RECIPES

Precaution • Innovation • Science

New gene-editing techniques:
a focus on CRISPR-Cas9 gene drives

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Abstract

The main research aim of this RECIPES case study is to understand the complexities and controversies around the possible application of the precautionary principle to CRISPR-cas9 based gene drives. The study focuses on the risk governance of gene drives at the EU level, while taking into account the broader international context.

Synthetic gene drives could be used to spread artificially modified genes through wild populations faster. The development of this technology has taken flight since the 2012 discovery of CRISPR-cas9, a new tool capable of engineering the genomes of diverse species. Gene drives promise to enable the suppression or even elimination of a population, or to make a population more resilient. So far, CRISPR-cas9 based gene drives laboratory research has been done in yeast, fruit flies and three different mosquito species.

Gene drives are increasingly becoming important areas of public health and biosecurity research. They are aimed at the improvement of human health through the elimination of vector borne-disease, for conservation purposes through the elimination of invasive species or gain of function of the species under threat, and for agriculture, through the elimination of pests and weeds. The main promise of a gene drive is that it would spread itself, but at the same time, release into the environment can also give rise to systemic risks. In addition, gene drives could have economic and social effects that are beneficial in the short term, but fail to take into account more fundamental issues like poverty or climate change.

Experience with current methods of risk assessment offers little knowledge about the release of a gene drive into the environment. In order to reduce epistemic uncertainty, research activities (field trials) must be undertaken that themselves pose risk. This translates into great challenges for the regulation of gene drives that are further exacerbated by the technology being able to spread beyond regulatory borders.

The EU works under the Convention on Biological Diversity (CBD) and the Cartagena Protocol on Biosafety, that allow for some, well-regulated risks in gene drives research. Currently in the EU, CRISPR-cas9 and gene drives are within the scope of GMO regulations. GMO developers have to apply for authorization under the Deliberate Release Directive. This application process has not resulted in authorization for cultivating GMOs in the EU since 1998.

In 2018, the European Food Safety Authority (EFSA) was mandated by the European Commission to identify potential risks in terms of impact on human and animal health and the environment that gene drive modified organisms could pose and to look for potential novel hazards of gene drive modified organisms. They have concluded that the risk assessment approach for gene drives can build on the existing comparative risk assessment paradigm for GMOs, but that some aspects, including the effect on a population level of the inheritance of the selfish genetic element and the large step to open field-testing, require further consideration or updated guidance.

The possible risks associated with gene drives have also been governed in ways other than laws and regulations. As gene editing techniques become more accessible and democratized, there is a rapidly expanding international ecosystem of actors involved in a heated discussion around this technology. Scientists are taking it upon themselves to fill the regulatory gap by designing soft rules for application, engaging with the public, and also developing technological ways to reduce the risks of field testing.

The findings of this study suggest that a precautionary approach does not need to block innovation. All stakeholders involved seem to agree that a precautionary approach to gene drives is necessary, including the scientists developing gene drives. However, there is less agreement on what this approach would entail. Some argue that if applied in an earlier

research phase, precaution could lead to other innovation pathways that depart from the underlying causes of the problem. Others see a solution in building precaution into gene drives that are safe by design. In both approaches, the engagement of a broad group of stakeholders in early research phases is crucial. Risk governance should not only focus on mitigating risk, but also on the promotion of research opportunities with aims and in contexts that justify the use of particular types of gene drives and have a responsible business model- while keeping in mind alternative ways of approaching the problem that gene drives aim to solve. This is not something that gene drive scientists can do alone.

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List of abbreviations

CA	Consortium Agreement
CBD	Convention on Biological Diversity
CC	Consortium Committee
DARPA	Defence Advanced Research Projects Agency
DOA	Description of Action
EFSA	European Food Safety Authority
ERA	Environmental Risk Assessment
FDA	Food and Drug Administration
GA	Grant Agreement
GMA	Genetically Modified Animal
GMO	Genetically Modified Organism
LMO	Living Modified Organism
PCG	Project Coordination Group
PO	Project Office
RIVM	Dutch National Institute for Health and the Environment
WP	Work Package

1 Introduction

Usually, a genetic change in one plant or animal takes a long time to spread through a population. That is because the gene is inherited by only half the offspring (Ledford 2015). Gene drives promise to facilitate the spread of artificially modified genes through entire populations (Frieß et al, 2019). This way, populations in the wild could be suppressed or replaced by a genetically modified one. Gene drives are present in nature, and using CRISPR-cas9, a new genetic modification technique, they can also be created synthetically. Gene drives promise to contribute to public health, the conservation of nature and agriculture. So far, CRISPR gene drives laboratory research has been done in yeast, fruit flies and three different mosquito species (Raban et al, 2020).

The past years have however witnessed a heated debate about the application of gene drives. For the layperson –and this includes many regulators– it is difficult to make sense of the disparate viewpoints represented in the debate: extreme benefits versus extreme danger, worst versus best case scenario's.

Gene drives promise to promote public health by eradicating populations of organisms that transmit infectious pathogens between humans (vectors), such as mosquitos transmitting dengue or malaria. For the conservation of species, gene drives can be used to either eliminate threats (for instance, invasive pests) or to adjust the threatened population. Potential benefits of using gene drives compared to other technologies are its potentially rapid effect targeted to a specific population, and the ability to reach remote areas that are difficult to access.

However, the capability of gene drives to spread and invade, which is necessary to genetically engineer wild populations of animals and plants, can also be considered its greatest risk. A lack of spatio-temporal control could potentially affect whole species and/or associated ecosystems (Cotter et al, 2020). The uncertainty about these risks is substantial, and the interaction between gene drives and the environment requires an entirely new field of knowledge. Problematically, the field trials necessary to learn more about these risks are themselves not without risk. Caution is therefore warranted in taking the (research) steps necessary for implementation.

In 2019, calls for a global moratorium at the United Nation Convention of Biological Diversity were dismissed, although precautionary steps were taken in requiring a step-by-step, case-by-case risk assessment of gene drives research. There are layers of uncertainty, complexity and ambiguity present in both the scientific evidence and the governance of risks associated with gene drives. This makes this technology an interesting case for learning about the complexities and controversies around the application of the precautionary principle- the main aim of RECIPES WP2.

The study focuses on the risk governance of gene drives at the EU level. As gene drives are a technology that can cross regulatory boundaries, the broader international context was also taken into account. The research was conducted through a literature review, and results were validated during three interviews with gene drive experts.

Key timeline

Political	*Legal*	*Science/risk assessment*	*Public debate*	*Other*

Year	Event	Relevance to case study
1960	Craig, Hickey and VandeHey publish 'An Inherited Male-Producing Factor in Aedes aegypti' in *Science.*	First proposal theoretical concept for gene drives.
2001	The EU Directive 2009/41/EC on the contained use of genetically modified micro-organisms becomes effective.	This Directive explicitly takes the precautionary principle into account and sets out a step-by-step approach for introduction of a GMO into the environment.
2003	Burt publishes 'Site-specific selfish genes as tools for the control and genetic engineering of natural populations' *in Proceedings of the Royal Society.*	First proposal to synthetically engineer gene drive using homing endonucleases.
2003	The Cartagena Protocol on Biosafety to the Convention on Biological Diversity becomes effective.	The Biosafety Protocol makes clear that products from new technologies must be based on the precautionary principle.
2009	The EU Directive 2009/41/EC on the contained use of genetically modified micro-organisms becomes effective.	The Contained Use Directive establishes that risks to human health and the environment of the contained use of a new GMO must assessed before research commences.
2012	Jinek et al publish 'A programmable dual-RNA–guided DNA endonuclease in adaptive bacterial immunity' in *Science*.	First proof of principle that CRISPR-cas9 can be used to perform genome editing.
2014	Oye et al publish 'Regulating Gene Drives' in *Science*.	First CRISPR-cas9 gene drive reported.
2015	Liang, P. et al publish 'CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes' in *Protein Cell.*	First successful applications of CRISPR Cas9 in humans.
2016	At the Conference of the Parties of the Convention for Biological Diversity, environmental activist organizations call for a global moratorium on field research.	A global moratorium would invoke a strong interpretation of the precautionary principle (this call was rejected).
2018	The European Commission gives the European Food Safety Authority (EFSA) a mandate to determine whether the existing guidelines for risk assessment are adequate and sufficient for gene drive modified organisms.	First time the EU considers gene drives as a new genetic technique that warrants a potentially specific approach.
2019	Again, at the Conference of the Parties of the Convention for Biological Diversity, environmental activist organizations call for a global moratorium on field research.	A global moratorium would invoke a strong interpretation of the precautionary principle.

2019	See above. A global moratorium is rejected, and the Convention allows some, well-regulated risk in gene drives research.	This is a "weak" interpretation of the precautionary principle.
2020	The EFSA publishes 'The 'Evaluation of existing EFSA guidelines for the adequacy for the molecular characterization and environmental risk assessment of genetically modified insects with synthetically engineered gene drives'.	The EFSA concludes that the risk assessment approach for gene dives can build on the existing comparative risk assessment paradigm for GMOs, although some aspects need specific consideration. What this means in practice remains yet unclear.

2 Gene Drives

Essentially, a gene drive is a genetic element that allows a trait to be inherited more frequently than normally seen in Mendelian inheritance. In other words, they cause more offspring to have the driven genetic trait than individuals in the parent population, allowing "one to affect many" (Esvelt, 2017).

