo'otz Kuxtal Voluntary Guidelines for the development of mechanisms, legislation or other appropriate initiatives to ensure the "prior and informed consent", "free, prior and informed consent" or "approval and involvement", of indigenous peoples and local communities when accessing their knowledge, innovations and practices, for fair and equitable sharing of benefits arising from the use of their knowledge, innovations and practices, and for reporting and preventing unlawful appro-

priation of traditional knowledge. These guidelines, while voluntary, set out standards for the international community on this issue.

The Voluntary Guidelines set out in detail the meanings, principles and procedural considerations of the terms (paragraph 7):

a. *Free* implies that indigenous peoples and local communities are not pressured, intimidated, manipulated or unduly influenced and that their consent is given, without coercion;

b. *Prior* implies seeking consent or approval sufficiently in advance of any authorization … respecting the customary decision-making processes in accordance with national legislation and time requirements of indigenous peoples and local communities;

c. *Informed* implies that information is provided that covers relevant aspects, such as: the intended purpose … ; its duration and scope; a preliminary assessment of the likely economic, social, cultural and environmental impacts, including potential risks; personnel likely to be involved … ; procedures [that it] may entail … ;

d. *Consent* or *approval* is the agreement of the indigenous peoples and local communities … or the competent authorities of those indigenous peoples and local communities, as appropriate, … and includes the right not to grant consent or approval;

e. *Involvement* refers to the full and effective participation of indigenous peoples and local communities, in decision-making processes …. Consultation and full and effective participation of indigenous peoples and local communities are crucial components of a consent or approval process.

Whether "prior and informed consent", "free, prior and informed consent" or "approval and involvement" is the standard applied, depends on the national requirements of each country; it is not a menu of options to choose from. The implementation of these requirements, which is voluntary, is however subject to national rules. For example, Malaysia's Access to Biological Resources and Benefit Sharing Act requires any person intending to access traditional knowledge associated with biological resources to show evidence that the prior informed consent of the relevant indigenous and local community has been obtained. Failure to do so could result in penalties such as fines and imprisonment. The law does not specify full details of how the prior informed consent is to be obtained; therefore, the Guidelines offer useful guidance to CBD Parties in this respect.

According to the Voluntary Guidelines, these requirements should be implemented within a context of "full respect for indigenous peoples and local communities", which means "a continual process of building mutually beneficial, ongoing arrangements … , in order to build trust, good relations, mutual understanding, … and includes the full and effective participation of indigenous peoples and local communities, taking into account national legislation and customary laws, community protocols and practices of indigenous peoples and local communities…" (paragraph 8).

The grant of "prior informed consent", "free, prior and informed consent" or "approval and involvement" is temporal unless otherwise agreed. The Voluntary Guidelines also set out procedural considerations related to relevant authorities and other elements, and details on respecting community protocols and customary law.

No similar international guidelines exist yet for obtaining the "prior and informed consent", "free, prior and informed consent" or "approval and involvement" of potentially affected indigenous peoples and local communities when considering the release of GDOs. However, since the COP 14 decision refers to the Voluntary Guidelines in relation to the differentiated levels of consent and approval required from indigenous peoples and local communities at national level, it would be prudent and responsible to only consider introducing GDOs into the environment when these details, as set out in the Voluntary Guidelines, are met.

Box 2: Conflicts of interest

A conflicts of interest procedure to limit the influence of private sector industry and other economic and vested interests from unduly influencing decisions in CBD fora was also adopted at COP 14 (Decision 14/33). This decision is not specific to gene drives or GDOs; however, it was adopted as a direct consequence of specific cases of conflicts of interest in relation to gene drive experts.

In 2017, a number of civil society organisations made public their findings from open records requests in the US and Canada (under the US Freedom of Information Act and the Canadian Access to Information Act), dubbing them the 'Gene Drive Files'. These findings revealed that a number of experts that had been appointed to the CBD's AHTEG on Synthetic Biology were working for institutions that received over US$100 million combined in US military and philanthropic funds, expressly to develop and test gene drive systems.

And yet, these experts were part of the expert group advising the COP's decision-making on the very same subject. These conflicts of interest had not been declared, partly because there was no requirement to do so in the CBD processes. They were only revealed because of the due diligence done by civil society.

The COP 14 decision contains a procedure for avoiding or managing conflicts of interest in technical expert groups that serve the CBD's COP, the Cartagena Protocol's Conference of the Parties serving as the meeting of the Parties (COP-MOP), and the Nagoya Protocol on Access and Benefit Sharing's COP-MOP, or any of their subsidiary bodies. It applies to all nominated experts, regardless of who they are nominated by.

It contains, in an appendix, an 'Interest Disclosure Form', that any person nominated to serve on a technical expert group such as an AHTEG, including as Chair, would have to complete and submit to the CBD Secretariat. COP 16, to be held in 2022, may consider updates and amendments to the current procedure.

The procedure specifies that conflicts of interest "constitutes any current circumstances or interest that could lead a person to reasonably believe that an individual's objectivity in carrying out his or her duties and responsibilities for a specific expert group may be in question or that an unfair advantage may be created for any person or organization."

Each nominated expert must complete the interest disclosure form prior to the selection of experts to disclose "any situations, financial or otherwise, that might be perceived as affecting the objectivity and independence of the contribution that the expert makes and thus affect the outcome of the work of the expert group."

In the interest disclosure form, various relevant financial and professional interests and activities are specified, such as employment and consulting relationships, financial investments, intellectual property and commercial interests, sources of private-sector research support, and former employment and/or other affiliation(s). In addition, relevant financial interests, of not just the individual concerned, but also their employer or the organisation nominating them, must be declared.

Apart from contact details, the contents of the interest disclosure form are publicly available upon request. This allows for the information provided or withheld by the nominated expert to be verified, thus providing some integrity to the procedure. It is also possible for any member of the public to bring relevant information that indicates a potential conflict of interest to the attention of the CBD Secretariat.

This conflict of interest procedure will help to maintain the integrity of the expert advice provided to the CBD processes. This is fundamental to good governance and is necessary in any policy and decision-making arena where technical inputs and expertise are required, such as in the case of gene drives and GDOs.

Limitations

The COP or 'Conference of the Parties' is the supreme decision-making body of the CBD, which is an international treaty that is legally binding on the countries that are Party to it. Decisions of the COP are not legally binding *per se*, in the same way that the CBD itself is binding on countries that are Party to it.

A COP decision (and a COP-MOP decision of the Cartagena Protocol and the Nagoya – Kuala Lumpur Supplementary Protocol) is a formal agreement between Parties that are signatories to a legally binding international treaty, which creates a variety of implementation obligations on those Parties. Among other things, decisions of the COP may be considered as a "subsequent agreement between the Parties regarding the interpretation of the treaty or the

application of its provisions" (Vienna Convention on the Law of Treaties, Article 31.3).

The CBD only has general provisions that are applicable to GDOs, as highlighted above. There are currently no specific regulatory mechanisms to address GDOs, as specific regulation of LMOs is covered by the Cartagena Protocol on Biosafety, which was negotiated to give effect to the CBD provisions related to potential adverse impacts of LMOs resulting from biotechnology. Nevertheless, decisions of the COP further the work of the Convention, and are necessary for developing broader policy measures related to GDOs, such as its recent decision on GDOs or on issues relevant to the governance of GDOs, such as on conflicts of interest and on the free, prior and informed consent of indigenous peoples and local communities as illustrated above.

The CBD has no mechanisms for its enforcement, but a dispute settlement system between Parties in the event that there are differences in the interpretation or implementation of the CBD, and this has never been used. At the same time, when Parties implement international treaties at the national level, domestic laws are usually enacted to do so, and these may give legal enforceability to these rules developed internationally.

Despite these weaknesses in terms of application, it is a mature environmental treaty which has been in force for more than 25 years. It has two Protocols and a Supplementary Protocol (which are legally binding international treaties linked to their parent, the CBD), subsidiary bodies and working groups and numerous work programmes. It has the buy-in of 196 countries which implement it nationally through their national biodiversity strategies and action plans.

Global peer scrutiny and public accountability, rather than the legal enforceability of the CBD, will have to continue to pressure countries to adhere to international rules. For example, the CBD decision in 2000, calling on Parties not to approve genetic use-restriction technologies (GURTs) for field testing or for commercial use (Decision V/5, paragraph 23), was a result greatly helped by a highly visible and concerted global campaign by civil society. The GURTs decision effectively resulted in a moratorium on the technology, because of the high level of public concern.

The United States is the only country in the world that is not a Party to the CBD. This is a familiar problem across numerous other international fora, and is discussed in more detail in Section 3.2. GDOs are mainly being researched and developed in the US and Europe, but any COP decision on GDOs will not apply to the US as a non-Party.

Having said that, a significant number of major producer and exporter countries of GMOs are Parties to the CBD, but not the Cartagena Protocol on Biosafety. Hence, decisions of the CBD COP on these issues have a wider international reach than does the Cartagena Protocol.

2.1.2 Cartagena Protocol on Biosafety

Scope, objectives and key provisions

The Cartagena Protocol on Biosafety entered into force on 11 September 2003. As of 2019, there are 171 Parties to the Protocol. It is the first and only international law to specifically regulate genetic engineering and GMOs. (In the Protocol, GMOs are known as living modified organisms, or LMOs.)

As a global agreement that attempts to balance the competing interests of environment and health protection and commercial and trade interests, the Protocol straddles both somewhat awkwardly. This balance is reflected in the indeterminate preambular paragraphs of the Protocol that deal with this issue, that attempt to safeguard interests on both sides:

> *Recognizing* that trade and environment agreements should be mutually supportive with a view to achieving sustainable development,
>
> *Emphasizing* that this Protocol shall not be interpreted as implying a change in the rights and obligations of a Party under any existing international agreements,

Under ing that the above recital is not intended to subordinate this Protocol to other international agreements.

As such, the Protocol does not go far enough from the perspective of the protection of biological diversity and human health. In practice, countries implement the Protocol at the national level, working through their national interests and considerations, which may include obligations under other international agreements or fora such as the World Trade Organization (WTO). More specific limitations are discussed later in this section.

The Protocol's scope is *all* LMOs that may have adverse effects on biological diversity, "taking also into account" risks to human health (Article 4). This includes plants, food, pharmaceuticals, animals, insects, trees, LMOs for industrial use, etc. Living modified (LM) pharmaceuticals for humans are not covered by the Protocol if they are addressed by relevant international agreements made by other organisations (such as the World Health Organization, for example). The Protocol deals mainly with the transboundary movement (import and export) of LMOs, including illegal and unintentional transboundary movements.

Its objective is "to contribute to ensuring an adequate level of protection" in transferring, handling and using LMOs that may have adverse effects on biological diversity, "taking also into account" risks to human health, with a specific focus on transboundary movements (Article 1).

The language on human health is taken from the CBD. The constructive ambiguity around the language of "taking also into account risks to human health" allows some countries to argue that any risks to human health can be taken into account only if they result from an adverse effect on biological diversity. At the same time, other countries argue that any adverse effects on human health can be "taken into account" independent of adverse effects on biological diversity (Mackenzie et al. 2003, 11-12). This may lead to differences in national implementation.

For the first time in international law, there is clear recognition that LMOs are inherently different from other, naturally occurring organisms, that they may carry special risks and hazards, and therefore need to be regulated internationally. The Protocol addresses the fact that LMOs may have biodiversity and human health impacts, and that these impacts need to be risk-assessed. The Protocol also recognises that socio-economic considerations can be taken into account when making decisions on LMOs, an issue that is particularly important for developing countries.

Crucially, the Cartagena Protocol puts the Precautionary Principle into operation in decision-making i.e., in the absence of scientific certainty, a party should err on the side of caution and could restrict or prohibit the import of LMOs on account of their potential adverse effects. In addition, the Protocol requires that Parties must consult the public when making decisions on LMOs, in accordance with their laws and regulations.

Its 'advance informed agreement' (AIA) procedure governs only the first transboundary movement between Parties of a LMO for intentional introduction into the environment. This procedure essentially operationalises the principle of prior informed consent, that exports of LMOs require the informed approval of the importing country. It also establishes the right of the importing Party to say 'no' to a given request for import.

The AIA procedure involves three key steps. First, the Party of import must be notified by the Party of export or the exporter (such as the LMO developer, which could be a biotechnology company) of the latter's intent to send LMOs. Thus, countries have an international right to be notified that a LMO is going to be shipped to them.

The Party of import then evaluates the risk assessment which has been submitted by the Party of export or exporter, or alternatively conducts its own risk assessment if it is not satisfied with the risk assessment submitted, which is usually conducted by the developer of the LMO. Precaution is also one of the general principles of risk assessment.

Finally, the Party of import makes its decision based on precaution. The decision could be for unconditional approval, approval with conditions, prohibition, a request for additional relevant information or extension of the time period for further consideration of the application. For example, in 2018, the South African authorities did not approve an application for the general release (including for planting) of a GM maize variety engineered to be drought tolerant, insect resistant and herbicide tolerant (Executive Council under the GMO Act 2018). The decision was reached because the data provided by the applicant were insufficient to demonstrate the efficacy of the drought tolerance and insect resistance traits.

The AIA procedure thus places obligations on exporters to first seek the informed approval of importing Parties before the first transboundary movement for deliberate release into the environment (e.g. field trials, commercial plantings) can occur. It reverses the burden for importing Parties that usually have limited capacity and information to know what is entering into their territories and to regulate them accordingly. It also affords rights to importing Parties and places corresponding obligations on exporter countries.

In implementing this obligation, Parties either apply their domestic regulatory framework that is consistent with the Cartagena Protocol or apply the AIA procedure directly. In most cases, countries with domestic regulatory procedures would proceed in accordance with them. As such, for Parties that have national biosafety laws implementing this obligation, LMOs for deliberate release into the environment are no longer allowed to enter their territory unless their prior informed consent is sought, a risk assessment is carried out and a decision to allow the import is given. This is the case for most of the biosafety laws in force today, although implementation and enforcement may vary.

However, the Protocol excludes some LMOs from the AIA procedure – LMOs in transit, in contained use, and those intended for food, animal feed or for processing. Nonetheless, these LMOs are still covered by the Protocol, and all other provisions of the Protocol apply to them.

LMOs that are intended for food or feed, or for processing (LMO-FFPs) are the bulk of traded LMOs. A separate procedure applies for such commodity shipments: countries that make a final decision on domestic use must notify the Biosafety Clearing-House (BCH), an online portal administered by the Secretariat of the CBD. Potential importing countries can make a decision under its domestic laws that are consistent with the objective of the Protocol, or according to the procedure in the Cartagena Protocol for LMO-FFPs. In some domestic laws, Malaysia's Biosafety Act for example, applications for approval are necessary for the import of LMOs for intentional introduction into the environment as well as for LMO-FFPs, as both types of LMOs could end up propagating in the environment, despite their intended purpose.

Parties implement their obligations under the Cartagena Protocol through national measures. In doing so, Parties interpret and apply their international obligations, often crafting comprehensive national biosafety laws and regulations dealing with all aspects of biosafety regulation, and sometimes with higher biosafety standards (see Section 3.2).

Relevance to gene drive organisms

As living organisms containing engineered gene drives fulfil the criteria of (i) being a living organism; (ii) possessing a novel combination of genetic material; and (iii) resulting from the use of modern biotechnology, the Cartagena Protocol is fully applicable to them. Therefore, the Protocol's requirements pertaining to the transboundary movement, transit, handling and use of all LMOs that may have adverse effects on the conservation and sustainable use of biological diversity, including consideration of risks to human health, apply.

At the current juncture of development of GDOs, the applications are still at the laboratory research stage. It is thus also worth remembering that while LMOs destined for contained use are exempt from the AIA procedure, Parties have the right to subject

all LMOs to an approvals procedure, including risk assessment, prior to decisions on import, release or even contained use. In addition, Parties have the right to set standards for contained use within their jurisdiction.

As mentioned above, Parties to the Protocol implement their international obligations through national biosafety laws and regulations. Therefore, these national biosafety rules in relation to contained use must also be examined closely (see Section 3.2).

Ad Hoc Technical Expert Group on Risk Assessment and Risk Management

Article 15 deals with risk assessment and is the core business of the Cartagena Protocol, upon which decisions on import, release, etc. are made. In 2008, Parties established an AHTEG on Risk Assessment and Risk Management, and tasked it with developing further guidance on specific aspects of risk assessment and risk management.

The resulting 'Guidance on Risk Assessment of Living Modified Organisms and Monitoring in the Context of Risk Assessment' comprises three parts: (i) a 'Roadmap' for risk assessment of LMOs, which explains how to conduct a risk assessment; (ii) a series of guidelines on conducting risk assessments on specific kinds of LMOs and traits – Living modified (LM) plants with stacked genes or traits; LM plants with tolerance to abiotic stress; LM trees; and LM mosquitoes that act as vectors of human and animal diseases; and (iii) guidance on monitoring of LMOs released into the environment.

The guidance on risk assessment of LM mosquitoes includes some general consideration of self-propagating or self-sustaining strategies that rely on gene drive systems. Elements for consideration include characterisation of the LM mosquito, unintended effects on biological diversity, vertical and horizontal gene transfer, persistence of the transgene in the ecosystem, evolutionary responses, unintentional transboundary movement, risk management strategies, and finally, containment of the LM mosquito. However, the guidance is not focused on one particular type of technology or genetic mechanism; thus additional and more specific guidance may be necessary when conducting a risk assessment of a gene drive mosquito.

The AHTEG on Risk Assessment and Risk Management also recommended the development of additional guidance on risk assessment of LMOs developed through synthetic biology. To facilitate this, the AHTEG prepared an outline of guidance on 'Risk Assessment of LMOs developed through synthetic biology'.

The outline recognised that synthetic biology may lead to the development of LMOs containing new and significantly different features from those in the original organism or from those in nature. The potential of gene drives to alter wild populations, species and ecosystems was one consideration specific to risk assessment that was identified. The outline noted that synthetic biology tools, such as high throughput DNA sequencing and computational analyses, may make it easier to develop LMOs containing gene drive systems. It highlighted that gene drives may cause irreversible adverse effects on beneficial organisms and ecosystems and that risk assessment methodologies may need to be adapted in order to fully assess these effects.

At COP-MOP 9 in 2018, Parties adopted a decision (9/13) that establishes a new AHTEG on Risk Assessment and Risk Management (paragraph 8). It calls for broad international cooperation, knowledge sharing and capacity-building to support Parties and others in assessing the potential adverse effects of, *inter alia*, LMOs containing engineered gene drives (paragraph 5).

Importantly, specific work on LMOs containing engineered gene drives is set out as well. GDOs are the subject of a study commissioned by the CBD Executive Secretary, which would be subsequently reviewed, and analysed by the AHTEG, in order to inform the application of criteria intended to facilitate the process of identifying and prioritising specific topics that may warrant consideration for developing risk assessment guidance (paragraph 11(a) and Annex II). Parties will also consider GDOs as a topic

for possible additional guidance on risk assessment at COP-MOP 10 in 2020 (paragraph 7).

Ad Hoc Technical Expert Group on Socio-economic Considerations

GDOs will clearly have socio-economic impacts, which will need to be assessed and taken into account in decision-making.

Under the Protocol, Parties have the right to take into account socio-economic considerations that arise from the impact of LMOs on biological diversity, "especially with regard to the value of biological diversity to indigenous and local communities" when taking decisions on importing LMOs (Article 26). Under national laws, socio-economic considerations or assessments may also be required as part of decision-making on GMO applications. This issue has been particularly important to developing countries, which are concerned about impacts on the livelihoods and culture of their local communities and indigenous peoples.

Under the CBD, COP 13 invited Parties to take into account socio-economic, cultural and ethical considerations when identifying the potential benefits and adverse effects of synthetic biology organisms, components and products (Decision XIII/17, paragraph 8). For example, there is concern that the use of synthetic biology to engineer microbes that can excrete compounds that mimic valuable substances, such as those found in vanilla, stevia, shea butter and silk, will threaten the market for natural products and adversely affect the livelihoods of farmers and indigenous peoples who cultivate or harvest the products (BICSBAG 2018).

COP-MOP 7 established an AHTEG on Socio-Economic Considerations in 2014. In 2016, the AHTEG's composition was extended to include a representative of indigenous peoples and local communities. The outcome of its work is the 'Guidance on the Assessment of Socio-Economic Considerations in the Context of Article 26 of the Cartagena Protocol on Biosafety'. However, the AHTEG has not addressed GDOs specifically to date.

The Guidance provides principles for the assessment of socio-economic considerations and outlines the stages of the assessment process. Parties and other Governments are invited to make use of the Guidance.

The AHTEG however noted that further work was needed, in particular on the application of methodologies and examples of application of socio-economic considerations. As decided by the Parties to the Cartagena Protocol at COP-MOP 9 in 2018, the AHTEG will continue its work to supplement the Guidance, following the collection of information and case studies via submissions from Parties and discussion in an online forum (Decision 9/14).

Decisions on unintentional transboundary movements

The issue of unintentional transboundary movements is particularly relevant to GDOs. While the central pillar of AIA in the Protocol is important for all LMOs in general, when it comes to GDOs, more attention must be paid to unintentional movements across borders. Gene drives are designed to spread genetic modifications, and the likelihood of the resulting spread of GDOs or escape from containment is high. In such cases, Article 17 of the Cartagena Protocol on 'unintentional transboundary movements and emergency measures' applies.

The provisions of Article 17 are triggered when a Party knows of a release in its jurisdiction that leads, or may lead, to an unintentional transboundary movement of a LMO that is likely to have significant adverse effects on biological diversity, taking also into account risks to human health. As soon as it knows, a Party is required to notify affected or potentially affected States, the Biosafety Clearing-House, and, where appropriate, relevant international organisations. Information that must be provided includes the estimated quantities and characteristics and/or traits of the LMO, the circumstance and estimated date of the release, the intended use of the LMO, information about the possible adverse effects on biological diversity, as well as the possibility of risks to human health, with possible risk management measures.

