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.