The idea of 'driving' a particular gene through a population is not new. In 1950, Hermann Muller, who was awarded a Nobel Prize for his work on radiation-induced genetic mutations, received a letter from entomologist Edward Knipling asking him whether genetically sterilized pest insects could be used to eradicate damaging species. This led to the rearing and release of hundreds of millions of irradiated insects to successfully eradicate screwworm, a major cattle pest in the US. In order to broaden the reach of this technology, researchers continued to think about means by which genetic traits could spread through a population even though they decreased the insect's fitness (Brossard 2019). This idea would however take several decades to be put into practice. A theoretical concept for gene drives was proposed in 1960 by Craig, Hickey and VandeHey (1960) and Hastings (1994) suggested to use so called "selfish genes" for that purpose. In 2003, Burt introduced the possibility of using naturally occurring selfish 'homing endonucleases', a genetic element that copies itself onto the competing allele. This made gene drive research possible, but because this enzyme is sequence-specific, it remained a challenge to target specific sequences of DNA of interest (Champer, 2016). It was only after *CRISPR-Cas9* (see box 1) was discovered that the technology for creating gene drives became more effective.

Box 1: Synthetic biology, CRISPR-cas9 and genetic engineering

Synthetic biology is a multidisciplinary field of science that seeks to develop innovative approaches for engineering new biological systems or re-designing existing ones for useful purposes. Recent advancements in this field have provided broadly applicable tools capable of engineering the genomes of diverse species, the most promising of which is CRISPR-cas9 (Champer 2016).

The acronym CRISPR stands for Clustered Regularly Interspaced Short Palindromic Repeats. These are particular patterns in the DNA code that were discovered in bacteria in 1987. It took until 2007 before its function was understood: it is part of a natural defense mechanism of bacteria against viruses, together with the so-called Cas9 enzyme (CRISPR-associated protein-9 nuclease) that can cut the double helix of DNA. So-called guidance RNA tells the Cas9 enzyme in which precise location in the DNA it should cut. Inspired on this mechanism a precision genome editing tool named CRISPR Cas9 was

developed in 2012 (proof of concept) and first successfully applied on mouse and human cells in the lab in 2013 (Ledford 2015).

CRISPR Cas9 has become a very popular tool for genetic engineering of its many benefits. First, it is applicable to all species. Second, it is cheap and fast: what was a 4-year PhD project with the previous genome editing tools you can now do in a few days. Third, it is precise: it can recognize sequences of as little as 20 base pairs and can edit single base-pairs. Fourth, it is supported by widely accessible online tools to design and order the target sequence and to online-order the matching guidance-RNA for the target. Fifth, it is easy to use: BSc level biology lab skills are enough and the required basic lab-equipment can be ordered online by all, making the technology accessible and suitable for amongst others DIY/garage biologists (Ledford 2015).

CRISPR is a genome editor that differs from conventional genetic engineering used in most genetically modified organisms (GMO's). Conventional genetic engineering is based on recombinant DNA, which involves either the combining of DNA from different genomes or the insertion of foreign DNA into a genome.

In gene drives, the CRISPR mechanism -essentially molecular scissors that cut DNA at specific locations and delete or replace sections- is inserted into the reproductive cells of the organisms, together with the new, 'driven' gene. This allows a mutation made by CRISPR on one chromosome to copy itself to its partner in every generation, so that nearly all offspring will inherit the change (Ledford, 2015). As a result, with each generation, the driven gene will be present in a larger part of the population. Gene drives can be used to supress or even eliminate a population when they decrease fitness, induce sterilization, or lead to death before propagation. Gene drives that increase fitness can be used to make a population more resilient.

Gene drives are becoming increasingly important areas of public health and biosecurity research. They have attracted significant investment, with the Gates Foundation pledging US$75 million and the Defence Advanced Research Projects Agency (DARPA) awarding US$65 million (Faunce et al, 2018).

However, despite having a history of half a century, gene drives research is still in an early stage. Although it has been hypothesised that gene drives could be developed for most species that reproduce sexually (Faunce et al, 2018), engineered gene drive systems for vertebrates are currently only theoretical. Technology development for application to invertebrates is further developed, both in-silico (mathematical modelling on computers) and in the laboratory (Redford et al, 2019). In March 2015 the first successful CRISPR gene drive application in the lab was reported (Gantz and Bier, 2015).

Potential applications

All the benefits that will be described below are hypothetical, as the gene drive has yet to leave the lab. The benefits of gene drives would differ per application. There are gene drive approaches aimed at the improvement of human health, for conservation purposes, agriculture and for the advancement of scientific knowledge (Redford et al, 2019). In some applications benefits would be multifold: a reduction of the use of pesticides in vector control or agriculture would also better the environment.

The main focus of gene drives research encountered in the literature is human malaria. Malaria has led to an estimated 435.000 deaths worldwide in 2017 (WHO, 2018). Travel, trade and climate change could bring these infections to new regions (Mitchell et al, 2017). Infected persons require long periods of treatment and recovery, and can suffer life-long losses of capacity and productivity (WHO, 2018). Target Malaria[1], a large, non-profit

1 See https://targetmalaria.org/ . This organisation is primarily funded by the Bill & Melinda Gates Foundation and the Open Philanthropy Project.

research consortium, is researching the reduction of the mosquito population with the aid of genetically modified mosquitoes, preferably with a trait that will manifest itself in the mosquito population through a gene drive. This could be done by spreading infertility amongst female mosquitoes, or by eliminating the trait that makes it possible to find blood.

Endemic diseases and parasites impose large burdens on tropical and sub-tropical regions. Using gene drives to eliminate or greatly reduce the malaria mosquito and other vectors that transmit endemic diseases and parasites would therefore have indirect economic and demographic effects and could increase wellbeing. Resources available to fight these diseases would become available for other purposes (STOA, 2019).

Another example of vector control is the theoretical plan to release genetically modified mice in Martha's Vineyard, an island on the East coast of the US, to battle Lyme's disease. Because mice are the primary host of the ticks that carry Lyme's disease, their elimination would lead to the reduction of this disease (Elvin, 2017).

Gene drives could potentially also be used for conservation. When natural barriers that isolate natural populations break down, invasive species can cause great damage to the functioning of ecosystems, infrastructure and agriculture.[2] For example, invasive rodents are threatening endemic bird populations in New Zealand. When gene drives are used to eliminate invasive species, this would reduce the need for current control techniques, which include chemical and physical management (Redford et al, 2019).

Gene drives could also possibly contribute to conservation by genetically adapting the population under threat. This is referred to as 'genetic rescue' and examples are improving species resilience/resistance to climate change or disease, or their viability by increasing genetic diversity (Redford et al, 2019).

Last but not least, gene drives could provide agricultural benefits. Researchers are pursuing applications that enable controlling a number of economically significant agricultural pests like Lepidopteran insects and spotted wing Drosophila (Brown, 2017). They could also be used in weeds to eliminate any developed resistance to herbicides. This is a contested application as this would benefit the planet less than the corporation selling the herbicides (Kahn, 2020).

What is the innovation of synthetic gene drives?

The main promise of gene drives is that they would spread themselves, making it possible to manipulate populations in the wild and to reach areas difficult to access. Gene drives could thus benefit people's health in remote communities or eliminate invasive pests in large conservation areas. An additional advantage of gene drive vector control methods could be that once released in a particular area, all people living in that area will receive equal benefit. Furthermore, when gene drives for specific organisms have already been developed, they can be used to respond relatively rapidly and precisely to pests or disease (Redford et al, 2019). For example, in New Zealand, the invasive rodents would otherwise keep returning, as they arrive with ships on a regular basis.

In order to further understand which innovation gene drives bring, we compare them to specific other technologies and alternative measures. In the literature, a comparison is often made between CRISPR-Cas9 gene drives and genetic modification, especially when organisms are modified on a population level. Some researchers consider gene drives to be a special class of genetic modification with a potentially high technological power and range (Frieß et al, 2019). However, the application of gene drives is limited to organisms that reproduce sexually and have short generation spans. Therefore, they cannot be used to synthesize or modify bacteria and viruses (as they reproduce asexually), and would not be effective on humans (as they have a long life span) (NASEM, 2016).

2 See https://www.theatlantic.com/science/archive/2017/11/new-zealand-predator-free-2050-rats-gene-drive-ruh-roh/546011/

As shown in the other RECIPES case on GMOs (Kozarev, 2020), GMOs have been widely criticized for negatively influencing the availability of genetic and knowledge resources and ecological sustainability. Currently, most GMOs are applied in the agricultural sector (Mitchell and Bartsch, 2020). However, due to their nature, gene drives in agriculture would serve a different purpose. While genetic modification is used to enhance crops, gene drives would be used to change the pests threatening those crops. Gene drives are less applicable to crops and livestock: crops are kept under human control as new seed is planted each season and livestock have a relatively long life cycle.

In recent years, GMOs have been used for vector management. For example, a number of field tests have been carried out in Brazil and Panama, among others, with genetically modified (GM) mosquitoes of the species Aedes aegypti. This mosquito species is responsible for transmitting the Zika virus, yellow fever and dengue, among others. The company Oxitec changed the male mosquitoes' DNA in a way that they live for only four days and their offspring never develops beyond the larval stage. When these males are released in nature in large quantities, they compete with the natural population, and the mosquito population decreases. Oxitec has published positive results[3], although a report by Gene Watch strongly doubts the effectiveness of this method (2018). However, this approach would require the release of millions of genetically modified insects –a problem that would be solved by using gene drives.

For some proposed applications of gene-drive modified organisms there are other existing strategies to address the issue (NASEM, 2016). Alternatives for gene drives are for example mosquito nets, bug repellents, vaccination, the use of pesticides but also the conventional breeding or genetic modification of disease resistant crops. Gene drives are mostly being thought of a technology that can be used in addition to other measures: for malaria, mosquito nets and DDT would still remain in use. They are also seen as 'last mile' interventions: the final stages of an elimination or eradication programme, when disease is still circulating, although at much reduced levels (Redford et al, 2019).

3 Risks and scientific uncertainties

3.1 Risk/threat

Stirling (2008) describes the conventional science-based understanding of risk as the combination of what may happen – the hazards, possibilities, outcomes – with the likelihood that it might happen.[4] But this raises the question: what constitutes a hazard? It is not possible to consider risk without also taking into account cultural values (Shrader-Frechette, 1991) because 'what is at stake' will be considered differently by different actors. In the following section, we describe risks from this broad point of view.