Incidents of unintentional transboundary movements of LMOs worldwide have occurred with alarming frequency. A total of 396 known contamination incidences and illegal releases were recorded across 63 countries between 1997 and 2013 (Price and Cotter 2014). A well-known example is that of Starlink corn, which entered the global food supply, even though it had not been approved in the US (where it was grown) for food purposes, and was subject to numerous recalls (Price and Cotter 2014, 11). Another example involving a Party to the Protocol was the unintentional export from China of rice products containing a GM variety not approved for human consumption (Zi 2005), which led to recalls in European and other countries (Price and Cotter 2014, 11). In this and similar cases, Article 17 requires the Party responsible to also immediately consult the affected or potentially affected States in order to determine appropriate responses and initiate necessary action, including emergency measures.

In the context of GDOs, the application of these obligations may soon become all too commonplace, if the rules that were put in place with more 'conventional' LMOs in mind continue to be utilised. A relevant issue to be considered is whether, for GDOs, an extended model of AIA should be considered, which can facilitate prior informed collective consent amongst *all* potentially affected parties, before any release can occur (see Section 4.2).

In recent COP-MOPs, a number of decisions have been taken on Article 17, bringing its implementation forward. Among other things, COP-MOP 6 urged Parties to put in place appropriate measures to prevent unintentional transboundary movements of LMOs, and to establish a mechanism for emergency measures, in cases where significant adverse effects on biological diversity or risks to human health are likely (Decision VI/16, paragraph 1).

COP-MOP 8 adopted operational definitions of the terms 'unintentional transboundary movement' and 'illegal transboundary movement' (Decision VIII/16, paragraph 1). In Article 25 of the Protocol, Parties are required to adopt domestic measures aimed at preventing and penalising illegal transboundary movements, which are in contravention of domestic measures taken to implement the Protocol (usually national biosafety laws). Such measures, for example, could include the rejection of shipments of unapproved LMOs, such as when China rejected GM corn from the US in 2013 because that particular variety had not yet been approved in China, making it illegal (BBC News 2013).

The operational definition of unintentional transboundary movement attempts to limit the measures required under Article 17 (notification and consultation) only to situations where the LMO in question is likely to have significant adverse effects in the affected or potentially affected States, on biological diversity, or carries risks to human health. However, the fact is that in many jurisdictions, unintentional transboundary movements are also illegal transboundary movements, and measures to prevent and penalise illegal transboundary movements would also apply to those unintentional transboundary movements, regardless of whether or not the LMO concerned is likely to have significant adverse effects on biological diversity or human health.

Network of Laboratories for the Detection and Identification of LMOs

The detection and identification of GDOs would be paramount, especially in a situation of unintentional release into the environment. Detection and identification become particularly important for GDOs in the context of liability and redress. There could, however, be challenges in obtaining the sequence information and reference materials that are necessary for countries to be able to detect and test for GDOs in their territory. Without these, regulation of unintentional and illegal transboundary movements cannot be effectively enforced. Regrettably, competent authorities are sometimes not readily provided sequence information and reference materials in such cases, and this is particularly so for LMOs in field trials. The same is likely to be true for GDOs as well.

In 2010, Parties to the Cartagena Protocol on Biosafety established the Network of Laboratories for the Detection and Identification of LMOs. The Network operates largely electronically, as a hub where

experts can interact and exchange experiences on the use and development of LMO sampling and detection techniques (CBD, n.d.). The Network has developed technical tools and a draft training manual for capacity-building activities on detection and identification. It will be reviewed and finalised, and online discussions and meetings of the Network, along with capacity building efforts, particularly for developing countries, will continue (Decision 9/11).

The AHTEG on Synthetic Biology suggested that the Network might be able to contribute to the assessment of the availability of tools for the detection of organisms developed through synthetic biology techniques, which include GDOs (AHTEG on Synthetic Biology 2017, paragraph 36). It could also assist with the identification of best practices, as well as advising on any gaps and challenges in existing methodologies that might need to be addressed.

COP 14 of the CBD therefore requested the Executive Secretary to collaborate and convene discussions, including through the Network, for sharing experiences on the detection, identification and monitoring of organisms, components and products of synthetic biology, and to continue inviting laboratories, including analytical laboratories, to join the Network (Decision 14/19, paragraph 17(f)). The specific challenges posed by the detection and identification of GDOs need to be taken up in this work.

Limitations

The Cartagena Protocol is deficient in several respects. It was the lowest common denominator that could be agreed among big GMO exporter countries and importing countries with little capacity. Since it was negotiated with 'conventional' GMOs in mind, its deficiencies as an instrument for regulating GDOs are even more pronounced.

The major GMO-producing and exporting countries are also not Parties to the Protocol; this includes the US, Canada, Australia, Argentina and Chile. However, as discussed earlier and in Section 3.2, other pathways for biosafety compliance exist, and these countries and their exporters will nevertheless have to comply with the national laws of countries implementing the Protocol.

Most countries did not have national biosafety legislation or regulations prior to becoming Parties to the Protocol. When developing them, the Protocol's focus and standards were domesticated into their national laws, along with domestic regulatory issues. For countries with national biosafety laws and regulations, this is really where scrutiny is needed.

With regards to GDOs, most of the current research is taking place in the US, Australia, New Zealand and in the EU, of which the latter two are Parties to the Protocol; the Protocol's membership is not as universal as the CBD's. However, several prominent proposals for research (including field trials) and eventual deployment are in countries that are Parties to the Protocol. It is highly irresponsible for gene drive research and deployment to take place in the absence of effective international governance, and even more so in countries that are not Parties to this Protocol.

The Protocol, as an international instrument, is largely focused on intentional transboundary movements of conventional LMOs. For the big producer and exporter countries, unimpeded trade in commodities has been their major concern. Because of this concern to allow trade in commodities to continue, the Protocol is structured around AIA and the procedure for LMOs intended for direct use as food or feed, or for processing, with provisions on unintentional and illegal transboundary movements. With GDOs, this structure is deficient, as gene drives are designed to spread genetic modifications. A single country's approval structure with inadequate provisions dealing with unintentional and illegal releases is clearly insufficient.

The Protocol's approach is centered around biosafety assessment and decision making. Indeed, it has often been criticized as being facilitative of LMO approvals. This is a valid concern. In practice, countries are also legally bound by other international instruments that they are Party to, such as those under the WTO, which may have competing paradigms.

The Protocol, like the CBD itself, also lacks strict enforcement measures. Its provisions on compliance are largely facilitative and focus on cooperation, advice and assistance, unlike the WTO's dispute settlement mechanism for example, which entails fines and other censures.

Furthermore, under the Protocol, socio-economic issues are merely *considerations* that countries may take into account, or not, in their decision-making. Socio-economic issues are treated as conceptually separate from risk assessment. With GDOs, these issues and their assessment are arguably even more pressing than they have been with LMOs. Enlarging the space to address the broader questions such as problem formulation, alternative solutions, research and technology choices and power relations in respect to decision-making structures, is also a major challenge that needs to be addressed.

2.1.3 Nagoya – Kuala Lumpur Supplementary Protocol on Liability and Redress

Box 3: Liability and redress

Liability is an obligation of a (natural or legal) person to provide compensation or take redress measures for damage resulting from an action or a situation for which that person is responsible. Liability arises when it is established in fact and in law that there has been damage caused. It must further be established that there is an identifiable person who is responsible. At that point, the issue of compensating for or redressing the harm done can be dealt with (Nijar 2007).

The purpose of liability rules can be four-fold; they have a (i) preventive function, in that they provide incentives for the implementation of and compliance with existing rules; (ii) they include an absorptive function, by internalizing the environmental, health, socio-economic and other costs of an activity; (iii) they also have a punitive function, as they impose sanctions against wrongful conduct and help implement the 'Polluter Pays' principle; and (iv) they exert a corrective function, that requires the restoration of the damage (Secretariat of the Convention on Biological Diversity 2011).

Scope, objectives and key provisions

The Nagoya – Kuala Lumpur Supplementary Protocol on Liability and Redress to the Cartagena Protocol on Biosafety is a separate treaty that deals specifically with the issue of liability and redress for damage resulting from the transboundary movements of LMOs. It entered into force in March 2018, and there are currently 44 Parties.

As an international law only newly in force, it is expected that more countries will become Parties. However, this may be a slow process, given that some countries still do not have their national biosafety systems in place, much less any liability and redress rules for LMOs. It is also probable that not as many countries as are Parties to the Cartagena Protocol will become Parties to the Supplementary Protocol, as the political landscape has shifted, 16 years after the entry into force of the Cartagena Protocol. Developing countries, who were the strong proponents for international liability and redress rules, are now more involved in experimenting with, planting and commercialising LMOs. The application of these liability rules to real situations of damage arising from LMOs has not yet been tested, so it remains to be seen how effective the Supplementary Protocol will be.

The Supplementary Protocol's objective is "to contribute to the conservation and sustainable use of biological diversity, taking also into account risks to human health, by providing international rules and procedures in the field of liability and redress relating to living modified organisms" (Article 1). This mirrors the objectives and the language of the Cartagena Protocol.

The Supplementary Protocol requires Parties to provide at the national level for rules and procedures that address damage from LMOs where such damage falls under the definition set out in its Article 2. As discussed earlier, under the Cartagena Protocol and hence also under the Supplementary Protocol, GDOs clearly fall within the definition of LMOs.

Damage is defined in the Supplementary Protocol as an adverse effect on the conservation and sustainable use of biological diversity, and also takes into account risks to human health. This means that damage is not restricted to damage to biological diversity alone; damage to human health is also considered. Like the Cartagena Protocol, there is ambiguity about exactly how to interpret this inclusion of human health; this is left to Parties to implement at national level.

The Supplementary Protocol applies to damage resulting from LMOs that find their origin in a transboundary movement (Article 3). The LMOs referred to are those (i) intended for direct use as food, feed or for processing; (ii) destined for contained use; and (iii) intended for intentional introduction into the environment. It also applies to damage resulting from unintentional transboundary movements and illegal transboundary movements.

Furthermore, domestic law implementing the Supplementary Protocol shall also apply to damage resulting from transboundary movements of LMOs from non-Parties. This means that Parties are obliged in their domestic laws to ensure that all transboundary movements of LMOs, even from non-Parties, are addressed. This is an important issue, as some of the major producers and developers of LMOs, such as the United States and Argentina, are non-Parties to the Cartagena Protocol and hence are also not Parties to the Supplementary Protocol. In practice, Parties' national biosafety laws would apply to transboundary movements of LMOs regardless of whether the LMOs originate from countries that are Parties to the Protocol or not. The Supplementary Protocol simply makes this mandatory and explicit. However, if there is transboundary movement between two non-Parties, the Supplementary Protocol will not apply, only the two countries' domestic liability rules.

The central obligation that Parties to the Supplementary Protocol assume is to provide for response measures in the event of damage, or a sufficient likelihood of damage, resulting from LMOs (Article 5).

It must be pointed out that the Supplementary Protocol takes an 'administrative approach', whereby liability would be a matter to be resolved between the liable entity and the executive arm of a government, and response measures are required of the operator (person or entity in control of the LMO) or the competent authority (the national entity responsible, usually an environment agency), if the operator is unable to take response measures.

The operator is defined as any person in direct or indirect control of the LMO, and could include the permit holder, person who placed the LMO on the market, developer, producer, notifier, exporter, importer, carrier or supplier. This is determined by domestic law.

Response measures are defined as reasonable actions to (i) prevent, minimise, contain, mitigate or otherwise avoid damage, as appropriate; and (ii) restore biological diversity. Measures must be implemented by, and in accordance with, domestic law. Response measures are required in both situations where damage to biodiversity has already occurred, and when there is a sufficient likelihood that damage will result if timely response measures are not taken.

It is understood that the operator is responsible for paying for the costs incurred in the exercise of its obligations under the Supplementary Protocol. In addition, the competent authority has the right to recover from the operator the cost and expenses of, and incidental to, the evaluation of the damage and the implementation of response measures. In terms of damage to biological diversity and the response measures required, the costs could be enormous. The Supplementary Protocol does not provide for financial guarantees, in case the operator does not or cannot pay. It merely acknowledges the right of countries to require financial security in their national laws. As with many of these agreements, the Supplementary Protocol lacks an enforcement mechanism.

Relevance to gene drive organisms

As discussed earlier, under the Cartagena Protocol and hence also under the Supplementary Protocol, GDOs clearly fall within the definition of LMOs.

In relation to GDOs, impacts on the environment and biological diversity, human and animal health, and on socio-economic conditions are likely to be greater than with 'conventional' GMOs. High-risk technologies demand high levels of responsibility and accountability. The irreversible nature of their impact and possible wide geographic spread once released mean that there is high potential for serious harm. The likelihood of unintentional and illegal transboundary movement is high.

A strict and legally binding international liability regime that is effective against the significant risks that GDOs pose is therefore essential. However, the Supplementary Protocol falls far short of what was envisaged when developing countries called for its negotiation. Instead of the international instrument that would help to ensure the responsibility and accountability of the producers and exporters of LMOs, the threshold for establishing damage is high, and much of the burden has been shifted to the recipient countries themselves, without the advantage of the necessary financial guarantees. In the case of GDOs, these deficiencies are further amplified.

The Supplementary Protocol applies to damage from LMOs and GDOs that find their origin in a transboundary movement. With GDOs currently being researched and developed, this may not always be the case. Not all GDOs may be imported or exported; they may be intended for domestic use only, but may still cause significant damage. However, the Supplementary Protocol also applies to damage resulting from unintentional transboundary movements and illegal transboundary movements, which is particularly relevant to GDOs.

Limitations

The Supplementary Protocol is newly in force but it currently has limited participation, with only 44 Parties. This means that few countries have the necessary domestic rules to implement the Supplementary Protocol and for liability and redress for LMOs/GDOs.

The central approach of the Supplementary Protocol is an administrative approach, which may not be adequate to deal with the damages caused by LMOs and GDOs in particular (see Box 4). Civil liability approaches, whereby victims of damage can turn to national courts for redress and enforcement of judgments, that are specific to LMOs and GDOs are not required, just permitted, and Parties' rights to put in place domestic civil liability rules and procedures are preserved under the Supplementary Protocol. The first review of the Supplementary Protocol, five years after entry into force (in 2023), will include a review of the effectiveness of the provision of civil liability.

Box 4: Administrative approach, not civil liability

During the negotiations for the Supplementary Protocol, most developing countries had wanted a binding international regime that would set substantive rules on civil liability, whereby victims of damage from LMOs can turn to national courts for redress and enforcement of judgments.

However, due to the compromises made during the negotiations, the Supplementary Protocol takes an 'administrative approach', whereby liability would be a matter to be resolved between the liable entity and the executive arm of a government. 'Response measures' are required of the operator (person or entity in control of the LMO) or the competent authority (government agency), that is, if the operator is unable to take response measures. This is the approach taken in the EU Environmental Liability Directive, for example. It is however a novelty for an international environmental liability regime and it remains to be seen how it will work at the international level with the subject matter of LMOs.

The administrative approach of the Supplementary Protocol does however in effect employ a strict liability approach (see Box 5). When there is damage or sufficient likelihood of damage, then response measures should be implemented. Of course, a causal link needs to be established between the damage and the LMO in question.

Under the Supplementary Protocol, it is not necessary to establish the fault of the operator.

The action or inaction of the operator is not the trigger for establishing liability and providing for response measures. Damage, or the sufficient likelihood of damage, is what triggers the response measures that need to be taken.

In addition, the administrative approach itself theoretically allows for preventive action to "prevent, minimise, contain, mitigate, or otherwise avoid damage". It could also facilitate a speedier response in terms of restoring biological diversity, without having to go through a judicial process.

Reference: Nijar 2013.

The standard of liability that Parties should apply for domestic civil liability rules is left to national legislation. The Supplementary Protocol does not require Parties to apply a strict liability standard for civil liability rules on LMOs, which is a limitation (see Box 5).

Box 5: Strict liability is the necessary civil liability standard for GDOs

In common law jurisdictions, under a *fault-based liability regime*, it is necessary to establish that a person has a duty of care towards the victim, that there has been a breach of that duty, and that the breach of that duty has caused the damage. Multiple difficulties can arise with this, especially in the case of GMOs and GDOs. The burden of proof lies with the victim who has suffered the damage to show evidence of each element.

With *strict liability*, it is sufficient that the damage is proven and a causal link between the damage and the GMO/GDO is shown, which means that liability is established without proof of fault. The burden of proof is reversed, and instead the person responsible is required to show that its GMOs/GDOs are safe when there is damage. Defences are available and can be legally applied. Strict liability is commonly the standard for product liability, for example.

This is aligned with the biosafety approvals procedure, where the operator seeks regulatory approval by demonstrating through risk assessment that the LMO is 'safe'. The regulator applies the Precautionary Principle, and makes a decision.

It has been argued that the application of the Precautionary Principle and strict liability go hand in hand. The Precautionary Principle requires action to avoid or minimise risks, even in the face of scientific uncertainty, and full scientific certainty is not necessary for taking preventive or precautionary action. Strict liability assigns liability so long as causation between the GDO and the damage can be established. It dispenses with the need for establishing the breach of the duty of care of the responsible person.

In the case of GDOs, the risks are inherent to their nature and construction. For strict liability, the focus is on the actual performance and condition of the GDO. For fault-based liability, the focus is on the care taken by the responsible person. As such, strict liability is the necessary standard of liability for GDOs.

For activities involving ultra-hazardous risks especially, strict liability is already evolving to become customary international law. It has been argued that these risks include most of the serious risks arising from many other modern technologies, including activities which may cause a substantial change in the natural environment, significant pollution and the modification of biological processes. It is also the standard of liability in several international treaties dealing with environmental harm from hazards ranging from nuclear activities to oil pollution.

References: Nijar 2000; 2007.

Besides the issue of rules and procedures on civil liability, much of substance in the Supplementary Protocol is also left to national legislation. These include: defining the 'operator'; criteria to address damage that occurs within national jurisdiction; the application of damage from import of LMOs from non-Parties; establishing the causal link between the LMO and the damage; exemptions or mitigations; time limits; financial limits; and the provision of financial security.

In addition, the most important element of the Supplementary Protocol is qualified by reference to domestic laws – response measures are to be implemented "in accordance with domestic law" (Article 5.8).

In contrast to a legally binding international civil liability regime, which was what most developing countries had wanted, the administrative approach of the Supplementary Protocol places a large burden for addressing damage on national authorities.

The competent authority, which is the government agency responsible and could include a dedicated biosafety agency or a department of environment, has to identify the operator, evaluate the damage and determine which response measures should be undertaken. If the operator fails to implement appropriate response measures, the competent authority may do so. Although the competent authority may recover costs and expenses from the operator, substantial resources and capacity are still required, which most developing countries may not have.

Despite this, financial security, in terms of insurance or other means of guaranteeing redress, is not required under the Supplementary Protocol. Parties only retain their right to provide for financial security in their domestic laws. Even so, this right is qualified by reference to consistency with rights and obligations under international law, taking into account the careful balance struck in the Cartagena Protocol's preamble on the mutual supportiveness of trade and environment agreements. Compulsory insurance or other financial guarantees, as well as a supplementary compensation fund, are necessary, at a minimum, for GDOs.

However, in accordance with the provision on financial security in the Supplementary Protocol (Article 10), the first meeting of the Parties to the Supplementary Protocol in 2018 requested the Secretariat to undertake a comprehensive study on financial security for consideration at its next meeting in 2020. The first review of the Supplementary Protocol, five years after entry into force (in 2023), will also include a review of the effectiveness of the provision on financial security.

Furthermore, the Decision adopted at COP-MOP 5 on liability and redress states that where the costs of response measures have not been covered, such a situation may be addressed by additional and supplementary compensation measures. These may include arrangements to be addressed by the COP-MOP in the future.

These opportunities must be taken and seriously addressed as part of the mandated future work of the Supplementary Protocol, given the urgency and gravity of the potential damage from GDOs.

Another considerable hurdle in the Supplementary Protocol is that response measures are to be taken only if damage is measurable or otherwise observable, and must take into account, wherever available, "scientifically-established baselines recognised by a competent authority that takes into account any other human induced variation and natural variation" (Article 2.2(b)). Damage must also be "significant", for which determination is specified by the Supplementary Protocol (Article 2.3).

Only once a threshold of significant, measurable or observable damage has been met, that takes into account scientifically established baselines, does the requirement to take response measures arise. This is particularly challenging in the context of GDOs.

2.2 Other international agreements and standards of relevance to Gene Drive Organisms

This section will address some of the other international agreements and standards of more relevance to GDOs currently. The agreements and standards discussed here cover areas of specific governance of GDOs. These include the WTO's Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement) and two of the international standard setting bodies that are explicitly recognised by the SPS Agreement – the International Plant Protection Convention and the World Organisation for Animal Health.

The other international standard setting body recognised by the SPS Agreement, the Codex Alimentarius Commission, is not addressed in this section. This is primarily because Codex provides for the international regulation of food safety, and gene drive applications are not envisaged yet for food crops. This fact is also a matter of technical challenge, as current CRISPR-based gene drives cannot be easily developed in plants. However, there may be future applications that affect food safety,

for example if gene drives are successfully used to make weeds such as pigweed susceptible to herbicides; if such modifications spread to related amaranth species used for food in some countries, there could be unanticipated effects (NASEM 2016, 76), including on food safety. Gene drives could also theoretically be used as a tool for genome editing in livestock breeding (Gonen et al. 2016), resulting in gene drive animals potentially entering the food supply. These applications are pretty far in the future, although should any come to fruition and raise potential international food safety issues, then the Codex would become relevant.

The other agreements and standards that are reviewed in this section are those that are relevant to the potential hostile use of gene drives, given the 'dual use' nature of the technology. We also examine the UN Declaration on the Rights of Indigenous Peoples, which sets international norms on the rights of indigenous peoples, who could be affected by any release of GDOs, and to whom the CBD and its Protocols place particular importance, given their role as custodians of biological diversity.