Potential consequences of gene drives

New genetic engineering techniques can produce unexpected and unpredictable effects in the resultant organisms. In contrast to other genetic modification technologies, gene drives are designed to spread, invade and persist in the environment (Frieß et al, 2019). Their way of operating therefore make gene drives difficult to contain and these unexpected/unpredictable effects can be irreversible (Redford et al, 2019). We describe two elements of the technology's risk profile separately: the integration of the gene drive construct into the genome in the laboratory (contained use), and the release of the resulting modified organism in the environment.

The contained application of gene drives brings with it biosafety and biosecurity risks. These include accidents or the possibility of deliberate misuse. Gene drives cannot be used

3 See https://www.oxitec.com/en/public-health

4 See WP2's Conceptual Framework, pp 22.

for asexually reproducing viruses or bacteria with pandemic potential, but their propensity to spread beyond control could pose a major risk to the environment (NASEM, 2016).

Ultimately, release into the environment is an essential part of gene drives, if the technology is to be used for the modification of wild populations. This brings with it systemic risks that are mainly ecological risks but also concern our public health. The magnitude of these risks will differ by species and by nature of the change (Esvelt, 2017). Both the short- and long-term consequences of genetically engineered populations on the functioning of ecosystems and biodiversity are difficult to predict and could include impairment of ecosystem resilience.

When gene drives are used in the adaptation of species, there is a risk for adverse effects involving non-target impacts: the enzyme used for the gene drive may increase mutations in organisms it is applied for (STOA, 2019). Recent studies have shown that CRISPR Cas9 is not as precise as is sometimes proclaimed. Off-target mutations occur –and they do so more frequently in higher organisms (Fu et al, 2013)– because the bespoke guidance-RNA (see Box. 1) that tells Cas9 in which precise place it should cut (the target site) will also fit to off-target sites where duplicates of that code-sequence in the DNA are stored. There, it can have unintended effects. But unintended effects on target also occur: Kosicki et al (2018) reported that the natural repair mechanism of cells after double-strand breaks induced by CRISPR–Cas9 can lead to large deletions and complex rearrangements at the targeted sites in the DNA, with possible pathogenic consequences.

Gene flow, the transmission of genes from one species into the gene pool of another species (Cotter et al, 2020), is also possible. It has been observed in the Anopheles mosquito complex, a set of closely related species, some of which transmit the malaria parasite, but never between other species (STOA, 2019).

Where synthetic biology is used to alter the fundamental niche of a species, it could potentially alter the ecological and evolutionary trajectories for that species, with potentially adverse long-term consequences. For example, when an adaptation to climate change is engineered, and climate change is eventually reversed, the organism would be mal-adapted (Redford et al, 2019).

Releasing gene drives into the environment also brings with it a potential health risk. For example, other disease-spreading species could gain momentum if the mosquito species that spread malaria are supressed (STOA, 2019).

Wide accessibility and malicious intent

As described above in Box 1, CRISPR-Cas9 is a relatively accessible technology in terms of cost and skill required. In theory, this makes it possible for a single researcher to alter ecosystems (Esvelt, 2017). For example, a team of students competing at iGEM (a yearly student competition in synthethic biology) attempted to build gene drives. Although they did not succeed, this does show that the necessary tools are available (Redford et al, 2019). This amount of technological power in the hands of anyone capable of harnessing CRISPR technology is not without risks, even if thoroughly regulated.

Another risk difficult to regulate is the deliberately malicious use (dual use) of gene drives. In the past, insects have been used for biological warfare[5] (Lockwood, 2008). Just like mosquitos can be made unfit for carrying malaria, they can conceivably be designed to carry and spread an extra lethal cargo using gene drives (Gurwitz, 2014). Similarly, research into gene drive strategies for crop protection could also be used for agro-terrorism (Kupferschmidt, 2018).

[5] Regulated by the United Nations Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction, see https://www.un.org/disarmament/wmd/bio/

Secondary effects and moral hazard

The economic and social effects of this technology are not straightforward. Crop technologies can be profitable at the individual farm level and for early adopters, but used on a large scale they can also decrease prices and reduce farm income because larger supplies lead to lower prices (Mitchell et al,2018). This could also be true for vectored diseases: the technology could directly increase individual welfare, but may have more mixed aggregate effects. For example, with regard to malaria, the technology distracts from underlying conditions of poverty, inequality and lack of education that create human vulnerability to mosquitos in developing countries (Braverman, 2017). The development of technology aimed to correct symptoms of more fundamental socio-political problems result in a type of 'moral hazard', and some consider gene drives a technological fix that may distract from dealing with the system failures that cause public health and conservation issues in the first place (Redford et al, 2019).

What is more, gene drives are likely to continue the growing dependency on technologies, as we have already witnessed in modern agriculture. For instance, to keep populations of malaria mosquitos low, periodic releases of gene drive mosquitoes might be required (STOA, 2019). What if a disease is removed from the environment, only to return when local immunity is reduced (EFSA, 2020)?

With regard to conservation, the possibility of applying gene drives enable a vision in which traditional habitat and species protection can be replaced by technology that makes species and habitats resilient to new stresses (Redford et al, 2019). But the patenting of this technology would result in increasing dependence on biotech corporations for the preservation of ecosystems. This is a concern because these systems fulfil essential public services like food, clean air, water control, pest control, waste decomposition, medicinal resources, recreational services, resources for local economies etc. If the unintended effect of gene drives is the loss of ecosystem resilience, this hits those with low socioeconomic status harder and in this sense discriminatory. However, because these effects are indirect, they frequently are not taken into account in cost-benefit or risk analyses.

3.2 Scientific analysis

Although scientists have been investigating gene drives for decades, the assessment of risks did not seem pertinent because the technology was weak and its development was incremental. However, the scientific breakthrough of CRISPR-Cas9 has quite suddenly made applications possible that were not before, raising immediate question pertaining to safety and ethics more generally (Kahn, 2020). As discussed previously, the risk profile of gene drives consists of two elements which are researched (and governed) differently: the integration of the gene drive construct into the genome, and the release of the resulting modified organism.

Traditionally, biosafety focuses on work within laboratory spaces and transport between laboratories and the containment of agents that should never leave the laboratory. The key criterion for determining the risk of work in biological laboratories is the risk of harm to human health (Lunshof, 2017). However, scenarios using models of yeast, mice and fruit flies developed by the Dutch National Institute for Public Health and the Environment (RIVM) show that the escape of a gene drive organism would especially have unpredictable consequences for the environment. Moreover, a gene drive can spread rapidly and permanently in a population, and may also cross national borders (Van der Vlught et al, 2017). The experience with the current method of risk assessment offers little knowledge about these aspects.

Field release with research purposes is at least a few years away and expectations are that a fully evaluated technology to control disease vectors will not be available for another 10 years. This is partly due to the large amount of knowledge necessary to assess the technique's safety and efficacy (Redford et al, 2019).

Some aspects of this knowledge can be obtained by modelling environmental impacts and from experience with similar technologies or application domains (2020). Computational models have recently been used to model the potential spread and persistence of engineered gene drive organisms without actually releasing them into the environment. To feed the models, behavioural and demographic data and a good understanding of the mating system and of gene flow between target and non-target species is necessary (Mitchell and Bartsch, 2020). However, the assessment of hazards still lacks adequate criteria, methods and models (Frieß et al, 2019).

Scientists are also learning from experience with similar technologies or application domains, like situations where GMOs have been detected in wild plant populations due to seed or pollen movement and the control of pest animals (Mitchell and Bartch, 2020). Oxitec has already paved the path for genetic work on mosquitoes through its introduction of sterile male mosquito populations that are periodically released (Braverman, 2017).

The European Food Safety Agency (EFSA) has recently (17 feb 2020) released a draft opinion of the Scientific Panel,[6] assessing the adequacy of current guidelines for the environmental risk assessment (ERA) of genetically modified animals (GMAs) for gene drive modified disease-spreading mosquitoes and agricultural insect pests, and the potential for novel hazards/risks associated with deliberate release. This assessment was done based on the scientific literature and consultations with stakeholders. It takes into account ecology and population dynamics and experience from existing vector/pest control strategies.[7] According to the draft report, the following aspects require further consideration or updated guidance: gene drives in insects not intended for food/feed uses, the effect on a population level of the inheritance of the selfish genetic element, the large step to open field-testing, and the definition of case-specific information required to support risk assessment.

3.3 Scientific uncertainty

3.3.1 Complexity

According to Frieß et al (2019), the technology of synthetic gene drives constitutes a tipping point in the development of genetic engineering, due to their inherent capability to spread and invade. Once introduced into the wild, the technology could cause a cascade of population dynamics and evolutionary processes (NASEM, 2016). Not only do gene drives affect the environment, the environment also affects the gene drives. A complicated interwoven web of biotic and abiotic factors give rise to a large degree of ecological and evolutionary complexity (Frieß et al, 2019). Even with the most sophisticated computer models and risk assessment systems, the result of introduction into the wild is difficult to predict (NASEM, 2016). Importantly, the results may be partly or wholly offset by unintended, aggregate and long-term ecological and economical effects that play out through complex feedback loops (Mitchell et al, 2018).

Complicating this further is the imagined range of gene drive applications, each with their own impacts. Applications diverge with respect to the types of systems they are built into (i.e. health, agricultural or natural systems), their social contexts (in different regions of the world and in different types of applications) and the values underlying their application (Sandler, 2017).

3.3.2 Uncertainty

Gene drives are associated with a large degree of epistemic uncertainty. In the end, models of the application in nature will never perfectly capture ecological, biological and social

6 See http://www.efsa.europa.eu/en/consultations/call/public-consultation-gmo-panel-scientific-opinion-evaluation.

7 See https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2012.2501

contexts, especially in regard to long term impacts. In addition, more research data is required to determine if the modelled spread causes actual harm.

To challenge model predictions and solidify scientific understanding, experimental evidence is necessary (Redford et al, 2019). This is problematic, as inherent risks of the technology cannot be analysed without release into the environment, where control over the technology has to be given up, to some extent. There is no safe space (Guttinger, 2019). There is also no consensus on what type of (geographically isolated) field sites may be best for trialling genetic biocontrol (Redford et al, 2019). So in order to reduce epistemic uncertainty, research activities must be undertaken that themselves pose some risk (Redford et al, 2019). This trade-off between reducing uncertainty and avoiding risk will challenge the decision making process (Mitchell and Bartsch, 2020).

Furthermore, implementation of gene drives could also result in 'random' effects, as an ecological system –the wild– behaves in different and complex ways (variability uncertainty). Frieß et al (2019) argue that gene drives could have great spatio-temporal consequences, as they can be self-sustaining for multiple generations and potentially undergo mutational changes over time. The CRISPR/Cas9-gene drive technology could also fail, with unknown environmental effects. This means that the non-knowledge (known- and unknown unknowns) about the possible consequences of gene drives is high, reaching "from enormous scientific uncertainties to vast ignorance" (Frieß et al, 2019, p. 22). Taking into account possible malicious intent or an unstable international legal order further augments these uncertainties.

However, not all researchers agree there is uncertainty about risks that are potentially large. Experts at the Scientific Foresight Unit workshop on gene drives (STOA, 2019) argued that gene drive technology is not a silver bullet and that complete eradication of a species was deemed impossible, as even smallpox has not been completely eradicated. According to Kevin Esvelt (2017), a prominent researcher in the gene drives field, it is not easy to make changes to a system evolved to optimize reproduction –a gene drive would cause a fitness burden. He argues that "ecosystems are not so fragile that an accidental release from a laboratory would cause problems. It would take careful engineering to build a gene drive that can't be blocked by a natural DNA sequence variation" (genetic resistance). In addition, because it would take many generations for a population to become extinct, there would be enough time to block this process, for example by immunizing populations to the gene drive with a secondary gene drive.

3.3.3 Ambiguity

The literature also shows cases of interpretative ambiguity. Scientists from different research fields have different perspectives on the impact gene drives could have, just like they do in regard to GMO's (Hilbeck et al, 2020). Some reviews, like a meta-analysis by Frankham (2015), show that genetic rescue has increased the fitness of populations. Others argue that genetic rescue could create unforeseen problems and overlooks underlying problems that threaten species (Redford et al, 2019). Mitchell (2018) argues that this also holds true for economic effects: policy makers and researchers often focus on the direct effects, while applications could also generate unintended negative social impacts in the long term. We would argue that in such a complex field of study, it is not feasible for one person to have a complete overview and deep insight into the factors at play. For example, Braverman (2017) mentions that the gene drives scientists she interviewed were under-educated in all matters ecology related.

Another point of interpretative ambiguity is the extent to which gene drives should be considered 'synthetic biology' – and thus should be regulated as such-, as the modification of genes is limited. In addition, there is ambiguity about whether all CRISPR-Cas9 edited organisms are GMOs. It has for instance been argued that an organism in which a gene has been knocked-out with CRISPR Cas9 is not a GMO according to several of the present legal and scientific definitions of GMOs (see e.g. Dankel, 2017).

Gene drives also give rise to normative ambiguity. Normative questions we encountered in the literature are for instance: is it a morally right to "remake nature" through biological engineering? (Lunshof, 2017). Is it right to alter living organisms and the environment, to change relationships between humans and non-humans, and between humans and their environment? (Sandler 2017). Which kind of evolution is worth more: biological evolution or the cultural, technological kind (Sandler, 2017)? Should changes made through the means of synthetic biology be judged differently from changes that occur spontaneously, by "natural" causes? (Lunshof, 2018).

People with different value systems, including cultural and religious beliefs, will have different understandings of life, nature, the human relationship and responsibility to nature, and the value of technology and innovation, leading to different perspectives on the moral quality of gene drives as an intervention. Kuiken (2017) describes in more detail two perspectives at the different extremes of the spectrum: ecocentrists and technocentrists.

Many conservationists have an ecocentrist view: everything in the biosphere is interdependent, intrinsically valuable, and sacred. This perspective can lead to opposition of the concept of 'genetic rescue' due to concerns for the integrity or "naturalness" of species. In addition, there are concerns that such interventions are a "slippery slope". At what point should we bring a halt to genetic modification? Many conservationists tend to be conservative and risk-averse (Redford et al, 2019). They face a difficult dilemma: the conservation of species threatened by climate change increasingly requires new approaches that are in tension with commitment to preserving historical continuity and human-independent ecological processes (Sandler, 2018).

In contrast, the techno-centric view aims to disrupt current conservation models and harness innovation to improve efforts to end human induced extinction. Gene drive pioneer Kevin Esvelt for example, describes nature as "red in tooth and claw". According to him, existence in nature is unmitigated pain and suffering, and wilderness is a/immoral and tinkering with nature is not only a right but also a duty (Braverman, 2017).

The ethical dimensions of the use of CRISPR metaphors such as "editing the genetic code", "Cas9 scissor protein" and "CRISPR may soon become as reliable as a text editor" have been questioned too (Maben 2016): is it responsible to use such metaphors? According to Nordgren (2001) metaphors should not go beyond what is scientifically established at the time, while the example above does. Pauwels (2013) argues that describing genetic systems as though they are electrical ones (whereby genes are switched on and off with deterministic outcomes) works to a degree, but unlike switching on a light, the activation of a particular gene depends on numerous parameters and the genome is a complex system where other genes can take over the functions previously performed by a knocked-down gene. Blasimme et al (2015) warn that the currently skewed metaphors can silence the negative aspects of technology.

3.4 Relevance of the PP to the case

The precautionary principle is relevant to this case because there is a lack of scientific certainty with regard to serious risks. This technology is intended to achieve permanent genetic changes to the make-up of wild populations of animals and plants, and could potentially cause disruption to ecological and food production systems (NASEM 2016). There is scientific uncertainty about both the potential *hazard* of gene drives, the damage they could do, and the likelihood that this hazard would occur. Perhaps these risks are even unknowable, as experimental research on the effect of deliberate release of gene drive organisms into the wild presents a great challenge. Gene drives could also potentially give rise to what Nassim Taleb, in his strong interpretation of the precautionary principle (See the RECIPES D1.1 Stocktacking report), calls a 'black swan' (2007): unforeseen and

unforeseeable events of extreme consequence. Clearly, this technology warrants a precautionary approach.

Arguments underlying the use of the precautionary principle (see RECIPES D1.1. Stocktaking report) relevant to this case are the following. First, considering the potential serious, systemic and irreversible risks, the precautionary principle would hold parties involved morally accountable for unintended harm. Second, in such a complex research and –as we shall see- governance context, responsibilities would be shared amongst all parties involved in the value chain of the innovation. Third, we have seen that also with regard to gene drives, cost benefit analyses tend to discount future interests and needs: the focus is mainly on short term benefits, while long term social costs are taken into account to a lesser degree. Eliminating particular pests might be beneficial for one generation, while long term ecological effects tend to become visible after a long time. In addition, although benefits might be distributed more equally, the risks of gene drives are less 'non-discriminatory', as a loss of ecosystem resilience would hit those with low socioeconomic status harder. Fourth, the precautionary principle can be argued to give more voice to nature. Fifth, the ambiguity around the interpretation of evidence and the values of nature implies the need to emphasize mutual learning across academic, regulatory and other civil society communities.

4 Risk governance and the precautionary principle

4.1 Political/juridical dynamics

This section starts with a short description of the international regulatory context relevant to EU governance of gene drives. Next, we provide an overview of the EU regulations for GMOs, currently also in place for gene drives. Recently, the European Food and Safety Authority (EFSA) has published a draft report about the environmental risk assessment (ERA) of gene drives applications, which we discuss in some detail. Finally, we discuss the governance of gene drives in The Netherlands.

International context with regard to the Precautionary principle

The EU works under the Convention on Biological Diversity (CBD) and the Cartagena Protocol on Biosafety. The CBD has been ratified by all UN member states, with the exception of the United States. The precautionary principle is formulated in its preamble: "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 minimize such a threat."

Under the CBD, GMOs are covered by the Cartagena Protocol on Biosafety. It is ratified by 171 Parties, but in 2018, only 53% had fully enacted the necessary regulatory systems and developed appropriate enforcement bodies to meet the protocol's requirements (Faunce et al, 2018). Countries such as the United States, Canada and Argentina are not Parties to the Protocol but do have their own national laws on risk assessment and management in the context of biosafety (Redford et al, 2019).

The Cartagena Protocol aims to protect biodiversity and human health and sets international rules to ensure the safe handling and transportation of GMOs, which are referred to as living modified organisms (LMOs). The Cartagena Protocol requires Parties to "establish and maintain appropriate mechanisms, measures and strategies to regulate, manage and control risks" connected with the use, handling and transboundary movement of LMOs, including "possible adverse effects of LMOs on the conservation and sustainable use of biological diversity" [Arts. 15, 16]. Where LMOs are intended for introduction into

the environment, the decision to allow import must be based on a risk assessment and apply precaution [Arts. 7, 10(6), 15]. As discussed on page 11, it is ambiguous whether or not engineered gene drive would fall under the definitions of Living Modified Organisms (or GMOs), that are subject to the risk assessment requirements of the Cartagena Protocol. Deliberations are ongoing (Redford et al, 2019).

In 2019, the Convention held the fourteenth Conference of the Parties in Sham el Sheik, Egypt. This resulted in a "weak" interpretation of the precautionary principle (see the RECIPES D1.1. Stocktaking report) that has allowed for some, well-regulated risk in gene drives research (Redford et al, 2019). In short, depending on a case-by-case risk assessment, decisions will be made on risk management measures and involvement of local communities. Phrasings are used like "guidance may be useful" and "consultation might be warranted" and "as/where appropriate". The full text of this decision is available in Appendix 1.