None of the agreements or standards reviewed in this section has a biosafety impetus as its starting point. In particular, the SPS Agreement operates within a trade liberalisation context. (The uneasy relationship between trade and environment is discussed in Section 2.1.2, in so far as it plays out between the WTO and the Cartagena Protocol on Biosafety.) It sets out the permissible measures for WTO members on sanitary and phytosanitary action without falling foul of its international rules for advancing free trade.

2.2.1 Agreement on the Application of Sanitary and Phytosanitary Measures

Scope, objectives and key provisions

The Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement) is one of the WTO's agreements that were signed in 1994. WTO agreements are legally binding on WTO members, and the WTO is the only international organisation with a *formal and enforceable dispute settlement system*, giving it considerable legal force. In a dispute, a sanction of last resort could be the raising of duties on imports from the losing party, providing a strong incentive for members to comply with WTO dispute panel rulings. As of July 2016, there are 164 WTO members.

The SPS Agreement deals with sanitary and phytosanitary measures that "may, directly or indirectly, affect international trade" (Article 1.1). These measures include laws, regulations, requirements, procedures and decrees. A WTO member intending to apply measures to restrict trade for the protection of the life or health of humans, animals or plants has to comply with the SPS Agreement.

Annex A of the SPS Agreement defines a sanitary or phytosanitary measure as any measure applied to: (i) protect animal or plant life or health from risks arising from the entry, establishment or spread of pests, disease, disease-carrying organisms, or disease-causing organisms; (ii) protect human or animal life or health from risks arising from additives, contaminants, toxins, or disease-causing organisms in foods, beverages or feedstuffs; (iii) protect human life or health from risks arising from diseases carried by animals, plants or products thereof, or from the entry, establishment or spread of pests; or (iv) prevent or limit other damage from the entry, establishment or spread of pests.

WTO members are allowed to set their own standards, as long as the measures are applied only to the extent necessary to protect human, animal and plant life or health; are based on scientific principles and maintained with sufficient scientific evidence; are not a disguised trade restriction; do not arbitrarily or unjustifiably discriminate between members where identical or similar conditions prevail; and are not more trade-restrictive than required to achieve an appropriate level of protection (Chee and Lim 2007, 430).

WTO members are encouraged to use international standards, guidelines and recommendations where these exist, although they may use measures

that result in higher levels of protection if there is scientific justification (i.e. they have conducted an evaluation of available scientific information and have decided that the international standards are not sufficient to achieve their appropriate level of protection). Alternatively, there needs to have been a risk assessment conducted according to the SPS Agreement provisions as a basis for a sanitary or phytosanitary measure taken (Chee and Lim 2007, 430).

In general, while the SPS Agreement allows WTO members to restrict trade on the basis of sanitary and phytosanitary measures, the logic and rationale of free trade prevail. In effect, this means that any measures applied are the minimum necessary to protect human, animal and plant life or health.

Box 6: Existing application of the SPS Agreement to GMOs

The application of the SPS Agreement to GMOs has been confirmed by the disputes brought in 2003 by the United States, Canada and Argentina against the European Union: *European Communities – Measures Affecting the Approval and Marketing of Biotech Products.*

The dispute settlement panel concluded that the European Communities (EC) applied a general *de facto* moratorium on approvals of biotech products, which was in effect on the date of panel establishment, i.e., August 2003. However, the moratorium itself was not an SPS measure as it was not applied for achieving the EC level of sanitary or phytosanitary protection. The decision to apply a general moratorium, however, was deemed a procedural decision to delay final substantive approval decisions. The EC was thus found to have acted inconsistently with its obligations in that it did not ensure that procedures are undertaken and completed without 'undue delay'.

The issue of undue delay is relevant, as the SPS Agreement also covers the operation of sanitary and phytosanitary measures, and these operational measures include undue delays in a sanitary or phytosanitary-related approval process.

Similarly, the EC failure to consider for final approval applications concerning certain specified biotech products resulted in undue delay in the undertaking and completion of the approval procedures with respect to 24 of 27 biotech products.

The national marketing and import bans in some European countries on specific products already approved at Community level (so-called safeguard measures) were also subject to dispute. The panel found that the safeguard measures were not based on a 'risk assessment' as required by the SPS Agreement, and hence were inconsistent with requirements that SPS measures are based on scientific principles and not maintained without sufficient scientific evidence. The panel also found that there was sufficient scientific evidence for a 'risk assessment', thus the safeguard measures were inconsistent with the SPS clause that allows provisional measures only where "relevant scientific evidence is insufficient" (Article 5.7).

Reference: WTO 2017a, 120.

Relevance to gene drive organisms

It is likely that the SPS Agreement will apply to GDOs that enter international trade and that pose risks to animal or plant life or human health arising from the entry, establishment or spread of pests, diseases, disease-carrying organisms or disease-causing organisms. As yet, there are no such commercially traded GDOs, but this may be the case in the future.

If this is the case, measures taken by WTO members to address the risks of GDOs that are imported or exported would count as sanitary and phytosanitary measures and would have to comply with the requirements of the SPS Agreement. Such measures, which can also be biosafety measures, may include pre-marketing approval procedures, monitoring obligations, restrictions and conditions, and bans or moratoria.

Limitations

The rationale of the SPS Agreement, while allowing for sanitary and phytosanitary measures, is one that rests on ensuring that free trade can continue and that there is no disguised protectionism. WTO members, while balancing their biosafety interest, would need to navigate their biosafety measures related to GDOs in international trade carefully, if they are also sanitary and phytosanitary measures under the SPS Agreement.

Issues of undue delay and risk assessment, including whether or not temporary bans can be applied, can be expected to remain challenging. As seen in the EC case, procedural delays may fall foul of the SPS Agreement, while meeting its risk assessment requirements may be difficult. Moreover, recourse to Article 5.7, that is, the ability to apply provisional measures where scientific information is insufficient, is not that straightforward, as discussed below.

Articles 2 and 5.1 of the SPS Agreement stipulate that, while members have the right to take sanitary and phytosanitary measures necessary for the protection of human, animal or plant life or health, such measures have to be applied only to the extent necessary, are based on scientific principles, and are supported by scientific evidence. The measures must therefore be based on a scientific risk assessment.

In practice, the SPS Agreement provides a privileged role to scientific evidence in determining the proper scope of risk regulation (Peel 2004). This has resulted in a move away from broader and more holistic views of risk assessment (see for example, arguments by Wickson and Wynne 2012), to one that merely evaluates risk based on 'sound science'. As a result, while the SPS Agreement preserves a member's right to determine an acceptable level of risk, levels that may be motivated by domestic social considerations or other legitimate policy concerns, these will tend to be marginalised by this approach, which overtly links the justification for SPS measures to the scientific evidence of risk (Peel 2004).

In relation to GDOs, the question is whether such privileging of scientific evidence compromises our ability to thoroughly assess their implications. Where, for instance, the risk identified on the basis of scientific evidence suggests the risk is negligible or very low, any implementation of stringent risk management measures will appear 'disproportionate' and likely WTO-incompatible, even though such measures may be justified if a more broadly oriented assessment had been conducted (Peel 2004), such as one that includes socio-economic considerations or acknowledges scientific uncertainty (Wickson and Wynne 2012).

Any biosafety measure will be questioned as to whether it is the least trade-restrictive measure. Article 5.6 of the SPS Agreement states that measures should be "not more trade restrictive than required to achieve their appropriate level of sanitary or phytosanitary protection". A measure is deemed not more trade restrictive than required, unless there is another measure reasonably available that achieves the appropriate level of sanitary or phytosanitary protection, and is significantly less restrictive to trade.

While this might make sense from a trade perspective (i.e. ensuring that SPS measures still allow trade to continue), from the point of view of biosafety this is not necessarily fully protective of health and the environment. This could be especially so if there are scientific uncertainties, long time lags in the manifestation of risks (or in the collection of data or evidence), which are all valid scientific issues, as might well be the case with GDOs.

The SPS Agreement, in its Article 5.7, allows for temporary bans if they are provisional. Where scientific evidence is insufficient, provisional measures may be taken on the basis of available pertinent information, provided additional information is subsequently sought for a "more objective assessment of risk" and the measures are reviewed "within a reasonable time". These requirements – that there is insufficient scientific evidence, that there is some information on which to justify the measure, that there is continued seeking of additional information, and that the measures are periodically reviewed – have been judged to be cumulative in nature and equally important.[3] Whenever one of these requirements is not met, the measure concerned is inconsistent with Article 5.7.

Thus, in order to justify maintaining a provisional measure, all the requirements have to be met and continuously demonstrated, placing significant obligations and regulatory burdens on the authorities

3 As determined by the Panel in *Japan – Measures Affecting Agricultural Products* and upheld by the Appellate Body (WTO, 2017b, 37).

concerned. Moreover, the measures are only provisional and temporary, excluding more permanent moves that may be necessary in order to be fully protective of health and the environment.

It is likely that the SPS Agreement would offer limited protection from the risks of GDOs, as its imperative is to circumscribe sanitary and phytosanitary protection in the interest of free trade.

2.2.2 International Plant Protection Convention

Scope, objectives and key provisions

The International Plant Protection Convention (IPPC) is an international, legally binding treaty that sets international phytosanitary standards for plants. It has 183 contracting parties (as of September 2018) and the secretariat is hosted by the UN Food and Agriculture Organization (FAO).

The IPPC aims to protect wild and cultivated plants by preventing the introduction and spread of pests of plants and plant products, and by promoting appropriate measures for their control. The treaty is essentially a framework and a forum for international cooperation, harmonisation and technical exchange between its contracting parties. Its implementation involves collaboration by National Plant Protection Organizations (NPPOs), which are established by governments for the purposes of the IPPC, and Regional Plant Protection Organizations (RPPOs), which are regional coordinating bodies.

NPPOs are usually existing agencies with the mandate to address plant phytosanitary issues. For example, the US has its Animal and Plant Health Inspection Service – Plant Protection and Quarantine (APHIS – PPQ), and in Malaysia there is the Crop Protection and Plant Quarantine Division of the Department of Agriculture. An RPPO is an inter-governmental organisation functioning as a coordinating body for NPPOs at regional level; for example, all members of the Pacific Community are members of the Pacific Plant Protection Organisation. Such RPPOs provide advice on phytosanitary measures, for example, by issuing an 'Alert List' as early warning of certain pests that could be potential risks[4], or to highlight possible candidates for a Pest Risk Analysis.

While the IPPC itself is legally binding, the standards developed and adopted under it are not. However, the standards are explicitly recognised by the SPS Agreement as international standards for plant health. Phytosanitary measures that conform to IPPC standards are deemed necessary to protect plant life or health and are presumed WTO consistent, potentially shielding WTO members that conform to such standards from challenge at the WTO. This provides an incentive for WTO members to ensure that their phytosanitary measures conform to IPPC standards.

International standards for phytosanitary measures (ISPMs) are developed through the work programme of the Commission on Phytosanitary Measures. Non-contracting parties to the IPPC are encouraged to observe these standards.

Box 7: Existing application of the IPPC to GMOs

In April 2004, the Interim Commission on Phytosanitary Measures endorsed a supplement on pest risk analysis for LMOs, resulting in an integrated standard: ISPM No. 11 'Pest risk analysis for quarantine pests including analysis of environmental risks and living modified organisms'. It includes guidance on evaluating potential phytosanitary risks to plants and plant products posed by LMOs.

ISPM No. 11 harmonises and standardises the way countries analyse risks that LMOs may pose to plant health. A country may use the standard to determine which LMOs pose a threat and if necessary can prohibit or restrict their import and domestic use. The standard is not just restricted to genetically modified (GM) plants, but also covers other LMOs that may be harmful to plants, such as GM insects, fungi and bacteria. Direct and indirect effects on plants or plant products are both considered.

The standard includes the assessment of the risks of LMOs to plants, in so far as they are pests

4 See an example from the European and Mediterranean Plant Protection Organization: https://www.eppo.int/ACTIVITIES/plant_quarantine/alert_list

of plants (e.g. if a GM plant subsequently becomes a weed or if a GM insect becomes a pest). Phytosanitary risks may result from certain traits introduced into the organism, such as those that increase the potential for establishment and spread, or from inserted gene sequences that do not alter pest characteristics but that might have unintended consequences.

Once a LMO is determined to be a potential pest, it goes through a pest risk assessment process, involving three steps: (i) pest categorisation; (ii) assessment of the probability of introduction and spread, including an analysis of both intentional and unintentional pathways of introduction and intended use. The probability of gene flow and gene transfer should be considered, as should the probability of expression and establishment of that trait, while the survival capacity without human intervention of the LMO should also be assessed; and (iii) assessment of potential economic consequences (including environmental impacts).

The conclusions from the pest risk assessment are then used to decide whether pest risk management measures should be taken. If no satisfactory measure is available to reduce risk to an acceptable level, the final option may be to prohibit importation of the relevant commodities. This is viewed as a measure of last resort. Nonetheless, the implementation of phytosanitary measures are not considered permanent, and should be monitored, reviewed and modified if necessary.

Relevance to gene drive organisms

The standards set by the IPPC have been identified to be possibly relevant to the components, organisms and products resulting from synthetic biology (Secretariat of the Convention on Biological Diversity 2015, 96-97). This would include GDOs. In particular, ISPM No. 11 as discussed in Box 7, is directly relevant.

Annex 3 of ISPM No. 11 identifies the potential phytosanitary risks from LMOs. Those relevant to GDOs include: changes in adaptive characteristics, which may increase the potential for introduction or spread, such as alterations in dispersal ability of pests; adverse effects of gene flow or gene transfer, such as the potential to overcome existing reproductive and recombination barriers which could result in pest risks; and adverse effects on non-target organisms, such as changes in host range, including cases where the LMO is used as a biological control agent or organism otherwise claimed to be beneficial.

These examples could reasonably be risks some GDOs are expected to pose, particularly given their potential for spread, both intended and otherwise. Currently, several agricultural insect pests are the targets of gene drive research, and a prominent example is work on the spotted wing fruit fly, which is a pest of soft fruit (Buchman et al. 2018). While the modifications are aimed at population suppression, any unintended effects that might, for example, change the characteristics of the pests, would have to be evaluated according to ISPM No. 11.

The analysis of unintentional pathways of introduction included in the pest risk assessment process is also particularly significant, given the high potential for unintentional dissemination of GDOs.

Limitations

The IPPC standard on LMOs would only apply to GDOs that enter international trade and are deemed to be plant pest risks. The determination of whether a GDO is a potential plant pest would be the crucial first step in order to conduct the pest risk analysis.

However, the application of the standard to GDOs that are not imported and exported or that do not disrupt international trade is currently limited, with the exception of the possibility of identifying unintentional pathways of introduction.

For WTO members, as the IPPC is essentially the implementation of the SPS Agreement applied to plant pest risks, the risk management measures that are recommended under ISPM No. 11 have to be non-discriminatory and least trade restrictive. This means that any measures taken have to be the minimum necessary to protect plant health, while ensuring that trade can continue as unimpeded as possible. This may not provide for adequate protection from the risks of GDOs.

2.2.3 World Organisation for Animal Health standards

Scope, objectives and key provisions

In 1924, the international agreement that led to the creation of the Office International des Epizooties (OIE) was signed. In 2003, the OIE became the World Organisation for Animal Health, but kept its historical abbreviation. It is an intergovernmental organisation responsible for improving animal health worldwide, and, as of 2018, has 182 member countries.

The OIE is recognised by the SPS Agreement as the international organisation responsible for standard-setting regarding animal health. Within this mandate, it publishes health standards for international trade in animals and animal products. Phytosanitary measures that conform to OIE standards are deemed necessary to protect animal life or health and are presumed WTO consistent, potentially shielding WTO members that conform to such standards from challenge at the WTO. This provides an incentive for WTO members to ensure that their phytosanitary measures conform to OIE standards.

It publishes two codes and two manuals (Terrestrial and Aquatic), as the principal references for WTO members. The Terrestrial Animal Health Code and Aquatic Animal Health Code respectively are intended to ensure the sanitary safety of international trade in terrestrial animals and aquatic animals and their products. The codes traditionally addressed animal health and zoonoses, but in recent years have covered issues such as animal welfare.

Box 8: Existing application of the OIE standards to GMOs

In May 2005, OIE members adopted a Resolution on 'Applications of Genetic Engineering for Livestock and Biotechnology', which requested the constitution of an Ad Hoc Group on Biotechnology to support the development of harmonised technical standards for the regulation of biotechnology-derived animal health products, and GM production animals.

Members also asked the OIE to prioritise the development and adoption of standards, recommendations and guidelines for:

- research on the use of live attenuated vaccines in animal health
- use of DNA vaccines
- animal health risks linked to cloning
- assessing the health of embryos and production animals derived from cloning, and associated safety of cloned production animals and their products
- exclusion of unapproved animals and products from the livestock population and segregation from the feed and food supply
- identification, testing, and certification for international trade in animals and their products for which biotechnology procedures have been employed.

Relevance to gene drive organisms

Should animal GDOs or GDOs used to control animal diseases be imported or exported, the standards set up by the OIE would be relevant to them. For example, gene drive research is being carried out on Australian sheep blowflies, which cause 'blowfly strike', resulting in lesions in infested areas of the sheep's skin, thus affecting animal welfare and productivity (see Chapter 2).

Limitations

To our knowledge, there has been no work done yet at the OIE on GDOs. The OIE standards would only apply to animal GDOs or GDOs used to control animal diseases in international trade. As such, the standards would have limited relevance to GDOs currently.

2.2.4 Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction

Scope, objectives and key provisions

The Convention on the Prohibition of the Development, Production and Stockpiling of Bacterio-

logical (Biological) and Toxin Weapons and on their Destruction, also known as the Biological Weapons Convention (BWC), entered into force in 1975. There are currently 182 State Parties who are legally bound by this treaty.

The BWC was the first multilateral disarmament treaty banning an entire category of weapons of mass destruction (UNOG, n.d.). Article I prohibits the development, production, acquisition, transfer, retention, stockpiling and use of biological and toxin weapons. This applies to all naturally or artificially created or altered microbial and other biological agents and toxins, as well as their components, regardless of origin and method of production and whether they affect humans, animals or plants, *of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes.* Also banned are the weapons, equipment or means of delivery designed to use such agents or toxins for hostile purposes or in armed conflict.

Parties are required to take any necessary measures at the national level to prohibit and prevent the development, production, stockpiling, acquisition or retention of the agents, toxins, weapons, equipment and means of delivery (Article IV). Parties, particularly those with substantial biological defence programmes, have to provide annual reports on specific activities, including: data on research centres and laboratories; information on national biological defence research and development programmes; declaration of past activities in offensive and/or defensive biological research and development programmes; and information on outbreaks of infectious diseases and similar occurrences caused by toxins (UNODA, n.d.).

Box 9: Existing application of the BWC to GMOs

Advances in the life sciences have been acknowledged to make these technologies inherently 'dual use', meaning that they could be used for both peaceful and malevolent uses, and there may only be a fine line between the two. Clearly, this applies to genetic engineering and GMOs, making these relevant subject matters for the BWC.

As early as 1986, Parties recognised the "apprehensions arising from relevant scientific and technological developments, *inter alia*, in the fields of microbiology, genetic engineering and biotechnology, and the possibilities of their use for purposes inconsistent with the objectives and provisions of the Convention" (Final Declaration of the Second Review Conference 1986, 3). They reaffirmed that the undertaking in Article I to never in any circumstances develop, produce, stockpile or otherwise acquire or retain microbial and other biological agents and toxins that have no justification for prophylactic, protective or other peaceful purposes, applies to all such developments. Subsequent meetings have reiterated that "Article I applies to all scientific and technological developments in the life sciences and in other fields of science relevant to the Convention" (Final Document of the Sixth Review Conference 2006, 9).

In 2012, advances in genetic technologies such as gene synthesis, synthetic biology and whole genome-directed evolution were discussed. Parties identified the need for enhanced national and international oversight of dual use research of concern (Report of the Meeting of the States Parties 2012, 6-7). In 2013, Parties discussed the need for appropriate oversight measures (Report of the Meeting of the States Parties 2013, 7-8). However, "no concrete steps towards the development of an oversight framework, guiding principles or models to inform risk assessment and oversight of scientific research" have been taken to date (Secretariat of the Convention on Biological Diversity 2015, 93). Moreover, countries such as the United States, a BWC depository and central BWC actor, have largely relegated oversight of dual use research of concern to voluntary committees composed of professors and researchers.

Parties in 2014 and 2015 discussed various enabling technologies, including genome editing and synthetic biology tools (Report of the Meeting of the States Parties 2014, 7-8; Report of the Meeting of the States Parties 2015, 7-8). They recognised that identifying research of dual use concern necessitates greater national oversight along with a collaborative and informed assessment of the potential benefits and risks. The review of developments in the field of science and technology continues to be on the agenda, where genome editing was identified as a specific topic for discussion in 2018 (Report of the Meeting of the States Parties 2017, 6).

Relevance to gene drive organisms

The potential for malicious use of gene drives has been raised briefly at recent BWC meetings and indeed the BWC is considered the valid international forum for discussion of the security threats raised by gene drives. A presentation on gene drives was made at the Meeting of Experts in 2014, highlighting the potential security challenges (Oye 2014). Among the hostile scenarios envisaged were the use of gene drives to enable a species' ability to host diseases, suppression of crops and livestock in agriculture, or suppression of pollinators and other keystone species, all of which could have devastating impacts.

In the United States, where much of the research into gene drives has been occurring, the national security threat of gene drives has been discussed by the JASONs, a group of elite scientists which advises the US government on national security issues (Callaway 2017). The US Defense Advanced Research Projects Agency (DARPA) has been reported to be the largest funder of gene drive research (Neslen 2017). Another agency, the Intelligence Advanced Research Projects Activity (IARPA), which is part of the Office of the US Director of National Intelligence, is funding work on the national security implications of gene drives, including for detection and monitoring (IARPA 2017).

DARPA states that its 'Safe Genes' project is designed to develop "tools and methodologies to control, counter, and even reverse the effects of genome editing – including gene drives – in biological systems across scales" (DARPA, n.d.). The involvement of the US military in gene drive research has created discomfort, particularly because one strategy used by biodefence programmes is to deliberately create the actual threat itself, with the justification that the activity is necessary in order to learn how to defend against it. The vicious circle of such applied 'threat assessment' results in biodefence activities that are very similar to, and potentially difficult to distinguish from, offensive weapons development (Tucker 2004).

One scientist who has partnered with the DARPA-funded Genetic Biocontrol of Invasive Rodents (GBIRd) consortium has written, "Because the U.S. is funding these initiatives through the Department of Defense, rather than a civilian organisation, it's not hard to see how some in the international community may perceive these as potential bioweapons programs, rather than investments in purely defensive technologies" (Kuiken 2017).

GBIRd aims to use gene drives to eradicate invasive rodents on island ecosystems, in order to protect threatened bird species (GBIRd, n.d.). DARPA however has no biodiversity conservation mission, raising questions about the agency's motive in funding research with objectives seemingly outside its mandate. If understood as a threat assessment programme, however, DARPA's motives in promoting GBIRd become clearer – it is a politically more palatable proxy to achieve US national security research.

Freedom of information requests have revealed that GBIRd plans to target the gene drives of specific genetically-defined populations by linking drive activity to the presence of private or locally-fixed alleles – the small genetic differences that define related populations of animals, including humans (Edward Hammond, personal communication, 21 February 2018). The implications of this research (Sudweeks et al. 2019), particularly in a bioweapons context, raise serious concerns. While GBIRd itself may be naively exploring conservation purposes for its gene drives, the dual use implications of population-targeted gene drives need to be seriously addressed, particularly when DARPA occupies a privileged position as funder, with full access to data and details.

It is clear therefore that gene drive's potential for dual use is established and the BWC is undoubtedly an important international forum to address this.

Limitations

While the BWC, since its entry into force in 1975, sets an important international norm against a particularly egregious form of warfare, it has unfortunately not been able to develop implementation mechanisms or any form of international regulation. It thus provides a forum for discussion, but suffers

from a lack of political will by the major powers to actually take action to address the serious issues.

Lengthy efforts to negotiate a binding implementation regime, called the 'Verification Protocol', failed in 2001 (Leitenberg 2002). Most observers regard any return to discussions aimed at the adoption of binding international measures to oversee biological research as politically impossible, for the forseeable future. There are, simply put, three reasons for this: (i) no appetite among countries with large biodefence programmes to open up their facilities to verification procedures; (ii) strong resistance from industry and other vested interests; and (iii) too many doubts about the reliability of an international inspectorate and the quality of information that would emanate from it (Winzoski 2007).

Thus, while the meetings of the BWC provide a forum for exchange of information on new biotechnologies with security implications, and their confidence building measures provide limited information exchange, the BWC is institutionally handicapped and impaired from adopting any binding measures pertinent to the biosafety of GDOs.

Nonetheless, serious efforts should be made to ensure that any security threat posed by the misuse of GDOs is able to be more effectively addressed by the BWC, given that it is the treaty with the competence and mandate on these issues.

2.2.5 Convention on the Prohibition of Military or Any Other Hostile Use of Environmental Modification Techniques

Scope, objectives and key provisions

The Convention on the Prohibition of Military or Any Other Hostile Use of Environmental Modification Techniques, also known as the Environmental Modification Convention or ENMOD, prohibits military or any other hostile use of environmental modification techniques having widespread, long-lasting or severe effects as the means of destruction, damage or injury to any other State Party. It is a legally binding treaty that entered into force in 1978 and has 78 State Parties (UNOG, n.d.).

'Environmental modification techniques' are defined as "any technique for changing – through the deliberate manipulation of natural processes – the dynamics, composition or structure of the earth, including its biota, lithosphere, hydrosphere and atmosphere, or of outer space" (Article II).

ENMOD was essentially a response to US tactics used in the Vietnam War, particularly the use of Agent Orange to defoliate forests and thereby deny cover to Vietnamese guerrillas, and attempts at cloud-seeding to cause rain, in order to stymie the movement of people and material during the war. Its design was meant to address modifications to the environment such as defoliants, altering weather, deliberate desertification and deliberate triggering of earthquakes.

To understand ENMOD and how it came about in its final form, including the notorious 'troika' (see below), one must recall the political atmosphere of the mid-1970s. The only countries developing or, in the case of the US in Southeast Asia, using weapons designed to modify the environment, were the 'superpowers' (the US and the former Soviet Union) and their close allies. These countries exerted careful control over the ENMOD process, and as a result, the negotiations, while formally based in the UN, did not have the character of a modern multilateral process. Drafts of the Treaty were exchanged between Washington and Moscow, with the two megapowers agreeing on key details first. Both the US and the Soviet Union wanted to keep a free hand to use certain environmental warfare techniques, particularly in counterinsurgency (e.g. clearing vegetation in large margins around military bases). Underscoring the faux multilaterialism of the process, the last draft was prepared and accepted by Soviet and American negotiators, and then identical texts were submitted by the 'opposing' sides for adoption in Geneva (Pimiento Chamorro and Hammond 2001).

Relevance to gene drive organisms

Gene drives have the potential to artificially modify environments and may be misused for military or hostile purposes (see the discussion on dual use issues in Section 2.2.4).

As environmental modification techniques include "any technique for changing – through the deliberate manipulation of natural processes – the dynamics, composition or structure of the earth, including its biota", gene drives that result in population or species changes could arguably qualify as an environmental modification technique under ENMOD. As global gene drives may spread modifications to all populations of a targeted species and potentially result in widespread population changes or population or even species extinction, they may be deemed an environmental modification technique.

Limitations

While ENMOD could possibly be a forum to address military or hostile use of some GDOs, there remain some substantial limitations to the application of this treaty for such purposes. Firstly, it only applies to State Parties and that number is limited. Nonetheless, countries where most gene drive research is occurring, such as the United States and several European countries, are State Parties.

However, ENMOD State Parties have not met recently, and interest in convening mandated conferences of State Parties has waned considerably. The First Review Conference was held in Geneva in September 1984, with the attendance of 35 States Parties. The Second Review Conference took place in September 1992 with very little fanfare and no moves to strengthen the treaty, despite credible and current allegations that Iraq had waged environmental warfare in Kuwait when it set hundreds of oil wells alight (Ross 1992). Attempts by the Secretary-General of the United Nations in 2013 to convene the Third Review Conference did not receive the required number of affirmative responses in order to proceed (Secretary-General of the United Nations 2014).

Perhaps more significant is the fact that in order to be subject matter under ENMOD, the GDOs in question would have to meet the criteria of being used for military or for hostile purposes, and their effects would have to meet the high threshold of having widespread, long-lasting or severe effects (the so-called 'troika'). While it is certainly possible to imagine a GDO that could have such effects, for example one containing a global gene drive that could cause an economically valuable population or species to become extinct, it is much harder to imagine a nation state using one as a weapon in what would also have to be generally considered a war under international law. Furthermore, efforts to clarify or eliminate the restrictive troika clauses have been made since the original negotiations, as well as at the review conferences; but consensus on removing the qualifiers has not been reached (UNOG, n.d.), leaving the difficult-to-meet troika threshold firmly in place.

Notably, any GDO used as a weapon would be a biological weapon under the BWC, which also prohibits development and stockpiling (except for "peaceful and prophylactic purposes"). Therefore, even before a State Party reached the point of violating ENMOD, which only prohibits hostile use and not development, it would have already violated the BWC. Notwithstanding the limitations under the BWC itself, the BWC would be the more applicable instrument in the case of military or hostile use of GDOs.

2.2.6 United Nations Declaration on the Rights of Indigenous Peoples

Scope, objectives and key provisions

The United Nations Declaration on the Rights of Indigenous Peoples was adopted by the UN General Assembly in September 2007. A majority of 144 states voted in favour, while Australia, Canada, New Zealand and the United States voted against and 11 states abstained. However, the four countries voting against have since reversed their position and now support the Declaration (UN DESA, n.d.). Two abstaining countries have also since endorsed the

Declaration, bringing the current total of supporting countries to 150.

The Declaration, while not legally binding, is the most comprehensive international instrument on indigenous peoples' rights. It establishes a universal framework of minimum standards for the survival, dignity and well-being of indigenous peoples. At the same time, it elaborates on existing human rights standards and fundamental freedoms, as applied to the specific situation of indigenous peoples (UN DESA, n.d.).

Individual and collective rights are addressed, in addition to various provisions dealing with cultural rights and identity, rights to education, health, employment and languages. The Declaration outlaws discrimination against indigenous peoples, promotes their full and effective participation in all matters that concern them, as well as their right to remain distinct and to pursue their own economic, social and cultural development (UNPFII, n.d.).

Relevance to gene drive organisms

Indigenous peoples' rights to the lands, territories and resources that they have traditionally owned, occupied or otherwise used or acquired are strongly protected in the Declaration. Two key principles are reflected in various provisions – that of free, prior and informed consent, and that of redress.

Article 32 of the Declaration focuses on the rights of indigenous peoples in relation to the development or use of their lands and territories and other resources. States are obliged to consult with the indigenous peoples concerned "in order to obtain their free and informed consent prior to the approval of any project affecting their lands or territories and other resources, particularly in connection with the development, utilization or exploitation of mineral, water or other resources" (Article 32.2).

The issue of free, prior and informed consent is particularly relevant to the release of any GDO into the lands and territories of indigenous peoples, or that may affect their resources. For example, gene drive research on the Southern house mosquito is being conducted to address avian malaria in Hawaii, for which the mosquito is a vector, and which is affecting native birds (see Chapter 2). It would be feasible to assume that any proposed future release of the gene drive mosquito could occur in the lands and territories of indigenous peoples.

Indeed, this issue was recognised by the AHTEG on Synthetic Biology under the CBD, which pointed out that "a precautionary approach…, 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" (AHTEG on Synthetic Biology 2017, paragraph 25).

On this basis, SBSTTA, in July 2018, recommended that "…the free, prior and informed consent of indigenous peoples and local communities might be warranted when considering the possible release of organisms containing engineered gene drives that may impact their traditional knowledge, innovation, practices, livelihood and use of land and water" (Recommendation 22/3, paragraph 12).

This recommendation was taken up by COP 14 in November 2018. The decision that was adopted includes the condition that, where appropriate, "prior and informed consent", the "free, prior and informed consent" or "approval and involvement" of potentially affected indigenous peoples and local communities should be met when considering the release of GDOs into the environment, including for field trial and research purposes (see Section 2.1.1, 'Decision on gene drive organisms at CBD COP 14 (November 2018)').

Should indigenous peoples' lands, territories and resources be confiscated, taken, occupied, used or damaged without their free, prior and informed consent, Article 28 of the Declaration establishes the right of redress for indigenous peoples. States are further required to provide effective mechanisms for just and fair redress for any activities affecting

the land, territories and other resources of indigenous peoples, as well as to take appropriate measures to mitigate adverse environmental, economic, social, cultural or spiritual impacts (Article 32.3). In addition, States are obliged to provide effective mechanisms for the prevention of, and redress for, any action that has the aim or effect of dispossessing indigenous peoples of their lands, territories or resources (Article 8).

This principle of redress is particularly relevant to GDOs and the potential damage they may cause in the lands and territories of indigenous peoples or to their resources, whether the impacts are environmental, economic, social, cultural or spiritual. For example, a gene drive may cause a biological resource that is used by indigenous peoples to become extinct or to not perform as expected, or the modification could lower the value of the resource to indigenous peoples. The general rights of indigenous peoples over their land or territories and resources include that of their productive capacity (Article 29), and to genetic resources and seeds (Article 31). The issue of liability and redress is also a general important issue in the discussion on GDOs (see Section 2.1.3).

Limitations

UN Declarations are generally not legally binding in nature, which is a major limitation. However, the Declaration on the Rights of Indigenous Peoples sets forth international legal norms and reflects the commitment of states to move in certain directions, abiding by certain principles (UNFPII, n.d.). These principles are considered universal for indigenous people and are important in further clarifying their rights. They can also be the standard by which governments can be called to account on these matters.

The Declaration itself does not create new rights, but provides an interpretation of the human rights enshrined in other international human rights instruments of universal resonance, as they apply to indigenous peoples. It is in that sense that the Declaration has a binding effect for the promotion, respect and fulfilment of the rights of indigenous peoples worldwide (UNFPII, n.d.). Therefore, it is important that at national level, governments take action to codify these rights in national law, so as to ensure that these rights are fully respected, protected and fulfilled, including in relation to the impact of GDOs on indigenous peoples and their resources. However, so long as this is not done, then indigenous peoples remain vulnerable to violation of their rights.

2.3 Other guidelines of relevance to Gene Drive Organisms

2.3.1 Guidance Framework for Testing of Genetically Modified Mosquitoes

Scope, objectives and key provisions

In 2009, the World Health Organization Special Programme for Research and Training in Tropical Diseases (WHO-TDR) and the Foundation for the National Institutes of Health (FNIH) co-sponsored a technical consultation meeting to assess GM mosquito technologies. Participants recommended that the World Health Organization (WHO) and FNIH establish a working group to develop a guidance framework for assessing the safety and efficacy of GM mosquitoes, including addressing any legal, ethical, social and cultural issues.

The guidance framework was published in 2014. It proposes efficacy and safety testing standards for GM mosquitoes, in particular a phased testing pathway, with systematic assessment at each step. Four phases are envisaged: Phase 1, laboratory testing including caged trials; Phase 2, field testing under confined conditions which limit release into the environment and which could include geographical, spatial or climatic isolation; Phase 3, staged open release trials; and Phase 4, deployment of GM mosquitoes as a public health intervention (WHO-TDR 2014, 7-10).

According to this guidance framework, any GM mosquito development effort should provide proof of efficacy, acceptability and deliverability. Effective reduction in the transmission of the targeted pathogen(s) should be demonstrated, and the intervention must not be detrimental to the environment

and human health. Risk assessment and risk management are core biosafety considerations, with independent ongoing safety review and monitoring during testing recommended.

The guidance framework also examines the fundamental considerations for addressing public engagement and transparency needs in research on GM mosquitoes, as well as questions relating to ethical implications, including the obligation to respect host communities. The framework reviews existing regulatory requirements and guidance, including that for biosafety, human subjects and GMO regulation. It also discusses additional regulatory considerations such as public consultation, litigation, capacity and institution building, and transboundary movement.

Relevance to Gene Drive organisms

The guidance framework includes discussion of GM mosquitoes with gene drives, as one of the mechanisms being researched for GM mosquitoes, in order to self-sustain the modification and spread it indefinitely through the target population.

However, the phased testing approach set forth in the guidance framework is, in our view, inappropriate for GM mosquitoes with genes drives, particularly if the gene drive is global in nature and any release into the environment (even in a 'confined' setting, or in geographical isolation as proposed by Phase 2), could mean spread and persistence. Indeed, the AHTEG on Synthetic Biology under the CBD concluded 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" (AHTEG on Synthetic Biology 2017, paragraph 51 (b)). James et al. (2018, 28) further noted that in relation to mosquitoes, "genetic analyses indicate that neither lake nor oceanic islands will provide absolute confinement or inability to spread beyond the island".

Limitations

The guidance framework provides guidelines for testing of GM mosquitoes, including those with gene drives. It is not a legally binding document, nor was it developed inter-governmentally. Many of the contributors could be perceived as having conflicts of interest because they have either self-identified as having professional or even commercial interests in GM mosquitoes (see WHO-TDR 2014, 131).

The guidance framework does not represent the views of the WHO or FNIH, nor does it provide recommendations on what to do. It merely claims to bring together what was known based on research evidence at the time about how best to evaluate GM mosquitoes. However, given that the guidance framework was published in 2014 and the draft was written in 2012, well before any proof of concept for gene drives was demonstrated, it will not be a sufficiently updated reference on gene drive mosquitoes.

Nonetheless, the guidance framework recognises that there is no standardised procedure for addressing potential transboundary movement of gene drive mosquitoes. It acknowledges the need for a "multilateral regulatory process" when it comes to regulation of gene drive mosquitoes, due to the possibility of transboundary spread (WHO-TDR 2014, 99). Specifically, "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" (WHO-TDR 2014, xxv).

Table 1: Summary of relevant international legal and regulatory instruments and processes

Instrument	Application	Legally-binding?	Number of Parties/ members	
Convention on Biological Diversity	Conservation and sustainable use of biodiversity, fair and equitable benefit sharing	Yes	196	
Cartagena Protocol on Biosafety	LMOs that may have adverse effect on biodiversity, taking into account risks to human health	Yes	171	
Supplementary Protocol on Liability and Redress	Liability and redress rules for damage from LMOs	Yes	44	
WTO Agreement on Sanitary and Phytosanitary Measures	Sanitary and phytosanitary measures that affect international trade	Yes	164	
International Plant Protection Convention	Plant pest risks from international trade	Yes* * IPPC itself is legally binding, but its standards are not	183	
World Organisation for Animal Health standards	Animal health and zoonoses from international trade	No	182	
Biological Weapons Convention	Biological weapons	Yes	182	
Environmental Modification Convention	Environmental modification techniques	Yes	78	
UN Declaration on the Rights of Indigenous Peoples	Rights of indigenous peoples, including free, prior and informed consent	No	150*	
Guidance Framework for Testing of GM Mosquitoes	Testing of GM mosquitoes	No	N.A	

2.4 Regulation of contained use

2.4.1 Why contained use regulations are necessary for Gene Drive Organisms

Research and development of GDOs is currently occurring in the laboratory, with no reported releases into the environment yet. According to the US National Academies of Sciences, Engineering, and Medicine (NASEM 2016), gene drive organisms "are not ready for release into the wild" (Abbasi 2016, 482). Yet, there are no stringent international rules on contained use research. As such, this places an increasing onus on ensuring that stringent contained use laboratory research on GDOs is practiced and regulated.

The concept of 'contained use' aims to ensure that contact with the environment is prevented by physical means and associated personnel practices. For example, the Cartagena Protocol on Biosafety defines contained use as "any operation undertaken

	Key advantages in relation to gene drive organisms	Key gaps in relation to gene drive organisms
	Near-universal membership · Already begun to address GDOs · Precedence with wider policy issues on GDOs/new technologies	Lack of implementation and enforcement US not a Party
	Subject matter includes GDOs Already begun to address GDOs Specific regulation of GDOs, in so far as they are LMOs	Developed for conventional LMOs · Focused on decision-making by a country in the context of intentional transboundary movements · Inadequate provision for socioeconomic assessment · No elaboration of contained use rules · Lack of enforcement · US not a Party
	Subject matter includes GDOs Liability and redress rules important for GDOs Damage resulting from unintentional and illegal transboundary movements is included	Damage must result from LMOs/GDOs from another country · Administrative approach places burden on authorities · No financial guarantees · Limited number of Parties currently · US not a Party
	Economic aspects included in risk assessment Ability to take temporary precautionary measures with low likelihood of WTO challenge	Context of trade liberalisation · Focused on narrow scientific risk assessment with high tests to meet · Limited relevance to GDOs currently
	Applies to plant pest risks from all LMOs, which may be plants, insects, fungi, bacteria, etc. Addresses unintentional pathways of introduction	Limited relevance to GDOs currently
	Specific focus on animal health and animal disease agents	Limited relevance to GDOs currently
	Mandate clearly addresses hostile use with clear prohibition on development, use and stockpiling for such purposes	No oversight framework on biotechnology research Lack of political will to develop implementation mechanisms
	Prohibits hostile and military use	Moribund; limited membership and political will High 'troika' threshold to meet
	Universal framework of minimum standards, sets international norms Free, prior and informed consent an established right	* Not legally binding, but endorsed by 150 members of the UN General Assembly
	Specific focus on GM mosquitoes	Not developed inter-governmentally Flaws in approach to gene drive mosquitoes

within a facility, installation or other physical structure, which involves living modified organisms that are controlled by specific measures that effectively limit their contact with, and their impact on, the external environment" (Article 3). When these conditions are not met, the situation is therefore one of 'intentional introduction into the environment', as recently reiterated by the Parties to the Cartagena Protocol (Decision 9/12, paragraph 2). Such conditions are also not likely to be met by 'semi-field testing' in outdoor cages that may be a stage in the development pathway of gene drive mosquitoes (James et al. 2018, 22-25), and hence should not be considered as contained use.

However, the risk of accidental or unintentional release from contained use into the environment always remains, either through laboratory accidents or human mistakes. The novel capabilities of synthetic biology, gene drives in particular (due to their proliferative design), and their potentially increased impacts on biodiversity merit a serious assessment

of risks stemming from contained use. A series of recent incidents at high containment laboratories, including repeated accidental releases by laboratories regarded as being highly professional and secure, draw attention to the inevitability of containment failure. Recent examples include accidental distribution of potentially pandemic influenza viruses by the US Centers for Disease Control and Prevention (CDC 2014a), the discovery of improperly stored and forgotten samples of viable smallpox virus at the US National Institutes of Health (CDC 2014b; Christensen 2014), and numerous incidents of accidental distribution of viable anthrax bacteria by the US Army's Dugway Proving Ground (Chappell 2015).

For GDOs especially, the consequences are great, because even a small unintentional release, particularly of a global gene drive, can result in an extensive spread of the gene drive (Esvelt and Gemmell 2017, 2; Noble et al. 2017; Simon et al. 2018, 3), possibly throughout an entire species. The very properties that make GDOs desirable – spread and persistence – mean that contained use will need to be especially stringent. As such, the safe handling of GDOs in contained use merits special attention. A combination of multiple stringent confinement strategies and safeguards to prevent the unintentional release of gene drive systems from the laboratory has been recommended by leading gene drive researchers (Akbari et al. 2015).