EU GMO regulations

CRISPR-cas9-based gene drives are a relatively new technology, and its regulation is based on the regulation of existing technologies. Currently in the EU, all new synthetic biology techniques involving transgenesis and non-physical, non-chemical mutagenesis are within the scope of GMO regulations, including CRISPR-Cas9 and gene drives.

GMO's are essentially regulated by two directives, which both take into account the precautionary principle (Mitchell and Bartsch, 2020):

• Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms (the Contained Use Directive)[8];

• Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the Deliberate Release into the Environment of Genetically Modified Organisms (the Deliberate Release Directive)[9].

The EU applies what is considered a 'process approach', meaning the way in which the technology is developed is the main trigger for oversight. Therefore, the definition of GMOs is broader, as an organism "in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination" (2001/18/ EC Art. 2(2)). Because all genetic modification is monitored and reviewed at the point of research, there is less risk to the community. Process-based regulatory models, however, are facing challenges because cutting-edge applications of CRISPR/Cas9 do not match up with existing process definitions- the technology is developing faster than regulation can keep up with.

The Contained Use Directive establishes that risks to human health and the environment of the contained use of a new GMO must assessed before research commences. Risk assessment is carried out on a case by case basis. This assessment results in the assignment of a risk category, with class 1 activities having no or negligible risk, and class 4 activities having high risk. The class determines the kind of safety measures appropriate for the purposes of the activity so that there is no risk to human health and the environment.

The Deliberate Release Directive sets out a step-by-step approach for introduction of a GMO into the environment, including an ERA and monitoring and surveillance. The application process starts with the applicants submitting his application to the national

8 The Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms is available at https://eur-lex.europa.eu/legal-content/en/TXT/?uri=CELEX%3A32009L0041 (Accessed on 13/4/20).

9 The directive 2001/18/EC of 12 March 2001 on the deliberate release into the environment of genetically modified organisms is available at https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32001L0018 (Accessed on 13/4/20).

authority, who then forwards this to the European Food Safety Authority (EFSA). EFSA needs to finish its overall opinion within six months, but time is stopped for the periods that EFSA requests additional information from the applicant. Once EFSA has delivered its scientific opinion, the European Commission formulates a draft decision on how to manage any potential risks highlighted by EFSA and whether or not to grant EU-wide permission to import or cultivate that GMO (STC, 2015). Member states must then, by a qualified majority, approve any release based on the scientific evidence. If member states fail to reach a decision, the application then passes to the European Commission which can approve or deny the application based on the scientific opinion of EFSA (Post Notes, 2010).

Even if a genetically modified plant is authorized for the EU market, member states have powers to "opt out" and close areas and even the whole country to its release (Winter, 2016). In addition, other laws may prevent the release of GMOs for specified areas. In Germany for example, farmers have agreed to declare regions GMO-free (Redford et al, 2019).

Risk assessment under the Deliberate Release Directive does not consider costs, while risk management (monitoring and surveillance) can consider regulatory costs and other concerns, depending on the wording of the applicable law (Winter, 2016). The evaluation of impacts on human health and the environment include (1) general surveillance for unanticipated adverse effects and (2) case-specific monitoring**.** General surveillance is not based on specific indicators, and it can be unclear which aspects should be considered (interview 2). Indicators can differ per member state. In The Netherlands for example, there are specific 'Habitat guidelines' that provide monitoring recommendations. Case specific monitoring checks for effects identified beforehand in the ERA.

The precautionary principle on the EU's regulatory approach to GMOs is visible in the language used in the current legislation. The Deliberate Release Directive states that "the precautionary principle has been taken into account in the drafting of this Directive and must be taken into account when implementing it."(8)[10]. The Deliberate Release Directive also takes into account ethical issues broader than safety. Socioeconomic advantages and disadvantages of each category of GMOs authorized need to be considered in a report to be issued every 3 years by the EU Commission (Mitchell and Bartsch, 2020).

Environmental risk assessment of gene drives

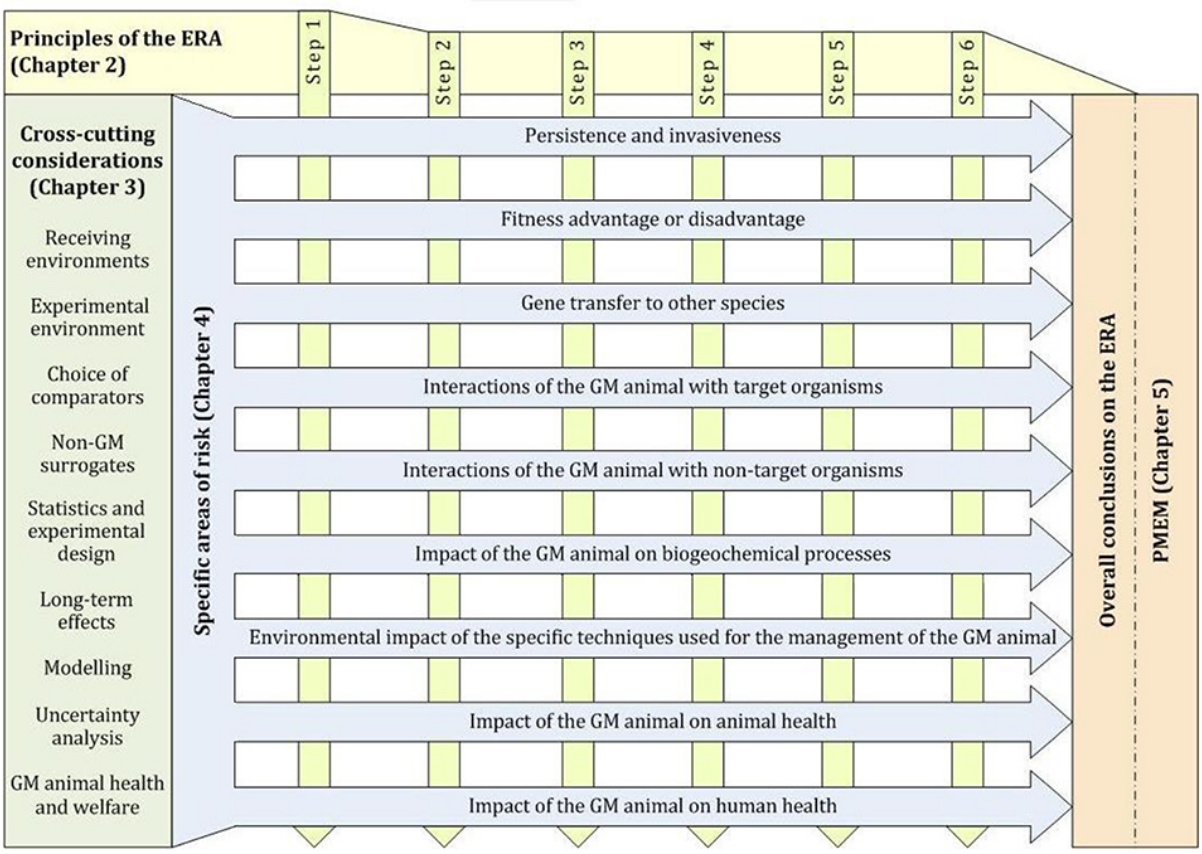
The ERA required by the EU Directive on deliberate release into the environment of genetically modified organisms is defined as "the evaluation of risks to human health and the environment, whether direct or indirect, immediate or delayed, which the deliberate release or the placing on the market of GMOs may pose (…)" (EU Directive 2001/18/EC, arts. 2(8), 4(2)). The principles for the ERA of GMO's are described in Annex II of the Directive on Deliberate Release. Here, reference is made to the precautionary principle as underlying a number of general principles that should be followed when performing the ERA:

"- identified characteristics of the GMO and its use which have the potential to cause adverse effects should be compared to those presented by the non-modified organism from which it is derived and its use under corresponding situations;
- the ERA should be carried out in a scientifically sound and transparent manner based on available scientific and technical data;
- the ERA should be carried out on a case by case basis, meaning that the required information may vary depending on the type of the GMOs concerned, their intended use and the potential receiving environment, taking into account, i.a., GMOs already in the environment;
- if new information on the GMO and its effects on human health or the environment becomes available, the ERA may need to be readdressed (…)"

10 See https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32001L0018

An important characteristic of this assessment is the familiarity approach, described as a "comparison of the characteristics of the GMO(s) with those of the non- modified organism under corresponding conditions of the release or use". This helps identify potential adverse effects arising specifically from the genetic modification (Redford et al, 2019). Details of this approach in the ERA of genetically modified animals are shown in figure 1.

Figure 1: Structure of the EFSA Guidance document on ERA of GM animals (source: EFSA, 2013)



Evaluation is done of the potential consequences of each adverse effect if it occurs (hazard) and of the likelihood of the occurrence. An estimation of the risk to human health or the environment posed by each identified characteristic of the GMO should be made as far as possible, given the state of the art, by combining the likelihood of the adverse effect occurring and the magnitude of the consequences. When risks that require management are identified, a risk management strategy is defined. The interpretation and implementation of these stipulations however remain highly controversial. As mentioned in the Ambiguity section, EFSA and other scientific groups have made different interpretations of the evidence and come to contrasting conclusions about possible risks.

To date, the EU has granted approval for the import of over 40 genetically modified (GM) food and feed varieties. However, since 1998, every attempt to reach an EU decision on cultivation a GM crop has resulted in an inconclusive vote amongst member states, with no qualified majority for or against the proposed authorisation. According to the UK Science and Technology Committee (2015), a result of this is that "several applications for GMO cultivation have become 'stuck' in the regulatory system for many years while others have been withdrawn." Only one GM crop is currently authorised for cultivation in the EU: a variety of insect-resistant Bt maize, which was approved in 1998, before the current regulations were in place (STC, 2015).