Indeed, that subset of GDOs that are designed to eradicate populations or species (e.g. mosquitoes, rodents) may far more closely resemble dangerous pathogens than other types of GMOs. Such GDOs, currently under development, are intended to be 'infectious' (through mating), lethal (i.e. severe in consequence), and difficult (probably impossible) to treat or to remove from the environment. They have the capacity, indeed are designed, to spread widely through a population or entire species. These are key characteristics that traditionally define dangerous organisms (usually pathogens) that are assigned to higher risk groups, and which in turn typically require high containment facilities and associated stringent personnel practices.

The AHTEG on Synthetic Biology under the CBD has pointed out that the development and implementation of well-designed strategies, which includes physical containment, might be needed for the organisms, components and products of synthetic biology (including GDOs) under contained use, in order to effectively limit their survival or spread and to prevent or minimise their exposure of the environment (AHTEG on Synthetic Biology 2017, paragraph 18).

Despite this great need, amply demonstrated by numerous incidences of accidental releases of pathogens in contained use, however, "there are currently no dedicated guidelines on the required risk assessment and minimal control measures applicable to gene drive organisms in contained use" (van der Vlugt et al. 2018, 25).

2.4.2 Contained use regulations at the international level

LMOs destined for contained use are subject to the provisions of the Cartagena Protocol on Biosafety, since its scope applies to the transboundary movement, transit, handling and use of all LMOs (Article 4). However, the Cartagena Protocol does exclude LMOs destined for contained use from its AIA procedure, if the transboundary movement is undertaken in accordance with the standards of the Party of import (Article 6). Nonetheless, the Protocol preserves the rights of Parties to subject LMOs in contained use to risk assessment prior to decisions on import and to set standards for contained use within its jurisdiction.

This all points to the importance of national regulations on contained use for LMOs, which would also be applicable to GDOs, and indeed, many countries already may have such national standards.

However, there are no international contained use regulations or standards, and furthermore, there are none that are specific to GDOs. This is a major gap, especially because of the potential for unintentional releases of GDOs that might result in

transboundary movement or the crossing of national borders, requiring an international response.

The need for internationally agreed standards for effective containment of GDOs, in order to avoid accidental releases from laboratory facilities, has been duly acknowledged by the AHTEG on Synthetic Biology (AHTEG on Synthetic Biology 2017, paragraph 51(c)).

2.4.3 Regional standards and other contained use guidelines

Currently there do exist regional standards and other contained use guidelines that provide some useful insights for contained use regulation of GDOs, and their salient features are summarised below. The EU's 'Directive on the contained use of genetically modified micro-organisms' is a regional law for EU member states. There are other non-legally binding guidelines for contained use that have become the *de facto* international standards, although they remain voluntary. These include the WHO's 'Laboratory Biosafety Manual', the US Department of Health and Human Services' manual on 'Biosafety in Microbiological and Biomedical Laboratories', and the US National Institutes of Health's (NIH) 'Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules'.

EU Directive on the contained use of genetically modified micro-organisms

The European Union's 'Directive on the contained use of genetically modified micro-organisms' is a regional standard that is legally binding on EU member states, which have to implement it through their national laws. The Directive is restricted to GM microorganisms, and is therefore largely concerned with the identification of the risks to human, animal, and plant health that could be caused by pathogenic properties. While there are currently no pathogenic GDOs, the parallels with pathogens, as discussed above, necessitate stringent regulations for contained use, in that the aim is to prevent their escape into the environment.

Therefore, the general principles of the Directive are a useful framework for identifying potential adverse effects of GDOs and their likelihood of occurrence, as well as assigning risk classes to a contained use activity with a GDO (van der Vlugt et al. 2018). In addition, the Directive is already applicable to any GDO that is a microorganism in contained use.

The Directive obliges EU member states to conduct a risk assessment of the contained use of GM microorganisms in terms of the risks to human health and the environment. The results are then used to assign four classes of activities, ranging from no or negligible risk and low-risk up to moderate-risk and high-risk, which correspond to four levels of containment. Notification to the competent authority is required prior to any contained use activity, with classes 3 and 4 requiring prior consent or approval from the competent authority. Emergency plans are required to be drawn up before any contained use activity commences.

Member states report regularly on laboratory accidents involving GM microorganisms. In the event of an accident that could affect other member states, there is a regional alert and consultation process. The member state concerned has to alert and consult other member states likely to be affected, on the proposed implementation of emergency plans.

WHO Laboratory Biosafety Manual

The WHO Manual is a reference and guidance document intended to help countries, particularly developing countries, implement basic concepts in biological safety. This is encouraged through the development of national codes of practice for the safe handling of pathogenic microorganisms in laboratories, although there is no obligation for countries to do so. The third edition, published in 2004, adds text on the safe use of recombinant DNA technology.

Inherent in the Manual is the idea of classifying microorganisms according to risk groups[5] and

5 Risk Groups 1 to 4, ranging from a microorganism that is unlikely to cause human or animal disease, to a pathogen that usually causes serious human or animal disease and that can be readily transmitted, and for which effective treatment and preventive measures are not usually available.

of designating laboratory facilities according to biosafety levels.[6] Biosafety level designations are based on a composite of various factors, such as design features, construction, containment facilities, equipment, practices and operational procedures. Establishing the appropriate biosafety level for laboratory work requires a risk assessment that takes the risk group, facilities available and other factors into account.

The Manual sets out the factors to consider in conducting a microbiological risk assessment and advocates a precautionary approach when there is not enough information available. It details the minimum requirements necessary for all biosafety levels. Comprehensive guidelines are provided for basic laboratories – Biosafety Levels 1 and 2 – as these are fundamental to all laboratories regardless of their biosafety level. The guidelines for Biosafety Level 3 and 4 laboratories modify and add to the basic guidelines, and are designed for work with more hazardous pathogens.

The Manual also sets out guidelines for laboratory animal facilities, including the designated containment levels. These apply the contained use standards to animals that are inoculated with microorganisms from the various risk groups. Additional precautions that are necessary for certain arthropods, particularly flying insects, are also listed. These could possibly be adapted for use in relation to GDOs that are animals or flying insects.

The Manual includes a chapter on laboratory biosecurity, which addresses situations when there is loss, theft, misuse, diversion or intentional release of pathogens and toxins. This is relevant to the dual use issue that is inherent to technologies such as gene drives.

Biosafety in Microbiological and Biomedical Laboratories

The US Department of Health and Human Services publication, 'Biosafety in Microbiological and Biomedical Laboratories', deals with safe microbiological and biomedical laboratory practices. It is an advisory and guidance document recommending voluntary best practices for the safe handling and containment of infectious microorganisms and hazardous biological materials. Two principles of biosafety – containment and risk assessment – are paramount, aiming to protect laboratory workers, the environment and the public from exposure to infectious microorganisms and to prevent laboratory-associated infections (LAI).

Four ascending levels of containment, offering increasing protection and referred to as biosafety levels 1 through 4, are currently established.[7] The risk assessment process identifies the hazardous characteristics of a known or potentially infectious agent or material, the activities that can result in a person's exposure to an agent, the likelihood that such exposure will cause a LAI, and the probable consequences of infection. The risk assessment guides the selection of appropriate biosafety levels. At each level, the microbiological laboratory practices, suggested safety equipment and facility safeguards are described.

The issue of laboratory biosecurity is also discussed. The objective of biosecurity is to prevent loss, theft or misuse of microorganisms, biological materials and research-related information. A biosecurity risk assessment is recommended to analyse the probability and consequences, while providing the basis for risk management decisions. These elements may be useful to address the dual use potential of gene drives and to safeguard against misuse.

6 Laboratory facilities are designated as: basic – Biosafety Level 1 and Level 2; containment – Biosafety Level 3; and maximum containment – Biosafety Level 4.

7 Biosafety level 1 (BSL-1) is the basic level of protection and is appropriate for agents that are not known to cause disease in normal, healthy humans. Biosafety level 2 (BSL-2) is appropriate for handling moderate-risk agents that cause human disease of varying severity. Biosafety level 3 (BSL-3) is appropriate for agents with a known potential for aerosol transmission, for agents that may cause serious and potentially lethal infections and that are indigenous or exotic in origin. Exotic agents that pose a high individual risk of life-threatening disease by infectious aerosols and for which no treatment is available are restricted to high containment laboratories that meet biosafety level 4 (BSL-4) standards (Department of Health and Human Services 2009, 3).

Arthropod Containment Guidelines provide principles of risk assessment, recommend biosafety measures for arthropods of public health importance and address the unique containment challenges. Four Arthropod Containment Levels (ACL 1 – 4) add increasingly stringent measures and are similar to biosafety levels. The Guidelines are relevant to GDOs that are insects, for example, gene drive mosquitoes. As an example, one research project with mosquitoes containing population suppression gene drives reported that the work was conducted in ACL-2 and in a temperate region, which offers some level of protection due to the lesser ability of mosquitoes to survive in such climates (Kyrou et al. 2018, 1067). In our view however, this may not be stringent enough and clear legally binding standards specific to GDO contained use experiments are still needed.

NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules

The NIH Guidelines provide guidance for research involving the construction and handling of: (i) recombinant nucleic acid molecules; (ii) synthetic nucleic acid molecules, including those that are chemically or otherwise modified but can base pair with naturally occurring nucleic acid molecules; and (iii) cells, organisms, and viruses containing such molecules. A risk assessment is required, and four risk groups are established according to the pathogenicity of the agents. A final consideration of the risk is then the basis for setting the appropriate containment conditions or biosafety levels for the experiments.

The Guidelines apply to all recombinant or synthetic nucleic acid research within the US, if the research is conducted at or sponsored by an institution that receives support for such research from NIH, including research performed directly by NIH. All recombinant or synthetic nucleic acid research performed abroad that receives NIH funds must also comply. Voluntary compliance is encouraged of those not otherwise covered by the Guidelines and many institutions have reportedly adopted the Guidelines as current best practice.

The Guidelines are meant to be implemented primarily through Institutional Biosafety Committees (IBCs), which comprise researchers at the institution who have differing expertise, along with other stakeholders not affiliated with the institution, who represent community interests in regard to health and the environment. All research involving recombinant or synthetic DNA must be reviewed and approved by an IBC.

Questions have been raised about the effectiveness of the IBC system in the US where it was designed and where it remains the primary institutional level bulwark against GMO accidents. Numerous instances of IBCs that fail to meet, do not review research proposals, do not identify and review laboratory accidents, and do not report or act to sanction personnel responsible for accidents, have been identified (Race and Hammond 2008).

Whether the IBCs have the necessary expertise or resources to determine adequate containment measures for GDOs remains a concern, more so in the case of their ability to address issues of biosecurity or the intentional misuse of gene drives (Heitmann et al. 2016, 175; NASEM 2016, 170). It has however been suggested that the NIH could provide additional guidance specific to experiments using gene drive insects (Carter and Friedman 2016, 11).

The biocontainment measures that have been established by these standards and guidelines for pathogens or dangerous biological agents in laboratory facilities, discussed above, provide valuable insight on how nations and other authorities can regulate GDOs in contained use. However, the current situation applied to GDO research in the laboratory, which is dependent on *ad hoc* adaptations of existing contained use standards or guidelines, with no obligation for reporting or inspecting what biosafety levels are actually being used, or for compliance, needs to be urgently remedied. It is imperative that the international community develop and apply effective international, GDO-specific contained use regulations as a priority. The key elements that we view as necessary for contained use regulations of GDOs are discussed further in Section 4.1.

3 Towards an effective international legal and regulatory regime

3.1 A proposed home for international governance of Gene Drive Organisms

After consideration of the various relevant treaties, regulatory bodies and other instruments currently in place, it would appear that the CBD and its Protocols are the best overall structure in which to locate development of international law pertaining to GDOs. This would include responsibility for international contained use regulations (addressed in detail in Section 4.1), given the potential species and ecosystem implications, should escapes from the laboratory occur. The objectives of each of the three CBD instruments are multifaceted, but all of them include in their aims the conservation and sustainable use of biological diversity.

Of course, much more needs to be done to enable these instruments to be effective against the serious threats posed by GDOs, in particular to biological diversity. In fact, the purpose of some gene drive applications (see Chapter 2) is to supress populations, but may result in population and species extinction, which is directly contrary to the objectives of the CBD.

The CBD and the Cartagena Protocol on Biosafety have near universal application, with the US as the most notable exception. There are currently 196 CBD Parties and 171 Parties to the Cartagena Protocol. The Nagoya – Kuala Lumpur Supplementary Protocol has only recently entered into force, with currently 44 Parties.

It is clear from the overview in Section 2 that GDOs are currently covered by the scope of the CBD, the Cartagena Protocol and the Supplementary Protocol, in so far as GDOs are LMOs, and in so far as GDOs are likely to have a significant adverse impact on biological diversity. GDOs have also begun to be specifically addressed by the CBD and the Cartagena Protocol.

As such, the CBD and its Protocols can be said to be already 'seized of the matter', and that GDOs clearly fall under their jurisdiction, However, GDOs pose challenges and risks not foreseen when the Convention and its Protocols were negotiated, since 'conventional' LMOs were what the first drafters had in mind. As such, much needs to be done to enable the CBD and its Protocols to adequately address the governance of GDOs beyond governance of LMOs.

The on-going work on synthetic biology and risk assessment and risk management by the respective AHTEGs is preliminary and this work needs to be taken further. COP and COP-MOP decisions are also necessary to affect their recommendations.

In the Cartagena Protocol, work has already been undertaken on other issues particularly relevant to GDO governance: in the AHTEG on Socio-economic Considerations; by the Network of Laboratories for the Detection and Identification of LMOs; and on unintentional transboundary movements of LMOs. Additional work on these issues specific to GDOs should be undertaken further.

COP decisions on synthetic biology, including GDOs, have stressed the importance of the precautionary approach but, it is important to emphasise, have not required mandatory risk assessment, risk management or regulatory procedures specific to GDOs to be in place or undertaken before any release occurs. The time is ripe for the COP to decide on this as well as on any potential suspension of GDO activity, especially considering the absence of binding and effective regulation of GDOs at local, national or international levels to date. The COP 14 decision (14/19) already moves in this direction (see Section 2.1.1). As such, implementation of these governance aspects, at international and national levels, should be a priority.

Explicitly locating broader governance of GDOs under the CBD and allocating more specific regulatory governance to the Cartagena Protocol, with the Supplementary Protocol being designed to address liability issues, seems to be the obvious way to begin the serious work of ensuring that there are specific and binding international rules on GDOs.

Critical steps forward which should be initiated urgently include a thorough review of how the provisions of the Cartagena Protocol and the Supplementary Protocol may become actively responsive to the specificities and risks of GDOs.

A number of options with regards to legal form could be identified to address the areas that need to be strengthened to meet the challenges of GDOs. Among those options available under the Convention and its Protocols include amendments to the Convention and its Protocols, new Protocols, new annexes, or COP and COP-MOP decisions. Work can be undertaken in the SBSTTA, new or existing AHTEGs, or any other subsidiary body established by the COP or COP-MOP. These considerations should be part of the review, as the form required should follow on from the function of new or amended rules, as required.

In addition, serious efforts need to be made to ensure that the implementation of and compliance with the CBD and its Protocols are improved. For example, the Cartagena Protocol is extremely weak in monitoring how it is being implemented and whether Parties are in compliance with its obligations. Parties monitor their own implementation of obligations and report on the measures that they have taken to implement the Protocol. Compliance procedures and mechanisms under the Protocol are facilitative and cooperative in nature, which means there is little in the way of enforcement of its provisions and obligations, as well as few sanctions or other consequences if the Protocol's obligations have been violated. For example, there have been failures in the transboundary notification process when GM mosquito eggs were exported/imported between Parties (GeneWatch UK 2014). Despite civil society bringing this to the attention of the Parties concerned and the CBD Secretariat, no action was taken, as compliance measures are only triggered by one Party against another.

Other international agreements, regimes and fora present opportunities for specific aspects of gene drive and GDO regulation. In particular, the issue of potential dual use of gene drive technologies has to be addressed by the BWC, whose mandate clearly prohibits the hostile use of GDOs, and includes development, production, acquisition, transfer, retention, stockpiling and use for such purposes (see Section 2.2.4). Furthermore, the UN Declaration on the Rights of Indigenous Peoples rightly sets the international norms and standards on the issue of free, prior and informed consent (see Section 2.2.6).

While international laws are legally binding, and this is necessary for establishing legal obligations that are actionable, there are of course limitations in terms of their implementation and enforcement, funding levels (which may be a combination of mandatory and voluntary funds, and may be insufficient), adequate staffing, and so on. Nevertheless, binding international laws that oblige Parties to take action are far preferable to voluntary or self-regulation. At the international level, this usually means that some financial flows and capacity building efforts begin to occur, and support and infrastructure is provided to assist countries in their implementation. In the case of GDOs, having legal obligations extending beyond moral responsibility would increase the accountability of the research and development that is already taking place, regardless of any current limitations.

3.2 The role of national biosafety laws and national contained use regulations

The Cartagena Protocol on Biosafety is legally binding on the countries that have become a Party to it through their national legal process. Parties to the Cartagena Protocol are legally obliged to take national measures to implement their international obligations (Article 2.1).

In most cases, Parties to the Cartagena Protocol have national biosafety laws, regulations and administrative orders in fulfilment of this obligation. Parties interpret their international obligations and translate these into their national laws, regulations, etc.

The Cartagena Protocol sets minimum standards for biosafety, which means that Parties to the Protocol can regulate LMOs for the protection of biological diversity more strictly than the Cartagena Protocol. In so doing, however, the stricter biosafety action must be "consistent with" the objective and provisions of the Protocol, and be "in accordance with" the other international law obligations of that Party (Article 2.4).

In practice, many countries have both adapted and added to provisions from the Cartagena Protocol in their national legislation and regulations. Depending on countries' national interests, these laws range from those that are comprehensive, such as the European Union's various Directives and Regulations dealing with all aspects of biosafety, to those that may be narrower in scope and focused only on the minimum standards set by the Protocol.

However, some of the notable non-Parties to the Cartagena Protocol are the US, Canada and Argentina, which are also major producers and exporters of GMOs. This means that these countries are not bound by this Protocol, which creates a significant problem for international level cooperation and action. This has been a long-standing issue, made worse more recently. At the same time, US participation in international negotiations, for example, has been far from constructive, often undermining the processes and outcomes. In fora where the US in not a Party, procedural rules can limit its influence; however, in fora where the US is a Party, it has the full rights of any Party to engage in the process and negotiate.

GDOs are currently being researched and developed, mainly in the US and Europe. The US has shown no intention to ratify the CBD or its Protocols since they were negotiated, and is very unlikely to do so, either in the current political context or indeed, in the foreseeable future. It should be recognised that even if a specific instrument were to be negotiated for governance of gene drives and GDOs, it is highly unlikely that the US would become a Party to it. This is the reality that has to be worked with and around.

In this political context, if the Cartagena Protocol and the Supplementary Protocol are to be made effective to regulate GDOs, corresponding national rules will be the first line of defence for countries against the undesired spread of GDOs from other countries, especially non-Party countries.

If an importing or neighbouring country has national biosafety rules, producers and exporters from all over the world, including from countries which are not Party to the Cartagena Protocol, will have to comply with their national legislation.

That means that while countries that are not Party to the Protocol have no international obligations to ensure that their companies or exporters comply with the national legislation of other countries, the producers and exporters themselves will have to comply with the countries' national rules if they wish to access that market.

Countries that will most require effective national laws, in addition to or in the absence of effective international rules governing GDOs, are those where research and development of GDOs is taking place, along with those countries which are likely to be recipients of GDOs for release. In addition, neighbouring countries in which research and/or release occur will almost certainly be affected. For example, in the case of the Target Malaria gene drive mosquito, contained use research is taking place in Europe, while Burkina Faso is the proposed first location of release, a situation which potentially also affects neighbouring countries in West Africa.

3.2.1 Importance of contained use standards in national legislation and regulation for Gene Drive Organisms

Contained use issues are particularly important in the case of GDOs, as discussed in Section 2.4.1.

Contained use is covered by the Cartagena Protocol, but not by the Protocol's advance informed agreement (AIA) procedure – which confers an international right on Parties to make a decision on imports of LMOs for release into the environment prior to its shipment – *if* the transboundary movement is undertaken according to the contained use standards of the importing Party.

Some provisions in the Cartagena Protocol explicitly acknowledge the right of Parties to regulate at national level. Contained use is one such provision. The Cartagena Protocol acknowledges the right of Parties to make domestic decisions based on risk assessment for any contained use imports. It also acknowledges Parties' right to set domestic standards for contained use (Article 6.2). As such, the necessity for domestic standards on contained use is underscored.

No international regulations for contained use have been developed so far, and furthermore, there are none specific to GDOs. This means that domestic rules for contained use are going to be very important, especially with the advent of GDOs. Existing national regulations, if any, would need to be re-examined for their adequacy as they were likely developed with 'conventional' GMOs in mind.

3.3 The Precautionary Principle and Polluter Pays Principle are fundamental

The Cartagena Protocol and the Supplementary Protocol are primarily concerned with the risks posed by 'conventional' LMOs; but the risks posed by GDOs go well beyond them. GDOs carry their own inherent risks beyond those posed by LMOs, which means it is paramount that any regulatory framework for GDOs be underpinned by the Precautionary Principle and the Polluter Pays Principle – as this section details.

The Precautionary Principle is a normative principle that aims to guide environmental decision-making under conditions of scientific uncertainty. It has four central components: initiating preventive action as a response to scientific uncertainty; shifting the burden of proof of a potentially harmful activity to the proponents; exploring alternative means to achieve the same aims; and involving stakeholders in the decision-making process (Kriebel et al. 2001).

Principle 15 of the Rio Declaration on Environment and Development states that:

> In order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. 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.

This is reflected in the preamble of the CBD, which notes that "where there is a threat of significant reduction or loss of biological diversity, lack of full scientific certainty should not be used as a reason for postponing measures to avoid or minimise such a threat".

The Cartagena Protocol on Biosafety additionally reaffirms the precautionary approach in its preamble, and substantively aligns its objective to be "in accordance with the precautionary approach contained in Principle 15 of the Rio Declaration on Environment and Development", in its Article 1.

Precaution is further operationalised in the decision-making procedures of the Cartagena Protocol (Articles 10(6) and 11(8)):

> 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 order to avoid or minimise such potential adverse effects.

Precaution is also established as a principle in risk assessment (paragraph 4 of Annex III of the Protocol): "Lack of scientific knowledge or scientific consensus should not necessarily be interpreted as indicating a particular level of risk, an absence of risk, or an acceptable risk".

In the biosafety context, the Precautionary Principle essentially provides the policy space for countries to limit the use and release of GMOs where there is scientific uncertainty with regard to potentially adverse environmental and health effects. The implementation of the Precautionary Principle presupposes the following: that some threat of harm has been identified; that there is scientific uncertainty in relation to the potential harm; and that there are criteria to guide proactive and precautionary measures (Myhr 2007, 459).

The 'Polluter Pays' Principle is affirmed in Principle 16 of the Rio Declaration:

> National authorities should endeavour to promote the internalization of environmental costs and the use of economic instruments, taking into account the approach that the polluter should, in principle, bear the cost of pollution, with due regard to the public interest and without distorting international trade and investment.

The principle places the responsibility on the party producing the pollution to pay for any damage to the environment or human health. It is linked to Principle 13 (Chee 2012, 45), which addresses the issue of liability and redress, calling on States to "develop national law regarding liability and compensation for the victims of pollution and other environmental damage", as well as to cooperate to "develop further international law regarding liability and compensation for adverse effects of environmental damage" that have a transboundary nature.

With respect to GDOs, liability and redress is a clear pillar of biosafety; it ensures that if damage occurs, there will be compensation or redress made to the victims of that damage (see Section 2.1.3). The Polluter Pays Principle further delineates who should bear the responsibility for providing that compensation.

Both the Precautionary Principle and the Polluter Pays Principle are principles that underpin environmental law. They are likewise essential to any regulations addressing gene drive technologies and GDOs, in order to ensure that harm is avoided and anticipatory action taken earlier – rather than later in the process – and that there is justice for victims of harm. However, the two principles need to be implemented in national laws, and this has not always been the case. The result is that, in practice, these two important principles may be routinely ignored. The challenge then is to ensure that these principles are effectively put into operation for GDOs. In the next section, we turn to the key elements that are fundamental in a binding international legal and regulatory regime that is based on the Precautionary Principle and the Polluter Pays Principle.

4 Key elements for binding international governance of Gene Drive Organisms

A legal and regulatory regime that is responsive to the particular challenges posed by GDOs will need to build on existing biosafety law, address the prevailing gaps and put in place specific elements that address these challenges. What follows are some of the key elements that we ascertain are critical and need to be operationalised in any governance and regulatory regime for GDOs.

4.1 Strict international contained use standards specific to Gene Drive Organisms

Any release of a GDO, including a field trial, is a release into the environment. The regulatory distinction is between containment and release. It is essential, as argued in Section 2.4.1, that there are strict contained use standards specific to GDOs. This has to be developed at the international level as a priority and complemented by national rules. The standards have to be legally enforceable in order to be effective.

The AHTEG on Synthetic Biology recognised the need for internationally agreed standards for effective containment of GDOs (AHTEG on Synthetic Biology 2017, paragraph 51(c)). COP 14 called for the development or implementation of measures "to prevent or minimise potential adverse effects arising from exposing the environment to organisms, components and products of synthetic biology in contained use…" (Decision 14/19, paragraph 12). Scientists have also recommended that there be "international harmonization of standards for the minimum containment requirements for gene drive mosquitoes" (James et al. 2018, 18).

There are parallels in the responsibility of scientists working in the laboratory on self-propagating pathogens and on those working with GDOs: both have to ensure that these agents remain in the laboratory and do not escape to the outside world (Akbari et al. 2015, 927). The biocontainment precautions that are set for pathogens or dangerous biological agents in laboratory facilities therefore provide some insight on how to regulate GDOs in contained use (see Section 2.4.3).

The basic idea for regulating contained use activities is to set ascending levels of containment, which correspond to increasing levels of protection; these range from the lowest biosafety level 1 (BSL-1) to the highest at level 4 (BSL-4). Applied to GDOs, those GDOs with a high potential for spread or invasiveness, such as those containing global suppression drives, should be subject to higher containment stringency and management procedures (Benedict et al. 2018, 4; van der Vlugt et al. 2018). Current contained use measures, as applied to pathogens, may include some that are not relevant for GDOs, and others that may not provide adequately for the suite of controls necessary to contain GDOs. This means that there is a need to adapt the details accordingly, along with an additional focus on potential environmental hazards due to potential species and ecosystem effects (Simon et al. 2018, 3).

A framework for risk assessment and risk management of GDOs in contained use, involving three risk classes, has been proposed by van der Vlugt et al. (2018). Risk classes are assigned after consideration of the identity and nature of the potential adverse effects on human, animal and plant health and the environment; the severity of the adverse effects (e.g., expected persistence and spread); the likelihood that these adverse effects will occur; and connected to this, the characteristics of the activity with the GDO (e.g. scale of operations). Specific minimum requirements for physical measures and working practices are then proposed for risk management according to the risk classes. Generally, higher risk activities necessitate additional layers of physical containment, with more stringent access restrictions for the highest risk class, in order to reduce the likelihood of an unintentional release. Risk

management measures also include an emergency plan for the highest risk class.

At present, there is no standardised application of contained use standards to current GDO research and development, much less any internationally agreed regulations specific to GDOs. Current projects are adapting existing contained use standards (which range from the lowest biosafety level at BSL-1, to the highest level at BSL-4, or the arthropod containment equivalents) but in our view, too much is left to the individual researchers or their institutions, including the assignment of biosafety levels, monitoring and oversight requirements. This means that existing research may not sufficiently have in place the strict standards that are necessary for GDOs, especially those with global drives capable of potentially eradicating populations. For example, a freedom of information request has revealed testing of population suppression gene drives in New World screwworm in Panama, only at a BSL-2 facility (Edward Hammond, personal communication, 12 June 2018).

In our view, some GDOs, depending on their specific modifications, have parallels with pathogens that are classified as subject to BSL-3 and BSL-4 containment and therefore should also be subject to these higher containment standards. Specifically, if these particular GDOs escape, they are difficult or impossible to control and can be expected to have very negative consequences. In particular, research in contained use of gene drive systems that are capable of introducing deleterious or lethal traits requires the same safety level as for pathogens that would have similar effects if released. At least some GDOs would meet these criteria if they could result in widespread population or species extinction.

Multiple strategies are needed, as "any single confinement strategy could fail" (Akbari et al. 2015, 927). These strategies may be molecular, ecological, reproductive or physical. For example, work with gene drives in a location where the species under study is also present (or which it might breed with), even if not necessarily directed toward lethal traits, should be subject to higher biosafety scrutiny, given that even the smallest containment failure could result in introduction of the trait into the wild population(s). To reduce this possibility, it has been recommended that laboratory work with GDOs should not occur in areas where the wild population is present (Akbari et al. 2015, 928). There may be other situations where the wild population may not be present, but the environment is suitable for establishment and persistence of any escapees, which would require more stringent containment measures.

Furthermore, when it comes to insect GDOs, considerations beyond the provision of physical containment need to be taken into account. For example, greater attention is needed to strain management, including its distribution and identity confirmation (Benedict et al. 2018, 4-5; James et al. 2018, 18). This is because contamination within laboratories may happen, for example, of non-transgenic or wild-type strains which are often kept in the same laboratory as references, whereby subsequent transfer to another laboratory of that reference strain may not be appropriately handled at the right biosafety level.

All the above elements should be factored in when devising rules for contained use of GDOs. These regulations must be specific to GDOs, as none currently exist. Furthermore, the necessary oversight of GDO laboratory research is presently too piecemeal and is not sufficiently stringent. A strong case can therefore be made for requiring the licensing of experiments with GDOs in contained use (see Box 10), which would allow for appropriate oversight by the government agencies concerned. This national level action can be immediately implemented to complement the international rules for contained use of GDOs that are urgently needed.

Working out these specific details for GDOs in contained use requires time and effort and this should be a priority, given that research and development on GDOs is already underway in numerous laboratories around the world. Even if there are no releases of GDOs into the environment, there is a need to urgently address the issue of contained use in research and development, so that the risks of unintentional escape are effectively minimised.

Box 10: Licensure

In addition to generally-applicable biosafety rules, one option to ensure that GDO-specific biosafety requirements are observed, particularly in the context of large research institutions that simultaneously handle many protocols for research involving GMOs, is to require licensure of GDO experiments. Review and approval of GDO contained use applications by a national body enables more thorough, consistent and unified government oversight, and can create an important legal presumption that any unlicensed GDO experiment will be sanctioned, thereby discouraging poorly planned or inadequately equipped experimentation with potential legal penalties.

In addition to creating clarity and even-handed oversight, national licensure enables the creation of review panels that possess specialised expertise in gene drives and GDOs and their implications, a great advantage that is unlikely to be available at individual research institutions. In addition, because in some countries general biosafety rules apply unevenly to research sectors (e.g. exemptions for privately-funded research), by requiring licenses for GDO experiments governments can ensure that biosafety loopholes are not exploited and that experiments, of which the government is unaware, do not proceed.

Finally, given the strong transboundary potential of some GDOs, national level licensing of GDO experiments places a government in a more informed position, and likely gives it more options and the ability to respond more quickly, if transboundary issues arise, either from domestic research or the spread of an unauthorised GDO from abroad.

Strict containment measures should also apply to GDOs that are transported, to ensure that there are no escapes at this stage (James et al. 2018, 18-19). In this regard, Article 18 of the Cartagena Protocol on Biosafety relating to handling, transport, packaging and identification of LMOs applies, although to date, no specific international rules and standards exist.

While robust and stringent regulations for contained use are being developed, meaningful public participation is also necessary at all stages and especially at this particular one, so that research and development trajectories incorporate and address citizens' concerns and views from the start. Public engagement was highlighted by the National Academies of Sciences, Engineering, and Medicine as essential and integral to the planning, assessment, and regulation of *gene drive research* (Heitmann et al. 2016, 175, emphasis added).

Due consideration should also be given as to the most appropriate forum for the development of international contained use regulations and/or standards for GDOs (see discussion in Section 3.1). Under the Cartagena Protocol, no standards for contained use have been developed thus far. Developing such rules at the international level is therefore a priority.

The most suitable venue for such a process currently would be the CBD and its Protocols, which have clear jurisdiction over GDOs and where discussions in this regard are already advanced. While other fora, such as the WHO, could be involved in the discussions, its remit or sphere of activity is much more limited and would only apply to certain aspects of the technology, such as gene drive mosquitoes deployed for vector control.

At the same time, domestic regulations for contained use remain very important. Existing national rules, if any, would need to be re-examined for their adequacy with regard to GDOs.

4.2 Joint-decision making for intentional release into the environment

4.2.1 State responsibilities

Principle 2 of the Rio Declaration on Environment and Development recognises that state responsibilities in relation to environmental matters extend beyond national jurisdiction: "States have… 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" (see Box 11). This principle is reflected wholesale in Article 3 of the CBD.

Box 11: State responsibility under international law

States have a responsibility under international law to not cause harm in the environment of another State. This obligation is a clear principle of international law. If there are activities that present a risk of environmental harm, States also have an obligation to notify and consult with other potentially affected States. Both actions and omissions may result in States being held liable for violations of their international obligations.

These obligations remain on all States even if they are not a Party to an existing international agreement on liability and redress for a particular environmental harm, such as for damage resulting from LMOs under the Nagoya – Kuala Lumpur Supplementary Protocol on Liability and Redress. A State does not discharge its obligations to not cause harm in the environment of another State by becoming a Party to an environmental liability and redress treaty, even if the responsibility for the activity in question lies with a private entity.

Reference: Nijar 2000.

Furthermore, Principle 14 of the Rio Declaration calls for States to effectively cooperate to discourage or prevent the relocation and transfer to other States of any activities and substances that cause severe environmental degradation or are found to be harmful to human health. Fundamentally, the idea is that there should be cooperation among nation states to ensure there is no relocation or transfer beyond borders of any materials having adverse effects on the environment or health.

4.2.2 Joint decision-making

Joint decision-making can range from international rule-making by consensus, where countries make decisions jointly, to decision-making on specific applications by all potentially affected countries, in cases where any unilateral decision involving transboundary implications would be unfair (see Box 12).

Box 12: Joint decision-making in practice

Making decisions jointly is not an alien concept in international treaties and this is also the case for the CBD and its Protocols. Parties adopt decisions based on consensus, which means that they have to agree jointly when their governing bodies meet. This is also applied to decisions on specific actions in international law, such as those that restrict or ban the use of a substance. For example, the Montreal Protocol on Substances that Deplete the Ozone Layer sets legally binding limits on national production and consumption of ozone-depleting substances, which Parties jointly agreed to. The Stockholm Convention on Persistent Organic Pollutants likewise prohibits, and/or eliminates or otherwise restricts, the production and use, as well as import and export, of certain persistent organic pollutants, the list of which was jointly decided. Both the Montreal Protocol and Stockholm Convention have built-in provisions that set out the procedures by which Parties can add new chemicals to the list of those that are prohibited or restricted, which also requires joint decision-making.

The member states of the European Union practice a version of joint decision-making when it comes to EU-wide GMO approvals[8]. Whether for cultivation or for food and feed purposes, a GMO has to undergo an approval process, entailing risk assessment and decision-making by all member states. A decision to approve or reject a GMO is reached by a qualified majority. If there is no such majority, the European Commission may convene an Appeal Committee. If that Committee fails to reach an opinion by a qualified majority, the Commission then takes the responsibility for the final decision. If there is authorisation, member states can still legally restrict or prohibit GM crop cultivation in their territories or adopt safeguard clauses to address new risks to health or the environment that may be subsequently identified, thus preserving their right to make decisions in their national interest.

Given the transboundary nature of the potential spread and adverse effects of GDOs, a key element in their governance is therefore the need for decision-making by all potentially affected countries (Sustainability Council of New Zealand 2018, 24-27). This means that countries that are affected beyond the country of release must also have a stake in any release decision.

8 See https://ec.europa.eu/food/plant/gmo/authorisation_en for further information on GMO authorisations in the European Union.

Joint decision-making has also been termed 'collective consent', a concept that recognises that granting approval for certain activities should involve all affected parties (Sustainability Council of New Zealand 2018, 24-27). Applied to gene drives, this means that every country has a right to give or withhold its approval for a GDO release in another jurisdiction that could directly or indirectly impact its territory. 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" (Sustainability Council of New Zealand 2018, 26).

Even gene drive developers recognise that moving forward without the permission of every other country harbouring the target species would be highly irresponsible (Esvelt and Gemmell 2017, 3). They also agree that "regulatory approval must be obtained from every country that would be affected by an eventual deployment" (Min et al. 2018, S52). This is reflected in proposals for a multi-country or regional coordination, authorisation and decision-making process for gene drive mosquitoes (James et al. 2018, 12; James and Tountas 2018, 4793).

Joint decision-making is not about harmonising decisions at a regional level or allowing a regional entity to make a decision on behalf of all the countries; it is about ensuring that every country that is likely to be affected has a right to be consulted and to potentially withhold their approval.

4.2.3 Implementing joint decision-making under the Cartagena Protocol on Biosafety

Under the Cartagena Protocol on Biosafety, the principle of prior informed consent is already implemented through its advance informed agreement (AIA) procedure (Article 7), details of which are elaborated in Articles 8 to 10, and Article 12 (see Section 2.1.2).

The governance of movements of LMOs between countries that are Party to the Cartagena Protocol is premised upon obtaining AIA for intentional introduction into the environment of a LMO in another country. The obligation is on the Party of export to either obtain the consent, or require its exporter to obtain the consent, of the receiving Party before the transboundary movement can take place. If any transboundary movement occurs outside of this agreement, the provisions of Article 17 and Article 25 become relevant. The transboundary movement becomes unintentional and illegal in most cases (see Section 4.3).

In the context of GDOs, while AIA remains an important central tenet, joint decision-making would require extended modalities to be able to deal with the specific nature of GDOs and to account for the wider number of Parties that may be involved in a decision. Because gene drives have the propensity to spread genetic modifications in a transboundary manner and at the point of release, their effects cannot necessarily be confined to one country or to a specific import.

Furthermore, because a GDO domestic release will very likely result in spread and transboundary movement, there needs to be consideration of a shift, both in time and space, of when and where AIA is exercised. Essentially, the prior consent should be sought *before* the time and point of domestic release in one country, not at the time when the crossing of the border of another is anticipated or sought, as is currently the case with LMOs.

Detailed arrangements as to how such a system of joint decision-making could be implemented under the CBD and/or the Cartagena Protocol on Biosafety should be considered. Questions of whose consent should be sought for a particular application, what modalities should determine how collective consent is obtained and how far in advance such consent should be obtained, should be carefully considered. Whether or not, and how these details could be codified in the current legal texts or taken up in future decisions of the Parties would be another issue meriting serious discussion.

4.3 Effective measures for dealing with unintentional transboundary movements

Unintentional transboundary movements occur when there is inadvertent crossing of national borders of a GMO. For example, a GM rice variety had only been approved for field trials in China, but entered the food supply (Zi 2005) and was exported, resulting in unintentional transboundary movements to various countries, including the EU. Since the GM rice variety had not been authorised in the EU, it was also an illegal transboundary movement. This led to the EU imposing emergency controls on all rice products from China (Price and Cotter 2014, 11). These restrictions required consignments to be certified as not containing GM rice and imports subjected to sampling and document checks at the EU port of entry. The measures were first imposed in 2008 and further measures in 2011, resulting in delays and lost export revenue for Chinese rice exporters.

The characteristics of many GDOs make them amenable to unintentional transboundary movements, whether from contained use or from a domestic release. Gene drives are designed to spread genetic modifications in natural ecosystems and will not respect national boundaries. The transboundary nature of gene drives makes it highly possible that there will be unintentional and illegal transboundary movements of GDOs, for which only limited procedures are provided for in the Cartagena Protocol. (Article 17 of the Protocol on unintentional transboundary movements and emergency measures and Article 25 on illegal transboundary movements have been discussed in Section 2.1.2).

Near certain unintentional transboundary movements of high risk organisms are a key reason why joint decision-making is important to consider for GDOs (see Section 4.2). When unintentional and illegal transboundary movements occur, the country into which the GDO has entered will not be able to make its own assessment and decision on organisms that will likely be impossible to recall. Thereby, the central tenets of the Cartagena Protocol – the right of Parties to have their prior informed consent sought as well as to be able to make decisions on LMO approvals based on risk assessment and in accordance with the precautionary approach – would be circumvented.

Even if joint decision-making is successfully operationalised, when potentially affected countries do give their prior informed consent for any GDO release, this would only mean that the transboundary movement is permissible in those countries. There is still a high likelihood that unintentional transboundary movements will occur beyond these countries, to those that were not party to the joint decision. When this happens, procedures are needed to deal with such incidents.

Principle 19 of the Rio Declaration establishes the concepts of notification and provision of information in the case of transboundary environmental effects: "States shall provide prior and timely notification and relevant information to potentially affected States on activities that may have a significant adverse transboundary environmental effect and shall consult with those States at an early stage and in good faith."

Article 17 of the Cartagena Protocol on Biosafety requires Parties to take appropriate measures to notify affected and potentially affected States, the BCH, and other relevant international organisations, when it knows of an occurrence (which could also include escape from contained use or during transport) under its jurisdiction that leads or may lead to an unintentional transboundary movement of a LMO. Notifications must be provided as soon as the Party knows of such situations, and relevant information must be communicated to the affected or potentially affected States. Consultations with these States are also necessary in order to enable them to determine appropriate responses and initiate necessary action, including emergency measures.

In the absence of joint decision-making on specific GDO applications, notification, provision of timely information and consultations with potentially affected parties will all be necessary steps for dealing with unintentional transboundary movements. However, these efforts may be too little and too late. Preventative and precautionary measures

are first required to address these scenarios, for example by ensuring strict contained use standards (see Section 4.1).

Nonetheless, should unintentional transboundary movement occur despite the best efforts to prevent them, Article 17 requires measures to mitigate the effects, if at all possible. These should be further strengthened and could include, for example, a regional or sub-regional rapid alert system that immediately notifies all affected and potentially affected States. Such a rapid alert system is in operation in the European Union, whose Rapid Alert System for Food and Feed shares relevant information between its members and allows collective response (European Commission, n.d). This system has worked effectively to inform member states about GM contamination incidences in food and animal feed.

Furthermore, effective emergency and response measures are needed, including in a situation where there is damage or sufficient likelihood that damage will occur. This would require consequent links to liability and redress, as well as detection and identification to enable monitoring. There is also a need to adapt existing tools for detection of GDOs as well as to develop new ones. Measures such as these, which would attempt to deal with unintentional transboundary movements of GDOs as effectively as possible, need to be worked out in detail.

4.4 Genuine public participation and free, prior and informed consent

The need for public participation has been recognised in relation to gene drives and GDOs (see for example, NASEM 2016). Principle 10 of the Rio Declaration on Environment and Development recognises the three interlinked pillars of appropriate access to information: facilitating awareness; participation in decision-making processes; and access to judicial and administrative proceedings. It says:

> Environmental issues are best handled with participation of all concerned citizens, at the relevant level. At the national level, each individual shall have appropriate access to information concerning the environment that is held by public authorities, including information on hazardous materials and activities in their communities, and the opportunity to participate in decision-making processes. States shall facilitate and encourage public awareness and participation by making information widely available. Effective access to judicial and administrative proceedings, including redress and remedy, shall be provided.