To summarize, the release of GMO's into environment/market is not forbidden per definition in the EU. However, as part of a precautionary approach, the developer of a GMO has to apply for authorization under the Deliberate Release Directive. This application process, which includes extensive research on biosafety, takes many years and can cost the developer millions of euros. At the same time, one GMO authorisation could open the way for substantial changes in agricultural production methods and pesticide use across the EU. This is relevant to the assessment of the cost effectiveness and proportionality of measures taken with regard to GMOs in account of the precautionary principle. However, with regard to gene drives, no such assessment can be made yet, as there has been no application for the authorization of deliberate release of gene drive organisms.

For activities involving organisms with a gene drive under contained use, The RIVM has developed a new, adapted risk assessment method. As there is much discussion on how to even conduct a risk assessment in relation to uncontained use there is no risk assessment framework for deliberate release in place anywhere in the EU (interview 2). The EFSA is in the process of determining whether additional guidance is required with respect to the specific challenges gene drives bring, as we will describe in the next section.

EFSA guidance for risk assessment of gene drives

GMO regulations are accompanied by different guidance documents which detail how to compile GMO applications dossiers and what type of scientific data and other information must be included. This includes guidance on how to conduct risk assessments for specific types of GMO's.

In June 2018, the European Commission gave the EFSA a mandate to "identify potential risks in terms of impact on human and animal health and the environment that gene drive modified organisms could pose"; to "identify potential novel hazards of gene drive modified organisms"; and to "determine whether the existing guidelines for risk assessment are adequate and sufficient for gene drive modified organisms" (CEO, 2019) EFSA was not requested to develop new guidelines for the ERA of gene drive modified organisms and thus the current guidance on the ERA of GM plants and animals are still valid.

EFSA accepted the mandate in August 2018 and created a Genes Drives working group at the end of the year. This GMO Panel Scientific Opinion focuses on gene drive modified insects, as they are perceived to be the most likely cases for deliberate release into the environment at present. It has recently (17 Feb 2020) released a draft opinion for public consultation[11], and the report is due to be finalized around the time of writing.

The preliminary version of the report (2020) makes explicit reference to the Convention of Biological Diversity and the Cartagena Protocol on Biosafety. The precautionary principle is only mentioned in an appendix describing the comments raised at EFSA's stakeholder workshop "Problem formulation for the ERA of gene drive modified insects". The text reads as follows (p.6 of Appendix A):

"j. The precautionary principle does not provide sufficiently definite guidance on how to balance potential risks of GDMIs for deliberate release into the environment with the protection of the environment. Some participants considered that the deployment of gene drive strategies in insects can be compatible with the precautionary principle, as it states that "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'". However, since GDMIs designed for self-sustaining vector/pest control can have effects that may be unlimited in space and time, without an obvious way of containing or reversing environmental impacts, some other participants

11 The 'Evaluation of existing EFSA guidelines for the adequacy for the molecular characterization and environmental risk assessment of genetically modified insects with synthetically engineered gene drives is available at:
http://www.efsa.europa.eu/en/consultations/call/public-consultation-gmo-panel-scientific-opinion-evaluation

argued that the application of the precautionary principle would preclude the deliberate release of GDMIs."

The EFSA concludes that the risk assessment approach for gene dives can build on the existing comparative risk assessment paradigm for GMOs. In the case of gene drive modified insects, this is specially the EFSA Guidance on the ERA of genetically modified animals, which applies to insects.

According to EFSA (2020), the following aspects require further consideration or updated guidance: gene drives in insects not intended for food/feed uses, the effect on a population level of the inheritance of the selfish genetic element, the large step to open field-testing, and the definition of case-specific information required to support risk assessment.

4.1.1 Other regulations

Regulating risks across regional boundaries

The international regulatory context is especially important in relation to gene drives as this technology has the potential to cross regulatory boundaries. No nation has regulations in place for gene drives and no case of release of an organism with a gene drive has been recorded (Brossard, 2019). However, the technology clearly creates new regulatory interdependencies and raise questions related to coverage and implementation of existing frameworks for managing transboundary movement of GMOs and addressing transboundary harm (Redford et al, 2019).

With regard to GMO's, national regulatory regimes take different approaches. Where the EU, together with other countries like Brazil, India, China, Bolivia, Australia, Burkina Faso and New Zealand take a process approach, others, like The United States, Argentina, Canada, the Philippines and Bangladesh, have product-based approaches: oversight is triggered by characteristics of products considered to pose a risk, no matter by what processes the product was generated (Redford et al, 2019).

The EU's approach to GMO regulation is frequently contrasted with the US, where many GM products are approved and cultivated on a large scale. These include herbicide tolerant and insect resistant corn, cotton and soybeans, blight resistant potatoes and ringspot virus resistant papaya (Johnson and O'Connor, 2015).

Causes for the regulatory divergence are understood to be multicausal and decisions made in the respective systems are highly resistant to change (Pollack and Shaffer, 2009). In the US, there is no specific regulation to GMOs in place, there is no central GE testing authority, there are no labelling obligation for GMO products, and decisions are depoliticized in the sense that they are made by independent regulatory agencies, with States having no direct influence. Most importantly –considering the focus of RECIPES -, the US government frames their approach to the risk management of innovation as 'sound science based', rather than 'precautionary principle based' (Bühl et al, 2016).

Even if the US eventually chooses a different regulatory path for gene drives than it does for GMOs, other countries like China or in Africa could take the lead in gene drives research and application (STOA, 2019). The High-Level African Union Panel on Emerging Technologies has assessed that CRISPR-Cas9 gene drive for malaria elimination presents realistic options for achieving high-impact and large-scale malaria control and elimination (NEPAD, 2018). However, there is evidence of gaps in legal frameworks and capacity for regulatory oversight in many developing countries (Redford et al, 2019).

A lack of international standards for gene drives means that researchers can shift jurisdiction to sidestep tougher regulatory requirements. An example of this is the company Oxitec, who conducted field trials in Brazil and Argentina after experiencing regulatory delays in the US (Faunce et al, 2018). Several recent reports looking at engineered gene drive for malaria control have raised the importance of regional approaches (James et al,

2018), or coordination and communication between neighbouring countries (NASEM, 2016). However, it could also be important to establish minimum requirements at a global level (Faunce, 2018).

Other normative systems that apply to the governance of GMO's in the EU

The IUCN report (2019) shows how the possibilities of new genetic modification engage with our normative systems in a broad way: legal, customary and industry systems, at the international, regional, national and subnational levels are put under pressure not only concerning risk assessment and management, but also with respect to liability for harm, intellectual property and ownership, and the sharing of benefits. Relevant international frameworks include:

- **The Nagoya Protocol.** In 2017 the Secretariat of the CBD commissioned a report examining the impacts of digital sequence information as it relates to the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization (ABS) to the Convention on Biological Diversity (Wynberg and Laird, 2018). An Ad Hoc Technical Expert Group was also established to provide recommendations for member states on those impacts and a draft decision was submitted with vast disagreements (CBD/SBSTTA/22/ CRP.10, 2018). These deliberations continue.
- **The convention on International Trade in Endangered Species of Wild Fauna and Flora** (CITES). CITES has engaged in a discussion on the question of synthetic products that are indistinguishable from products from listed specimens and the status of modified organisms and products under the convention [Decisions 17.89 to 17.91, 2016; SC69 Doc. 35, 2017].
- **International Law**: A basic principle of international law is that states have sovereignty over natural resources in their territory as well as responsibility for activities within their jurisdiction or control that cause damage to the environment of other states or areas beyond the limits of national jurisdiction [Stockholm Declaration 1972, Principle 21]. States also have responsibility for transboundary harm. There is an international customary rule that a state must prevent and provide compensation for damage wrongfully caused from its territory to other states [ICJ Pulp Mills 2010]. In addition to the "ex post" liability approach, the principle of state responsibility for transboundary harm implicates an "ex ante" approach in the form of a responsibility to conduct environmental impact assessments where there is potential for significant transboundary adverse impact [ICJ Pulp Mills 2010; UNCLOS art. 206]. Depending on scope, this could apply in cases where synthetic biology or engineered gene drives cross boundaries (Redford et al, 2019).

4.2 Other governance dynamics

So far, governance of gene drives in the EU is only partly done through laws and regulation. As the technology is only just emerging, formal risk governance structures for the specific innovation that gene drives bring have not yet been put in place. The EFSA has come forward with recommendations for the guidance of risk assessment of gene drives, but these recommendations have not yet been implemented. This means there is a regulatory gap. However, there are also other modalities that can govern risk, as we shall see in the next sections.

Scientific-technological environment

Scientists seem to be getting increasingly wary of the societal backlash of technological harm, and in academic discussions about regulating gene drives, public trust is considered to be paramount. Braverman (2017) argues that in the absence of regulation, the implementation of social responsibility has been left solely to scientists, who she describes as 'scientist-regulator hybrids'. Scientists have for example represented public interest in applying for patents to protect the public from dangerous private interests. Gene drives researcher Kevin Esvelt has also written an article (2017) about the 'rules' scientists should follow in gene drives research- summarized as "be humble and start local".

Scientists are also researching technological ways to mitigate gene drives risks. Besides strictly regulated containment in the laboratory, biological containment mechanisms could render global gene drives local (Hurlburt, 2017). Scientists are for example thinking about the development of a daisy chain drive, in which the elements that the gene drive needs to copy itself are split up, so that the drive would vanish over a few generations (Esvelt, 2017). It could also be possible to develop secondary reversal drives or overwriting drives ('rescue gene drives') to make populations immune to another drive (Esvelt et al, 2014). Finally, if the targeted species is eradicated, it is possible to reintroduce it from lab populations (STOA, 2019). Not everyone agrees on the desirability and feasibility of these solutions, as they themselves not without risk, and all of them remain unproven (Frieß et al, 2019).

Hurlburt (2017) challenges containment strategies in the lab as a means of governing risk, warning against the idea of "preparing technology for the world" and the competence and authority claimed by synthetic biologists to govern their own creations. He argues that governance becomes matter of technical expertise and that risk is constructed in a narrowly technical way, governable within the laboratory. From this perspective, risk is solvable by technical but not by social means, constructing legal and political institutions as highly limited in their ability to manage risk without inhibiting beneficial technological innovation.