Article 23 of the Cartagena Protocol on Biosafety places a clear obligation on Parties to promote and facilitate public awareness, education and participation (including access to information) and also requires mandatory public consultation and disclosure of results of decisions to the public in the decision-making process.

Two other regional agreements – the Aarhus Convention and the Escazú Agreement – on access to information, public participation and access to justice in environmental matters – also set out important rights and obligations in relation to this issue (see Boxes 13 and 14).

Box 13: The Aarhus Convention

The UN Economic Commission for Europe Convention on Access to Information, Public Participation in Decision-Making and Access to Justice in Environmental Matters, also known as the Aarhus Convention, is a legally binding treaty that deals specifically with the issue of public participation. It entered into force in October 2001. The Convention covers Parties from the Pan-European region, including Europe, Caucasus and Central Asia, although it is open for ratification by any other country. It has been ratified by 47 countries, including the European Community.

The Aarhus Convention grants the public rights and imposes obligations on Parties and public authorities as regards access to information and public participation. There are three pillars: access to information; public participation; and access to justice. Public participation relies upon the other two pillars: the information pillar, to ensure that the public can participate in an informed fashion; and the access to justice pillar, to ensure that participation happens in reality.

Activities involving GMOs were not initially subjected to the Convention's participation

requirements, but were referred to national legislation. However, in 2002, Parties to the Aarhus Convention adopted the Guidelines on Access to Information, Public Participation and Access to Justice with respect to Genetically Modified Organisms. Known also as the Lucca Guidelines, they create a non-legally binding framework that provides guidance on the practical application of the Aarhus Convention's provisions relevant to GMOs.

Efforts for a legally binding approach culminated in May 2005 when agreement was reached on an Amendment that provides a legal obligation for Parties to provide the public with early and effective information, along with a means of public participation, prior to making decisions on whether or not to authorise a GMO release for experimental or commercial purposes. When decisions are made, due account has to be taken of the public participation outcomes. The GMO Amendment is however not yet in force, due to a lack of political will and strong opposition from the Parties which did not want a legally binding obligation.

Box 14: The Escazú Agreement

The Regional Agreement on Access to Information, Public Participation and Justice in Environmental Matters in Latin America and the Caribbean, also known as the Escazú Agreement, was adopted in March 2018. Rooted in the tenets of Principle 10 of the Rio Declaration, it is both a legal instrument for environmental protection as well as a human rights treaty. Not only does the Escazú Agreement address key aspects of environmental management and protection from a regional perspective, focusing on access rights to information, public participation and justice in environmental matters, it also includes the world's first binding provision on human rights defenders in environmental matters. It aims to include those that have traditionally been underrepresented, excluded or marginalised.

There are common elements in the aforementioned instruments which establish public participation as a right enshrined in legally binding treaties. Important among these is that they refer to the active provision of information, that is, the right of the public to receive information and the obligation of authorities to proactively collect and disseminate information of public interest, without the need for a specific request. They also refer to the need for public participation across different stages in a process (in policy making, specific decisions, etc.). Obligations are placed on governments to ensure transparency and accountability of responses. As with other international treaties, these provisions need to be implemented and enforced at national levels.

Furthermore, the need to obtain the "prior and informed consent", "free, prior and informed consent" or "approval and involvement", of potentially affected indigenous peoples and local communities, was reiterated at COP 14 as a condition that should be met before any introduction into the environment of GDOs, including for experimental or research and development purposes (Decision 14/19, paragraph 11(c)) (see Section 2.1.1).

There are no international guidelines yet for *obtaining* the "prior and informed consent", "free, prior and informed consent" or "approval and involvement" of potentially affected indigenous peoples and local communities, when considering the release of GDOs specifically. However, there are international norms and standards set forth in the UN Declaration on the Rights of Indigenous Peoples (see Section 2.2.6), which should be the basis on which any guidelines are developed. The Mo'otz Kuxtal Voluntary Guidelines on which the language of the COP 14 decision is based also provide guidance.

What specific international guidelines in relation to GDOs should look like in practice and how such consent is to be obtained at national and local levels needs to be further discussed and deliberated, drawing also from other experiences of obtaining the free, prior and informed consent of indigenous peoples. What the COP 14 decision makes clear is that there should not be an *a priori* assumption of consent, as would be the case with 'opt out' models, for example, which have been suggested for consideration by James et al. (2018, 32) for large scale field trials of gene drive mosquitoes.

4.5 Adapted risk assessment and risk management approaches with due acknowledgement of their limitations

COP 13 noted that risk assessment methodologies might need to be updated and adapted for living organisms developed through synthetic biology (Decision XIII/17, paragraph 6). The AHTEG on Synthetic Biology reiterated this, further adding that this might be needed to account for a universal lack of experience with the introduction of GDOs (AHTEG on Synthetic Biology 2017, paragraph 41). In addition, "existing risk assessment considerations and methodologies might not be sufficient or adequate to assess and evaluate the risks that might arise from organisms containing engineered gene drives due to limited experience and the complexity of the potential impacts on the environment" (AHTEG on Synthetic Biology 2017, paragraph 44). The AHTEG further highlighted that risk management strategies might similarly need to be adapted and complemented (AHTEG on Synthetic Biology 2017, paragraph 48).

The novel features of GDOs that make them distinct from 'conventional' GMOs, and hence pose challenges for risk assessment, include: (i) outcrossing and spread of the transgenes as a prerequisite; (ii) transferring the laboratory to the field; (iii) the modification of wild populations as opposed to cultivated plant species; (iv) the transition from indirect (modification against stressors) to direct modification of stressors such as pests; and (v) modification of common goods (Simon et al. 2018). Adaptations to current risk assessment methodologies are therefore needed, in order to conduct rigorous assessments for gene drives that are designed to spread genetic modifications and that may have irreversible impacts (see Chapter 2). However, such assessments must also be able to indicate when the data are not strong enough to make a decision or when the risks are too high.

In particular, there remains disagreement, including at the AHTEG on Synthetic Biology, as to the utility of conducting the risk assessment in a stepwise manner, that is, from contained use, to field trials and finally to open releases, with the results at each step informing the next step of the risk assessment, an approach that is common for GMOs. It is our view that such an approach is not appropriate at this stage of uncertainty about the impacts of GDOs on the environment, as it includes field-testing, which requires the release of GDOs into the environment.

Some scientists have proposed a phased testing pathway moving from contained use to small-scale geographically isolated releases, and then to small-scale and large-scale open releases for gene drive mosquitoes (James et al. 2018; James and Tountas 2018). This is also the approach recommended for GDOs by the National Academies of Sciences, Engineering, and Medicine (NASEM 2016) and others (e.g. Hayes et al. 2018). However, even so-called isolated releases of GDOs (for example on islands), may lead to further spread (e.g. wind-blown mosquitoes or rats on cars, boats, planes etc.), which is why the AHTEG on Synthetic Biology noted that islands are *not* ecologically fully contained environments (AHTEG on Synthetic Biology 2017, paragraph 51(b)).

For global gene drives, a field trial already represents widespread release because of the propensity to spread, contradicting the intended procedure to keep the field release limited or confined to some extent (Simon et al. 2018, 3). The AHTEG on Synthetic Biology likewise highlighted that "the step of release into the environment might be irreversible", and therefore called for a precautionary approach (AHTEG on Synthetic Biology 2017, paragraph 45). There is consequently a need for substantially more data and modelling, as well as a reconceptualisation of current approaches to risk assessment, including taking into consideration the long-term effects on ecosystems (Courtier-Orgogozo et al. 2017, 879). Other contained use studies such as long-term caged trials in simulated environments or microcosms could also yield useful data, provided that there is strict stringency for effective containment.

Both the COP 14 decision (14/19, paragraph 9) on synthetic biology and the COP-MOP 9 decision (9/13, paragraph 3) on risk assessment and risk management stipulate that before organisms con-

taining engineered gene drives are considered for release into the environment, specific guidance may be useful to support case-by-case risk assessment. The Parties to the Cartagena Protocol will consider, in 2020, whether additional guidance materials on risk assessment is needed for such organisms.

Therefore, it would be prudent and responsible for Parties and other Governments, as well as any would-be developer, to wait until such international guidance specific to the obligations in the Cartagena Protocol is available, before considering any introduction of GDOs into the environment.

4.6 Full assessment of socio-economic impacts including ethical concerns

Gene drives and GDOs are likely to have significant and wide-ranging social, cultural and economic impacts, which should also be the subject of detailed assessment and informed decision-making (Sustainability Council of New Zealand 2018, 31). The socio-economic and ethical issues raised by GDOs have been discussed in Chapters 3 and 4.

The Cartagena Protocol on Biosafety, in its Article 26, establishes the right of countries to take into account socio-economic considerations that arise from the impact of LMOs on biological diversity when making decisions about LMOs. It is clear that because of the extensive implications of GDOs, both in society and on the environment, a wider consideration of these issues that goes beyond scientific risk assessment is needed. As recognised by the National Academies of Sciences, Engineering, and Medicine, "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" (NASEM 2016, 9).

However, the approach offered by the Cartagena Protocol is clearly not enough, as the provision is weak and does not amount to requiring or conducting socio-economic impact assessments. Taking socio-economic considerations into account is not obligatory under the Protocol; it would be up to each Party to do so. There is also a lack of integration with the risk assessment process, with most regulators giving more weight to the assessment of environmental risks. Despite the development of the 'Guidance on the Assessment of Socio-Economic Considerations in the Context of Article 26 of the Cartagena Protocol on Biosafety' by the AHTEG on Socio-economic Considerations, this is still a work in progress.

Examples of national biosafety laws that attempt to incorporate socio-economic and ethical considerations (see Boxes 15, 16 and 17) provide insight as to how countries might ensure that these important issues find a place in biosafety regulation. How to factor in socio-economic and ethical considerations when making decisions on GDOs is therefore a critical aspect of their governance, one that needs further elaboration.

Box 15: The Norwegian Gene Technology Act and socio-economic considerations

Section 1 of the Act states that "the purpose of the Act is to ensure that the production and use of GMOs … takes place in an ethically justifiable and socially acceptable manner, in accordance with the principles of sustainable development and without adverse effects on health and the environment."

Section 10 of the Act states that "… in deciding whether or not to grant an application, considerable weight shall (also) be given to whether the deliberate release will be of benefit to society and is likely to promote sustainable development".

The Act also addresses ethical norms and values associated with humans and environmental ethical considerations.

Assessments of sustainability of GMOs apply not just domestically but also globally, and sustainability is recognised as an inter-generational issue. The assessments should include ecological, economic and social sustainability issues, including:

* Is biodiversity affected on a global scale?
* Is the fulfilment of basic human needs like food, shelter, health affected?
* Are emissions of greenhouse gasses affected?
* Is the distribution of benefits or burdens between generations affected?
* Is the distribution of benefits or burdens between rich and poor countries affected?

Benefit to society must be assessed prior to an approval, and has a domestic focus. Relevant questions in an assessment of benefit to society include:

* Is there a need for the product in terms of demand or otherwise?
* Will the product solve or possibly contribute to solving a societal problem?
* Is the product significantly better than equivalent products already on the market?
* Does the product create problems for existing production which should be preserved?

Excerpted from "The Norwegian Gene Technology Act and socio-economic considerations", Norwegian Directorate for Nature Management 2011.

Box 16: Swiss law and respecting the dignity of living beings

Switzerland is the only country in Europe that has a constitutional duty to take the dignity of living beings into consideration. Paragraph 2 of Article 120 of the Federal Constitution on 'non-human gene technology' prescribes that in legislating on the use of reproductive and genetic material from animals, plants and other organisms, the dignity of living beings, as well as the safety of human beings, animals and the environment, shall be taken into account. The concept of 'dignity of living beings' has further been related to the value of the individual organism *for its own sake* (Federal Ethics Committee on Non-Human Biotechnology 2008, 3).

The Gene Technology Act limits the scope of the term to animals and plants (Federal Ethics Committee on Non-Human Biotechnology 2008, 3). Article 8 provides for 'respect for the dignity of living beings', whereby genetic modification in animals and plants must not violate the dignity of living beings.

Violation is deemed to have particularly occurred if the modification substantially harms species-specific properties, functions or habits, unless this is justified by overriding 'legitimate interests'. Whether the dignity of living beings has been respected is determined by evaluating the severity of the harm suffered by animals or plants against the significance of legitimate interests as identified in the law.

Box 17: Bolivian Law of the Rights of Mother Earth

The Plurinational State of Bolivia adopted the Law of the Rights of Mother Earth in 2010. It is considered to be the first environmental law that gives legal rights to nature.

In 2012 the Government passed a revised version of the original longer piece of legislation: the Framework Law of Mother Earth and Integral Development for Living Well (*La Ley Marco de la Madre Tierra y Desarrollo Integral para Vivir Bien*).

The laws recognise the rights of Mother Earth (*Pachamama*, an indigenous goddess of the Andes) as a whole, along with "all beings of which she is composed". These rights are spelt out in the law: the right to life; to maintain the integrity of living systems and natural processes that sustain them, including capacities and conditions for regeneration; the right to the diversity of life, without being genetically altered or structurally modified in an artificial way; the right to clean water; the right to clean air; the right to equilibrium, such that the interrelationship, interdependence, complementarity and functionality of the components of Mother Earth are balanced, for the continuation of cycles and reproduction of vital processes; the right to restoration; and the right to pollution-free living.

The implementation of socio-economic considerations in these examples varies. For example, Norway has a strict biosafety regime and has not approved any GM crop for cultivation. It routinely takes socio-economic considerations into account in decision-making. On the other hand, in Bolivia, GM soya was approved before the Law of the Rights of Mother Earth came into force. Competing national interests has meant that GM soya is still widely cultivated in Bolivia, due to the strong agribusiness and trade lobby.

4.7 A technology assessment approach, including consideration of alternatives

Given the discussion in Sections 4.5 and 4.6, it would seem that neither a risk assessment alone nor a risk assessment supplemented by considerations of socio-economic impacts is sufficiently adequate for technologies such as gene drives. To this end, Simon et al. (2018, 3) suggest, for GDOs, "a technology assessment approach that goes beyond mere risk assessment and that is generally not foreseen in legislations". Technology assessment is the study and evaluation of new technologies. It "involves the collection, interpretation and evaluation of information and perspectives around contending technological options" (Ely et al. 2011, 7).

Such a technology assessment approach is not new. It was identified as an important issue in Agenda 21, the comprehensive plan for action on sustainable development that was adopted by the world's governments at the UN Conference for Environment and Development (the Rio Earth Summit) in 1992. An essential aspect was the need to build technology assessment capacity "with due regard to appropriate safeguards on the transfer of technologies subject to prohibition on environmental or health grounds" (paragraph 34.26).

This was reaffirmed in the outcome document of the Rio-plus 20 process, 'The Future We Want' in 2012. The section on technology includes a paragraph on technology assessment:

> We recognise the importance of strengthening international, regional and national capacities in research and technology assessment, especially in view of the rapid development and possible deployment of new technologies that may also have unintended negative impacts, in particular on biodiversity and health, or other unforeseen consequences (paragraph 275).

One critical aspect of technology assessment would be consideration of the appropriateness of the technology compared with other means to achieve the same goals or to address a stated problem (see Chapter 4). A *comparative approach* allows for a comparison of all the approaches that could achieve the same outcomes, and if there is one that is less risky, then this should be the preferred option (Sustainability Council of New Zealand 2018, 29-30). This requires a move away from evaluation of the attributes of a single technology, towards addressing a much broader range of options (Ely et al. 2011, 22). Such a comparison should be done at the start of technology development, when first considering a GDO as a possible response to a stated problem, and throughout any research and development. It would mean that investments and resources are not wasted on gene drives or GDOs if there are less harmful alternatives available or that could be developed and used (Sustainability Council of New Zealand 2018, 30).

Furthermore, as technology assessment has developed tools for feedback loops to society (Simon et al. 2018, 3-4), the issue of public participation once again would take centre stage. People must have the ability to decide which technologies they want and to provide input to ensure that these technologies meet their needs and priorities. There is also a need to broaden the expertise involved, so that it is not just limited to a small group of experts, but rather ensures that there are multidisciplinary inputs and specifically brings in perspectives of marginalised groups, an approach that tries to ask the right questions from the start (Ely et al. 2011, 21-22).

At the same time, there is a need to open up the outputs of participation exercises to wider governance processes and policy debates, allowing plural policy outputs that recognise multiple perspectives and priorities, while highlighting new options, neglected issues, areas of uncertainty and otherwise marginalised perspectives (Ely et al. 2011, 22-23).

4.8 Rigorous monitoring and detection

In the case of GMOs, monitoring is the systematic approach for observing, collecting and analysing data on potential adverse effects, based on a risk assessment following a GMO's release. Many jurisdictions provide for the monitoring of GMOs. For

example, in the European Union, Directive 2001/18 on the deliberate release into the environment of GMOs requires the submission of a monitoring plan in applications for approval. The monitoring plan includes both case-specific monitoring based on the risk assessment, and general surveillance for unanticipated adverse effects.

Monitoring is also an aspect of the Cartagena Protocol on Biosafety. Article 12 allows for reviews of decisions, particularly in the light of new scientific information on potential adverse effects. Article 16 on risk management also indirectly envisages monitoring as well as "an appropriate period of observation prior to intended use".

Annex III of the Protocol further recognises monitoring of the LMO, among other things, as appropriate "where there is uncertainty regarding the level of risk". The source of this uncertainty could be, for example: unanticipated effects on human health or key ecological functions; interactions with future LMOs; changes in management of the LMO; or uncertainty as to whether the conclusions of safety that may have supported a decision for environmental release are indeed correct (Heinemann and Quist 2012, 2).

The 'Guidance on Risk Assessment of Living Modified Organisms and Monitoring in the Context of Risk Assessment', developed under the Protocol, includes a section on monitoring of LMOs released into the environment. Monitoring was included because it was viewed as important for risk assessment and risk management and because no specific guidance on monitoring is available either internationally or from the Protocol.

The Guidance provides a robust, comprehensive approach for developing a monitoring plan that focuses on what to monitor, how to monitor, where to monitor, how long to monitor, and how to communicate the results of monitoring. It details two types of monitoring: case-specific monitoring to address uncertainties identified in the risk assessment; and general monitoring, to address uncertainties that were not identified in the risk assessment and which could include long-term effects that may be complex, cumulative, synergistic or indirect (Heinemann and Quist 2012, 3).

Article 7 of the CBD also obliges Parties to identify the processes and activities that have had or are likely to have significant adverse impacts on the conservation and sustainable use of biological diversity, and to monitor their effects.

Monitoring could result in withdrawal of a particular GMO from commercialisation because approvals are either time limited or subject to a review of decisions. However, this is not possible with GDOs, purely for the fact that once released, a GDO cannot be withdrawn in a biological sense (Simon et al. 2018, 2).

Monitoring in the case of GDOs would thus need to take the following approaches: tracking their movements and the potential spread of the trait through populations and across borders and ecosystems; and identifying unintended, harmful impacts during and after a GDO release, impacts that could lead to a change in or revocation of approval (Sustainability Council of New Zealand 2018, 31-32). This type of monitoring would also be important to fulfil other biosafety functions, such as liability and redress.

Monitoring of GDOs is also dependent on the capacity for detection, particularly of any unintentional transboundary movements, and would be subject to any limits to detection (see Section 2.1.2).

4.9 Stringent liability and redress rules

For GDOs, a minimum requirement would be an international civil liability regime with a strict liability standard (see Section 2.1.3). Although the Supplementary Protocol's approach is in effect a strict liability approach, it is also, however, an administrative regime requiring response measures to prevent, minimise, contain, mitigate or avoid damage, and/or to restore biological diversity – responses which may not always be feasible because of the persistence and spread of GDOs. It also places a

heavy burden on national authorities, without providing the necessary financial guarantees.

The first review of the Supplementary Protocol will include its financial security and civil liability provisions. This will take place in 2023, five years after its entry into force (which was in 2018). It is imperative that the Supplementary Protocol's rules on financial security and on civil liability are addressed at that time, and in a manner that also meets the challenges posed by GDOs.

There is a need for the international community to seriously explore the possible options for providing financial security regarding GDOs, measures which might include compulsory insurance or other financial guarantees, as well as a supplementary compensation fund. Requiring financial security from the developers of GDOs is necessary in order to ensure that adequate redress measures are undertaken in the event of adverse impacts from GDOs. Examples from other treaties on financial security are explored in Box 18. *Such arrangements must be in place before any GDOs are considered for release.* This should be considered in the comprehensive study on financial security that will be carried out and put for the consideration of COP-MOP 10 in 2020.

Box 18: Examples from other international liability instruments on financial security

The Basel Convention's Protocol on Liability and Compensation for Damage Resulting from Transboundary Movements of Hazardous Wastes and their Disposal requires compulsory insurance, bonds or other financial guarantees. Proof of means to address liability must be provided to the State before any transboundary movement can occur. The person who has suffered damage may sue the insurer directly or the person providing the bond or other financial guarantee, although a State can choose not to allow this.

The Convention on Civil Liability for Oil Pollution Damage 1969 (CLC) also requires compulsory insurance or other financial security. The sums are fixed by the CLC and adequate evidence of the insurance or other cover must be provided. The claimant may sue the insurer or the financial security provider directly.

Under the CLC, the owner of a ship is strictly liable with limited exceptions. A ship owner is allowed to limit his liability by constituting a fund. A government which has initially paid for the clean-up costs is entitled to claim from the limitation fund if the State has allowed for this under its national law.

Still, there were concerns that the victims of oil pollution damage might be left uncompensated and that the financial burden on ship owners was too great. A further instrument known as the International Convention on the Establishment of an International Compensation Fund for Oil Pollution 1971 (The Fund Convention) was agreed upon, to provide for an additional source of compensation in the event for example that the ship owners cannot pay or the claim exceeds the liability limits under the Convention.