Peer reviewed journals could also have a role to play in governance (Lunshof, 2018). For example, in 2011 research into the airborne transmissibility of a strain of influenza among ferrets and the consequences for transmissibility among humans triggered a worldwide debate on gain-of-function research. Upon initial submission of two manuscripts, both Nature and Science initially declined publication due to biosecurity concerns. Dissemination of information about the methods was seen as posing high risk by itself (Lunshof, 2018).

The topic of governing the risks of gene drives research and applications has also received quite some attention in academic research and in other reports- this literature itself thus contributing to the governance of gene drives. The technology poses a number of challenges for regulation that researchers are bringing to light. Engineered gene drives may fall into an area of regulatory ambiguity, uncertainty or even overlap – it may not be clear how they fit into existing governance frameworks (Redford et al, 2019).

Researchers are also contributing to new risk assessment frameworks that gene drive developers can use. Lunshof et al (2017) have developed an adaptive approach to risk assessment of contained use. They argue that the necessary minimum for safe research with gene drive technology requires a thorough biosafety risk assessment to be in place before the research commences, at least 2 stringent (molecular, ecologic, reproductive, or barrier type) confinement strategies, and that organisms carrying gene drive systems should not to be distributed to other laboratories until formal biosafety procedures have been established. Kuzma (2019) has made the case for a Procedurally Robust Risk Assessment Framework (PRRAF) for the deliberate release of gene drive organisms, based on existing frameworks for use in conditions of high uncertainty that go beyond the traditional linear and technical quantification of risk. With the PPRAF framework, the risk

assessment conducted by the FDA of Oxitec's genetically modified mosquito was assessed to have several shortcomings. Most importantly, it did not take into the account the severity of adverse effects.

In addition to the regulatory question, the potential of intended or unintended transboundary movement raises challenges for stakeholder engagement, to ensure that public consultation can be carried out at the appropriate level. Important questions raised in academic literature is which publics are relevant to a learning process about gene drives, and what their 'say' is. Will scientists endorse decisions made with public input? (Braverman, 2017) Should the public include non-humans? Who can speak for Nature and/or future generations?

In the literature on Responsible Research and Innovation (RRI), similar lines of questioning have been developed, an example of which is given in Figure 2 below. The goal of RRI is to better align research with societal needs. The clear link to the precautionary principle is that stakeholder engagement is a way of dealing with the ambiguity of uncertain risks. However, it goes beyond the scope of this case study to go deeply into RRI as a mode of governance, as it is not specific to gene drives. It should be mentioned that the Journal of Responsible Research and Innovation has published a special issue on gene drives[12].

Figure 2: Lines of questioning on responsible innovation (Stilgoe et al 2013)

Product questions	Process questions	Purpose questions
How will the risks and benefits be distributed?	How should standards be drawn up and applied?	Why are researchers doing it?
What other impacts can we anticipate?	How should risks and benefits be defined and measured?	Are these motivations transparent and in the public interest?
How might these change in the future?	Who is in control?	Who will benefit?
What don't we know about?	Who is taking part?	What are they going to gain?
What might we never know about?	Who will take responsibility if things go wrong?	What are the alternatives?
	How do we know we are right?	

Finally, as tools associated with synthetic biology are becoming increasingly accessible to private actors, the research field is expanding to include actors who may not have the backing of an established institution. As DIY biology becomes more accessible to users not associated with a particular institution, this may raise challenges for enforcement of biosafety and environmental regulations against actors with bad intent. While the community's own regulations may support safe practices among well intentioned operators, informal or illegal operators with bad intent may be difficult to identify and hold liable (Garrett, 2013). However, there are still limits on the capability of community

12 Available at: https://www.tandfonline.com/toc/tjri20/5/sup1?nav=tocList

laboratories to create organisms that would cause significant environmental damage, and to date there has been no evidence of attempts or intent to do so (Lentzos, 2016).

Economic dynamics

Interestingly, Mitchell et al (2017) argue that safer, self-limiting gene drives provide a better business model. With a self-sustaining gene drive, the initial release would need to generate the entire required economic return. In addition, the potential market for such gene drives would be quite small as there are not so many diseases or pests, and so little or no private investment would occur unless the individual contracts are of very high value. Possibly, the financial consequences of the potential risks involved also provide a barrier to companies. As a consequence, Mitchell et al expect that this type of problem may be targeted by public agencies or non-profits, or public–private partnerships. In contrast, releases of gene drives with spatial or temporal limits could attract more investments, generate more income, and further expand gene drive applications. The authors (2017) even go so far as to say that private companies will likely strategically lobby for high regulatory or safety thresholds based on various types of self-limitation or containment, not only to ensure a commercial gene drive market, but also as a deterrent to competition.

At the same time, emerging economies represent important potential markets for synthetic biology applications and products. Considering the regulatory gaps in many emerging economies, balancing a precautionary approach with potential economic benefits of gene drives could be challenge (Redford et al, 2019).

During the STOA workshop in 2019, participants argued that much depends on patent holder behaviour in the context of humanitarian applications of gene drives. In the case of Target Malaria, all research is published, which means that the novelty criterion for patents is not fulfilled. Target Malaria has one patent for gene drive in its entirety in order to protect the technology and avoid any attempts to patent applications of it for commercial instead of humanitarian use.

It is also necessary to mention here that the majority of synthetic biology funding in the US comes from DARPA, the defense advanced research projects agency (60% in 2014) (Kuiken, 2018). Military use of gene drives and the role of DARPA should be discussed internationally and in bio and chemical weapons treaties more broadly (Kuiken, 2018).

Societal interactions/norms

As gene editing techniques and possibly gene drives become more accessible and democratized, there is a rapidly expanding international ecosystem of actors (Redford et al, 2019), including scientists from different fields, DIY biohackers, NGO's, policy makers, and actors from industry, some of who are involved in a heated discussion around gene drives.

Different international environmental organisations have articulated grave concerns over the potential adverse impacts of gene drives on the environment and agricultural systems. The Corporate European Observatory question the independence of the European Food Safety Authority (EFSA) experts tasked to assess gene drives' potential risks (CEO, 2019). During the past United Nations Convention on Biological Diversity in Egypt, critics have called for a moratorium on field trials and some laboratory research (Cotter et al, 2020).

In an article in the New Yorker, journalist Jennifer Kahn provides an interesting account of this convention: "a coalition of activist groups compared gene drives to the atomic bomb and accused researchers of using malaria as a Trojan horse to cover up the development of agricultural gene drives for corporate profit". One of her interviewees from the ETC group, an international organization for eco-justice, argues that a high, disruptive, level of activism is necessary because from the beginning, the discussion has been framed around best-case scenarios in healthcare and conservation, with little discussion on how this

technology will be developed with regard to applications in agriculture, the food system and by the military.

In return, scientists working with the Gates Foundation that fund Target Malaria, accuse activists of trying to hijack the meeting and argued that activists' claims were non-scientific. But there is also evidence that the Gates foundation has paid a PR firm called Emerging Ag to recruit a covert coalition of academics to manipulate the UN decision-making process[13].

Kahn (2020) notes that the technology was new for many members and delegates at the United Nations Convention. For the layperson it is difficult to make sense of the disparate viewpoints represented in the debate: extreme benefits versus extreme danger, worst versus best case scenario's. The UN rejected the moratorium, but did agree to a weaker type of precautionary approach, as described in section 4.1.

5 The precautionary principle and its future

5.1 Reflection on the PP in the literature

In our literature research, we have not encountered any debate on whether the precautionary principle is applicable to gene drives- everyone seems to agree that application of the principle is in order. The 2016 National Academies of Sciences, Engineering, and Medicine (NASEM), the 2019 International Union for Conservation of Nature (IUCN), and the 2019 European Network of Scientists for Social and Environmental Responsibility (ENSSER) reports on gene drives all discuss the precautionary principle at length. There is however disagreement on how the principle should be applied: what do uncertain and potentially irreversible risks of gene drives mean in terms of regulatory measures?

In the NASEM report, it is argued that existing systems to govern biotechnology are adequate in the first phase of contained use of gene drives, but that a precautionary approach might be useful for their experimental release.

The IUCN report concludes that their report should feed into decision making on gene drives that takes place on a case-by case basis, considering the full range of appropriate stakeholders, operating with free access to all information, and informed by the framework of the precautionary principle.

The ENSSER report (2019) is very critical of claims that the precautionary principle slows innovation, arguing that objections come down to a misalignment of the technological pathways developed under it with corporate and private interests. In relation to gene drives, they conclude that

"….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." (p. 132)

They advocate that such an approach should commence at the very start of technology development, when first considering a GDO as a possible response to a stated problem. It requires a move away from evaluation of the attributes of a single technology, towards

13 See https://www.independentsciencenews.org/news/gates-foundation-hired-pr-firm-to-manipulate-un-over-gene-drives/

addressing a much broader range of options available for mitigating or solving the problem that is addressed, with a broad group of stakeholders.

Some, like The Civil Society Working Group on Gene Drives, call for a moratorium. They believe that "no case can be made for proceeding with gene drive experiments or developments at this time. Moreover, in our view, recent proposals to move ahead with real world gene drive trials are reckless and irresponsible […]."[14]

Others claim that a moratorium could cripple the field and block potentially beneficial advances. Bartsch (2017) for example laments how NGO's have used the PP to delay the application of gene drives: "Concerned non-governmental organizations are fully responsible for delaying the application of technologies that can be helpful, and I have hope that there is sufficient conscience for courageous solutions and innovative visions that are not poorly driven by fear".

According to Lunshof (2018), precaution is a valuable concept but cannot be applied in a broad manner to synthetic biology and other emerging technologies. In her view, the precautionary principle in decision making about risks can be effective only if applied to a concrete technology or research project: evaluation on a case-by-case basis is an absolute requirement (Lunshof, 2018).