The oil industry contributes to the Fund. The amounts are determined by a formula and are derived from an initial levy and an annual payment. This means that the whole industry shares the costs and ensures that funds are available for clean-up costs in the event a country is unable to bear the costs. It also ensures that no victim goes uncompensated fully.

Reference: Nijar 2000.

Countries do have recourse to their national civil liability laws; however in most cases, no specific civil liability laws with strict liability standards for GMOs or GDOs are in place. Such specific civil liability laws should be a priority for any country in which research and development of GDOs is happening or where potential deployment is planned.

5 The appropriate response to the legal and regulatory challenges posed by Gene Drive Organisms

5.1 Taking the time to get it right

The elements discussed in Section 4 are not fully in place and urgent efforts need to be undertaken to ensure they are translated into effective rules that are binding on all countries in order to remedy the serious gaps identified, *before* any release of GDOs is even contemplated. Even highly developed countries, let alone developing ones, are simply not equipped as yet to be able to manage gene drive technologies. The current legal and regulatory regime is not able to effectively regulate GDOs in a precautionary manner, and moreover already suffers from the many limitations described in this chapter.

For that reason, some parts of civil society have called for a 'moratorium'[9] on any further technical development and experimental application of gene drives, along with any environmental release of genetically-engineered gene drives. Others have proposed a 'constraint period', which would require withholding GDOs from any release into the environment or field trials until global governance arrangements are in place (Sustainability Council of New Zealand 2018, 49-50).

The International Union for Conservation of Nature (IUCN), comprising governments and civil society organisations, adopted a resolution in 2016 that called on its Director General and Commissions to refrain from supporting or endorsing research, including field trials, into the use of gene drives for conservation or other purposes, until an assessment of the implications of the technology and its potential impacts has been conducted (IUCN 2016).

The Norwegian Biotechnology Advisory Board, an independent body appointed by the Norwegian government to advise it on biotechnology issues, recommended a moratorium on the use of gene drives until international regulations for handling and risk assessment are in place (Norwegian Biotechnology Advisory Board 2017, 17).

There is precedence internationally for such pauses in technology development:

- In 2000, Parties to the CBD adopted a decision which recommends that Parties not approve genetic use-restriction technologies (GURTs) for field testing "until appropriate scientific data can justify such testing", nor for commercial use "until appropriate, authorized and strictly controlled scientific assessments with regard to, *inter alia*, their ecological and socio-economic impacts and any adverse effects for biological diversity, food security and human health have been carried out in a transparent manner and the conditions for their safe and beneficial use validated" (Decision V/5, paragraph 23). GURTs raised serious concerns because the technology renders seed sterile, thus preventing farmers from re-using their own seed, a practice integral to agriculture, particularly in developing countries.

- In 2008, the CBD requested Parties to ensure that "ocean fertilization activities do not take place until there is an adequate scientific basis on which to justify such activities, including assessing associated risks, and a global, transparent and effective control and regulatory mechanism is in place for these activities; with the exception of small scale scientific research studies within coastal waters" (Decision IX/16, part C, paragraph 4).

9 More than 170 civil society organisations signed a 'Common Call for a Global Moratorium on Genetically-engineered Gene Drives' in 2016. See: http://www.synbiowatch.org/gene-drives/gene-drives-moratorium/?lores

- The CBD in 2010 called on Parties to ensure that no climate-related geoengineering activities that may affect biodiversity take place, "until there is an adequate scientific basis on which to justify such activities and appropriate consideration of the associated risks for the environment and biodiversity and associated social, economic and cultural impacts, with the exception of small scale scientific research studies…" that are subject to conditions (Decision X/33, paragraph 8(w)).

The rationale for having such a similar 'time-out' in relation to GDOs would be to create a pause in terms of releasing GDOs into the environment, including in field trials, therefore allowing the time to work out the details and to operationalise the necessary legal and regulatory requirements, including those applied to contained use. Such regulations should be developed by, for example, relevant UN bodies, ensuring broad international consensus. In our assessment, the CBD and its Protocols are the best place to do this (see Section 3).

This period of developing necessary international and national rules for GDOs should also be coupled with robust and meaningful public participation processes, as well as a reconceptualisation of risk assessment and risk management, which should be adapted to purpose them for the challenges and data limitations posed by GDOs. The right of communities or countries to *withhold their consent* also needs to be respected at all times.

Taking the time to get things right should not be construed as stopping the technology. Indeed, getting it wrong – releasing GDOs before appropriate regulation is in place or settling for insufficient governance – may be more costly, time-consuming and politically challenging than the front-end effort to get the settings right. Gene drive developers estimate that "any unauthorized release of a gene drive system would quite likely delay applications by a decade or more" (Esvelt and Gemmell 2017, 4), and "…inappropriately conducted field trials have the potential to negatively impact the future success of other gene drive products; to undermine community, stakeholder, and/or public confidence in the technology; and to contaminate the regulatory and funding environment" (James et al. 2018, 9).

5.2 What the CBD decision entails

The Parties to the CBD at COP 14, in November 2018, considered language calling on Parties and other Governments, in accordance with the precautionary approach, to "refrain from the release, including experimental release, of organisms containing engineered gene drives". While no explicit moratorium was decided upon at COP 14, strict precautionary conditions have been spelt out. They should be met before any introduction into the environment of GDOs, including for experimental or research and development purposes. The precautionary conditions stipulated directly in the COP 14 decision (14/19) relate to (i) carrying out risk assessments; (ii) having in place risk management measures; and (iii) obtaining the free, prior and informed consent (or equivalent at national level) of potentially affected indigenous peoples and local communities (see Section 2.1.1).

That decision also recalls previous COP decisions that laid out additional elements. These collectively include:

- effective regulatory systems consistent with the principle in international law of States' responsibility to ensure that activities within their jurisdiction or control do not cause damage to the environment of other States (which is very relevant to GDOs given the high potential for transboundary spread);

- addressing issues such as food security and socio-economic considerations with the full participation of indigenous peoples and local communities;

- establishing the right to take precautionary measures (which could include bans and moratoria), even in a situation where scientific knowledge is lacking;

- environmental impact assessment and allowing for public participation in such procedures;
- dealing with the consequences of extra-territorial impacts by promoting reciprocity, notification, exchange of information and consultation;
- immediate notification as well as action to prevent imminent or grave danger or damage beyond national jurisdiction;
- emergency responses and international cooperation for joint contingency plans when there is a grave and imminent danger to biological diversity; and
- examining liability and redress, including restoration and compensation for damage to biodiversity.

Taken together, the Parties to the CBD have effectively raised the bar for any releases into the environment of GDOs. Most importantly, the international community has pointed to the serious issues that must be addressed before any releases are even considered. This would mean that there has to be requisite time set aside to deliberate, and adequate processes put into place, to properly address these precautionary conditions.

The CBD decisions place implementation obligations on Parties, to which the United States – a non-Party – and any would-be developer, who wishes to be seen as operating in good faith, should adhere. Gene drive research and development is not an unregulated space that can be experimented in at will. In practice, it is simply not acceptable to the international community for anyone to release a GDO without properly addressing the issues that Parties to the CBD have laid down. Neither would it be right for one country to approve a release without the consent of other potentially affected countries and the local communities concerned.

5.3 Critical steps forward

In order to allow for the space and time to put in place legally binding governance arrangements at the international level, which should include the establishment and operationalisation of the elements identified in Section 4 and build on the CBD decisions, the following are critical steps forward in the interim:

Firstly, there should be **no intentional releases into the environment, including field trials, of any GDO**. While there have been calls for a 'phased testing approach' for GDOs, for example by the US National Academies of Sciences, Engineering, and Medicine, which recommended proceeding with laboratory research and highly controlled field experiments (NASEM 2016), there still remain serious concerns at the intergovernmental level about any release into the environment of GDOs, however small or isolated, as evidenced by the recent COP 14 decision (14/19) putting in place strict precautionary conditions.

For there to be well considered, internationally-agreed rules and procedures for the governance of gene drives and GDOs, there has to be a thorough pause, during which no field trials are conducted, because even small or isolated releases of GDOs can spread, thus defeating the purpose of this important waiting period.

Secondly, there should be **strict contained use standards applied to existing research and development in the laboratory, as well as strict measures for any transport of GDOs, to prevent escape.** The best available standards should be applied immediately while an intergovernmental process should be established to develop mandatory international laboratory safety standards for contained use research involving GDOs.

At the same time, there should be full transparency regarding on-going research projects; a register should be established and maintained to keep track of developments. This could be done under the CBD's auspices, particularly through the horizon-scanning process that is envisaged for synthetic

biology developments. At the national level, governments can improve oversight by requiring the licensure of experiments with GDOs in contained use.

Thirdly, **monitoring and detection for unintentional releases and unintentional transboundary movements of GDOs have to be conducted during this period, with emergency response plans in place.** This has to be done by both the authorities that have oversight and by entities conducting the research and development. Such monitoring is necessary, as unintentional releases may occur at any time and governments should remain vigilant even during a period where no environmental releases are officially permitted. The tools and materials for detection of unintentional releases of GDOs must be quickly developed and/or adapted, in order to enable effective and timely detection and identification.

Finally, the **international rules for this period of constraint, including for their enforcement and for liability and redress should there nevertheless be damage, must be effectively operational, including at national level.** This is necessary because even during such a pause period there is a need for enforcement and to ensure that any unintentional and also rogue releases are adequately dealt with, particularly if any damage results.

Giving pause will allow governance arrangements at the international level to be established and made operational, including mechanisms for joint decision-making by all potentially affected countries. All governments need to engage in fully informed discussions about the seriousness of this issue, aided by the relevant expertise and genuine public participation. In addition, the issue of dual use of gene drives must be effectively addressed at the appropriate fora. Ultimately, political will is required to ensure that the world puts in place effective, legally binding and enforceable rules that are necessary for gene drive technologies.

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Author biographies

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She has worked at the University of Oxford's Biodiversity Institute as science policy officer and is currently a research assistant at EcoNexus, based in Oxford, UK.

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Elisabeth Bücking

Dr. Elisabeth Bücking has a Ph.D. in Molecular biology. Presently she advises a farmers' association in Southwestern Germany. She is a member of the Environmental Council of the Evangelical Church in Badenia and of the state's Advisory Board on Animal Welfare in Baden-Württemberg. She takes part in a programme for vegetation mapping of the German Federal Agency for Nature Conservation.

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Irina Castro

Irina Castro is a junior researcher at the Centre for Social Studies (CES), University of Coimbra, in the Research group on Science, Economy and Society. In 2009, she graduated in Applied Ecology at the University of Trás-os-Montes e Alto Douro, in Portugal. In 2011 she received her MSc in Environmental Engineering and in the same year she joined CES as a research fellow for the project "Biosense - Science engaging society: Life Sciences, Social Sciences and Publics", coordinated by João Arriscado Nunes and funded by the Portuguese Foundation for Science and Technology (FCT). Since then she has collaborated in the development, promotion and evaluation of science communication initiatives and in the promotion of science-society relations, with a particular focus on the relationship between society and bio/nanotechnology. In 2013, she began her PhD at the doctoral programme Governance, Knowledge and Innovation (sociology branch), at the Faculty of Economy, University of Coimbra. In 2016 she was awarded with a scholarship from FCT to finish her doctoral studies.

Currently she is a junior researcher in the project "JUSTFOOD - From Alternative Food Networks to Environmental Justice", coordinated by Irina Velicu and funded by FCT. She is the author of several opinion, political and analytical online articles regarding the economic, scientific, environmental and social impacts of genetically modified organisms

and the use of agrochemicals, directed to the Portuguese audience.

Selected publications

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Doug Gurian-Sherman

Dr. Gurian-Sherman is currently a consultant on agriculture with Strategic Expansion and Training, LLC, in Minneapolis, Minnesota. He has recently advised civil society coalitions and organisations in the U.S. and Europe on issues of climate change and agriculture, pesticide alternatives, and genetic engineering. He is also an Honorary Research Fellow with the Centre for Agroecology, Water and Resilience at Coventry University. Prior to his current position, he worked as a senior scientist for nearly two decades with U.S. NGOs including the Union of Concerned Scientists and the Center for Food Safety. He was a staff scientist working on pesticides and genetic engineering with the U.S. Environmental Protection Agency in the 1990s. He collaborates closely with several science-based organisations including Twin Cities Science for the People and the Agroecology Research-Action Collective.

His work emphasises the importance of agroecological farming systems to address the challenges of growing food that enhances and relies on biological diversity, builds resilience, is good for the environment, and promotes food justice and democracy. His work analyses and compares the functions and interrelationships between agroecological approaches to agriculture in contrast to industrial systems and technologies. His analysis recognises the fundamental social and political context that inevitably shapes the value of technologies to society. This perspective rests on the importance of farming methods and technologies as parts of social systems, as well as based on their physical risks and benefits.

He holds doctorate and master of science degrees in plant pathology from the University of California, Berkeley, and a bachelor of science in natural resources from the University of Michigan. Recent work includes co-authorship of a proposed platform for food and agriculture in the Green New Deal (https://agroecologyresearchaction.org/green-new-deal/) and critiques of pro-GMO documentary film "Food Evolution."

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Tamara Lebrecht is Senior Scientist at GeneWatch UK, a not-for-profit organisation which aims to ensure genetic science and technology is used in the public interest. She is also the Executive Secretary of the Swiss association Critical Scientists Switzerland (CSS).

Before joining GeneWatch UK in 2014, she worked at the Swiss not-for-profit organisation Public Eye (then Berne Declaration) with a focus on agriculture, intellectual property and biodiversity and as a scientific assistant at the Swiss Federal Institute of Technology (ETH) in Zurich.

She completed her Master of Science in Ecology and Evolution in 2012 at the ETH in Zurich with a thesis on synergistic effects of Cry toxins on the ladybeetle *Adalia bipunctata*. During her master she also developed a management plan for the bottom-up control of the invasive banana *Musa velutina* with native plants at the Nature & Community Project Refugio De Vida Silvestre Privado Nogal of Chiquita Brands International in Puerto Viejo de Sarapiqui, Costa Rica.

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Lim Li Ching

Lim Li Ching has a B.Sc. in Ecology and an M. Phil. in Development Studies. She is a Senior Researcher at Third World Network (TWN), an international non-governmental organisation based in Malaysia, where she coordinates the Biosafety and Sustainable Agriculture Programmes.

Li Ching is a member of the Ad Hoc Technical Expert Group on Socioeconomic Considerations established under the Cartagena Protocol on Biosafety and the Ad Hoc Technical Expert Group on Synthetic Biology established under the Convention on Biological Diversity. She is also a member of the International Panel of Experts on Sustainable Food Systems (IPES-Food).

She was involved in the biosafety capacity-building programme of TWN and GenØk-Centre for Biosafety, Norway, and was on the faculty of the international biosafety course *Holistic Foundations for the Assessment and Regulation of Genetic Engineering and Genetically Modified Organisms* (2003-2012) and several other regional courses.

Li Ching was a lead author of the East and South Asia and the Pacific sub-global report of the International Assessment on Agricultural Science, Technol-

ogy and Knowledge for Development (IAASTD). She is co-editor of *Biosafety First: Holistic Approaches to Risk and Uncertainty in Genetic Engineering and Genetically Modified Organisms* (Tapir Academic Press, 2007), and *Climate Change and Food Systems Resilience in Sub-Saharan Africa* (FAO, 2011).

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Lim Li Lin

Lim Li Lin has a Bachelor of Laws (LL.B). She is a senior legal and environment advisor at Third World Network, an international NGO based in Malaysia, where she works with the biosafety and climate change programmes.

She is an active participant at numerous international fora, particularly at the UN Convention on Biological Diversity and its Cartagena Protocol on Biosafety, and in the negotiations of the Supplementary Protocol on Liability and Redress. She has served on a number of Cartagena Protocol on Biosafety advisory committees, including the Liaison Group on Capacity-building for Biosafety and the Biosafety Clearing House Informal Advisory Committee.

She has been an Advisor to GenØk-Centre for Biosafety, Norway and was involved in establishing the biosafety capacity building programme of TWN and GenØk-Centre for Biosafety. She was also on the faculty of the international biosafety course *Holistic Foundations for the Assessment and Regulation of Genetic Engineering and Genetically Modified Organisms* (2003-2012) and several other regional courses.

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Christopher J. Preston is a Professor in the Department of Philosophy and a Research Fellow at the Mansfield Center's Program on Ethics and Public Affairs at the University of Montana. His research focuses on the new epoch of the Anthropocene and the ethics of emerging technologies.

His academic publishing is in environmental philosophy, climate ethics, the ethics of emerging technologies, rewilding, and feminist philosophy. His books include *Saving Creation: Nature and Faith in the Life of Holmes Rolston, III* (Trinity University Press 2009) and *Grounding Knowledge: Environmental Philosophy, Epistemology, and Place* (University of Georgia Press 2003). His newest book, *The Synthetic Age: Outdesigning Evolution, Resurrecting Species, and Reengineering Our World* was released by MIT Press in March 2018 and will be translated into Chinese, German, and Japanese. He is also editor of two collections on the ethics of climate engineering.

Author of more than three dozen articles in environmental philosophy, Preston has been co-PI on two National Science Foundation grants on ethics and emerging technologies. He has been an external reviewer for the IPCC and the Convention on Biological Diversity. He is also the recipient of a Templeton Foundation grant and a participant in a Research Council of Norway's SAMKUL grant on genetic technologies. He maintains a blog (https://plastocene.com) with accessible essays on his research interests.

Selected publications

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Ricarda Steinbrecher

Dr Ricarda Steinbrecher is a biologist and molecular geneticist based in Oxford, UK. She received a PhD from the University of London, UK, and a first class honours M.Sc. from the University of Kiel, Germany. First specialising in gene regulation and gene modification, she worked in the field of mutational analysis, gene identification and gene therapy. Since 1995 her focus has been on biosafety aspects of genetically modified organisms and their potential impacts. More recently her work focuses on synthetic biology, new genetic engineering techniques such as CRISPR/Cas9, and gene drive organisms.

Dr Steinbrecher is co-director of EcoNexus, a public interest research organisation consisting of scientists and dedicated experts focusing on new

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She has been actively involved in UN-led international processes since 1996, especially of the Convention on Biological Diversity (CBD) and its protocols, in particular the Cartagena Protocol on Biosafety (CPB). She served on the Ad Hoc Technical Expert Group on Risk Assessment and Risk Management of Genetically Modified Organisms (2009-2013) of the CPB and presently serves on the Technical Expert Group on Synthetic Biology of the CBD.

Dr Steinbrecher is a member of the Federation of German Scientists (FGS/VDW) whom she represents at the international UN negotiations, and a founding member and board member of the European Network of Scientists for Social and Environmental Responsibility (ENSSER).

Selected publications

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Helen Wallace

Dr. Helen Wallace is the Director of GeneWatch UK, a not-for-profit organisation which aims to ensure genetic science and technology is used in the public interest.

She has published widely on the social, environmental and human rights issues associated with the use of genetic technologies worldwide, ranging from genetically modified organisms (GMOs) to human genetic databases. Since 2010, her research has included issues associated with open releases of genetically modified insects into the environment.

Before joining GeneWatch UK in 2001, she worked as an environmental scientist in academia and industry and as Senior Scientist at Greenpeace UK. Dr. Wallace has a degree in physics from Bristol University and a PhD in applied mathematics from Exeter University.

Selected publications

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Mark Wells

Dr Mark Wells is a biological chemist and researcher for EcoNexus, a public interest research organisation, where he focuses on new genetic technologies. He has experience in the sustainability sector, most recently at the Centre for Sustainable Energy in Bristol, and prior to this nine years of research experience in molecular biology and protein chemistry. Mark completed his PhD studies in the biochemistry of prion diseases (of which BSE, or mad cow disease, is the best known example) at the University of Sheffield. He was a post-doctoral researcher at the Medical Research Council Centre for Protein Engineering in Cambridge, before joining a bio-technology start-up developing new bio-fuel technologies. He holds an M.Chem. in Biological Chemistry from the University of Sheffield, and a P.G.Cert. in Sustainable Development in Practice from the University of the West of England.

Selected publications

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Fern Wickson

Dr. Fern Wickson is the Scientific Secretary of the North Atlantic Marine Mammal Commission (NAMMCO) and a Senior Advisor at GenØk Centre for Biosafety in Tromsø, Norway. She completed an interdisciplinary PhD across the natural and social sciences at the University of Wollongong in Australia on the environmental regulation of genetically modified crops and attained a first class Honours degree in Environmental Politics from the University of Tasmania.

Committed to a politics of ecological care, Wickson seeks to integrate environmental science, policy and philosophy with a particular specialisation in the governance of new and emerging technologies. With her transdisciplinary work she specifically aims to advance ecological and feminist ethics, sustainable agriculture and agricultural biodiversity conservation, responsible research and innovation and resilient socio-ecological futures. She is author

of over 40 articles in peer-reviewed journals and co-author of the book *Nano meets Macro: Social perspectives on nanoscale sciences and technologies* (Pan Stanford Publishing: Singapore 2010).

Wickson has served as an expert delegate to the Intergovernmental Panel on Biodiversity and Ecosystem Services (IPBES) working group on the diverse conceptualisation of values in nature. She is also a member of the Norwegian Biotechnology Advisory Board and past president of the international Society for the Study of New and Emerging Technologies (S.Net) as well as former board member of the European Network of Scientists for Social and Environmental Responsibility (ENSSER). In 2018, she completed the Homeward Bound Global Leadership Program for Women in Science.

Selected publications

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Since 2015 the Critical Scientists Switzerland (CSS) promote independent and unbiased science and research as well as transdisciplinary and participatory research approaches and agendas. Science and research should serve the public interest and help our society during the necessary transition towards a more sustainable way of life.

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