5.2 Effect of the PP on innovation pathways

As there is no specific regulation in place for gene drives, it cannot be argued that the precautionary principle has 'opened up' new innovation pathways. It is too early to say whether a "weak" interpretation of the precautionary principle that we recognize in the Convention of Biological Diversity and the recent EFSA gene drives report (Redford et al, 2020) will lead to the exploration of other research pathways, with funding delegated to for example alternative malaria research.

Clearly, leading gene drives researchers are imbued by the necessity of precaution, which they interpret from a technocratic perspective. As mentioned in section 4.2, researchers are integrating a precautionary approach into their technological design: self-limiting drives or reversal drives that could undo the unintended consequences of intentionally released gene drives could provide room for field research- although this can never be *without* risks. It would be difficult for gene drive researchers to consider (technological) alternatives, as gene drives researchers are limited to their particular expertise, and it would not match their interests.

5.3 Innovation principle

With regard to GMO's more broadly, discussions about the innovation 'principle' are quite prominent, but these fall out of scope of this case study. We have found no reference to the innovation principle with regard to gene drives in official documents. It is therefore difficult to assess what such a principle would mean for the development and direction of this technology. Sandler (2018) argues that in light of precaution, promising applications of gene drive technology are those where the threat is local. Perhaps the applications of self-limiting gene drives in relatively contained environments could be in line with an innovation friendly legislative culture that also takes into account the precautionary principle –but these are not the great promises of gene drives -like the eradication of malaria- that have brought in the most funding.

14 See http://www.synbiowatch.org/2016/08/reckless-driving/?lores

6 Synthesis

The CRISPR-cas9 gene drive technology facilitates the spread of artificially modified genes through wild populations of a species of plant or animal. The capability of this technology to spread into the wild is argued to have great potential benefits, like combatting the malaria mosquito. At the same time, the resulting lack of control is considered the technology's greatest risk. A heated debate on gene drives technology shows disparate viewpoints on the technology's risks and how to govern them: extreme benefits versus extreme danger, worst versus best case scenario's and a global moratorium versus slight adaptations of current risk assessment frameworks.

As argued in section 3.4, most of the arguments underlying the use of the precautionary principle described in the RECIPES D1.1. Stocktaking Report are relevant to this case. Considering the potential serious, systemic and irreversible risks, the precautionary principle would hold parties involved morally accountable for unintended harm. Furthermore, in such a complex research and governance context, responsibilities would be shared amongst all parties involved in the value chain of the innovation. We have seen that also with regard to gene drives, cost benefit analyses tend to discount future interests and needs: the focus is mainly on short term benefits, while long term social costs are taken into account to a lesser degree. Eliminating particular pests might be beneficial for one generation, while long term ecological effects tend to become visible after a long time. Moreover, although benefits might be distributed more equally, the risks of gene drives are less 'non-discriminatory', as a loss of ecosystem resilience would hit those with low socioeconomic status harder. The precautionary principle can also be argued to give more voice to nature. Finally, the ambiguity around the interpretation of evidence and the values of nature implies the need to emphasize mutual learning across academic, regulatory and other civil society communities.

The following lessons can be learned from this case study about the complexities and controversies around the application of the precautionary principle:

First, this case is not about inconclusive evidence, but about a missing field of scientific knowledge: the field that combines the risks of genetic modification with evolutionary dynamics. Gene drives have not been tested outside of the laboratory, and inside of the laboratory the technology cannot be tested fully, as the integration of the gene drive construct into the genome is only part of the equation. For most other technologies studied as part of the RECIPES project, the relations between the technology and the damage to health or environment are difficult to measure because of complexity. However, in the case of gene drives, there is no (direct) evidence of harm, as there has been no field release.

Second, gene drives bring with it an interesting conundrum: in order to reduce the epistemic uncertainty, research activities (field trials) must be undertaken that themselves pose risk. It could be possible to test gene drives in an isolated location, but that would also make the test less applicable to most envisaged real life applications. This would mean that most promising cases for gene drives are those where the threat is local and relatively contained, not the further reaching conservation cases or vector-control cases. The question is whether field tests for the second type of case, necessary to better understand their risks, would ever be justified in light of the precautionary principle.

Third, even when field tests for these cases are assessed to be justified, the complexity of the risks of gene drives also mean that they have an unknowable quality. A complex system of biotic and abiotic factors give rise to a large degree of ecological and evolutionary complexity. Gene drives are a technology with high power: they can be self-sustaining for multiple generations and potentially undergo mutational changes over time. In this sense, gene drives can give rise to unforeseen and unforeseeable events of extreme consequence. Even if field trials would not provide evidence of any harm because the likelihood of hazardous events occurring is very small, it still can be argued that the precautionary

principle is in order. A stronger interpretation of the precautionary principle would therefore also effectively stop any gene drives research outside of the laboratory.

Fourth, just like the risks of gene drives are uncertain, complex and ambiguous, so are the benefits. During the STOA workshop (2019) is was argued by one of the experts that perhaps it would be unethical *not* to make use of gene drive in order to diminish/eradicate malaria. However, it is not certain that the technology will work, and if it does, it is not certain it will work the way scientists want it to, both directly and indirectly. The other RECIPES technologies will also be accompanied by promises that are uncertain, but as described above, gene drives have not been tested in practice at all.

Fifth, the governance of this technology also shows particular complexities/ uncertainties/ ambiguities. The current regulation of gene drives in the EU is based on existing regulation for GMOs. The EFSA recently concluded that the risk assessment of gene drives can build on the existing guidance for the risk assessment for genetically modified animals, although the effect on a population level and the large step to open field-testing need further consideration. It could however be argued that these two aspects are what define synthetic gene drives as a technology, and that they are the exact reason why they are such a challenging technology to regulate. Risk assessment of GMO's are based on a familiarity approach, meaning that the characteristics of GMO's are compared to non-modified organisms under corresponding conditions of the release or use. However, with regard to gene drives, it is unclear what corresponding conditions of release or use would be. For the regulation of gene drives, a clear understanding and analysis of the novelty of gene drives compared to existing technologies seems very important, but difficult to achieve in practice, considering the complexity of the knowledge field.

Sixth, the potential to cross regulatory boundaries sets this case apart. As of yet, no nation has regulations in place for gene drives and no case of release of an organism with a gene drive has been recorded. However, the future could change this, with or without the precautionary principle being followed. In the past twenty years we have seen that current EU regulations have led to a de facto moratorium on GMOs in Europe, but in other countries this has not been the case, resulting in trade tensions between Europe and the US. It could be argued that in order to have control over the direction of this technology, the EU needs gene drive research to take place in Europe.

Seventh, the potential of intended or unintended transboundary movement also raises challenges for stakeholder engagement. Learning from the history of GMOs, in the governance of gene drives attention needs to be paid to public perceptions and how they differ culturally. Especially in the context of uncertain risks, these perceptions need to be taken into account when making decisions about a technology.

So, what can this case teach us about how to deal with possible tensions between innovation and precaution? We have seen that precaution is deemed to be in the interest of both scientists and society. For gene drive scientists, societal trust is paramount, and they are taking it upon themselves to fill the regulatory gap by designing soft rules for application, engaging with the public, and also developing technological ways to reduce the risks of field testing. A safer, self-limiting gene drive also brings with it a better business model for gene drive developers, not only because they are innovating more responsibly, but also because they can sell more of their innovation. In the case of gene drives, we would argue that so far, innovation and precaution have not been in competition. Rather, the precautionary approach taken up by gene drive scientists has led to new research questions and technological approaches to risk mitigation.

Others question whether technology that is 'safe by design' is safe enough. Who will be responsible of the impact of the overall use of the technology? What would be the limit? If the incentive is to sell as much of it as possible, the overall impact might be huge, even though at risk assessment level it might look acceptable.

In any case, this means that scientists should be guided in this process more, research funding systems should allow for moving to alternative research pathways, and regulators could come into the scene earlier. Risk assessment on a case by case basis takes place when the thought and effort has already been put into the proposed research/application by scientists. We need to develop ways in which policy makers, together with representatives from science and society, can identify conditions for responsible research: modes of actions, aims and contexts that justify gene drives research and also have a responsible business model. However, it should also be financially possible to move away from research that has already been invested in. Only under these conditions, innovations can be developed to fit societal needs.

This also means that the use of gene drives needs to be put into perspective. Claims of large scale potential benefits, used by gene drives researchers and regulators alike, obscure the discussion. These claims are just as uncertain as the risks, fully disregard a precautionary approach, and can lead to societal backlash. If we want to further an innovation-friendly research culture in the EU, it is important to start small, with a realistic representation of the aims of a technology.

7 Conclusion

Gene drives research is accompanied with a large degree of uncertainty, complexity and ambiguity on different levels. This case is not about inconclusive evidence, but about a missing field of scientific knowledge about the environmental effects of genetic modification on a population level. In order reduce the epistemic uncertainty, research activities (field trials) must be undertaken that themselves pose risk. The complexity of the risks of gene drives also mean that they could give rise to unforeseen and unforeseeable events of extreme consequence. This all translates into great challenges for the regulation of gene drives, which are further exacerbated by the technology being able to spread beyond regulatory borders.

All stakeholders involved seem to agree that a precautionary approach to gene drives is necessary, including the scientists developing gene drives. However, there is less agreement on what a precautionary approach would entail in practice, whether this means the precautionary principle should be 'invoked'- and to which consequence. While gene drives scientists are theorizing about building precaution into their innovation, polarized discussions between stakeholder groups have focussed on how to assess potential risks. This points to a disconnect between the implementation of the precautionary principle and the development of innovation that is safe and in line with stakeholder interests.

The findings of this study show that a precautionary approach can lead to more responsible innovation when precaution and the interests of a broad group of stakeholders, including nature and future generations, are taken into account from the very start of the innovation process. Regulation, policy and funding structures should stimulate policy makers, researchers and stakeholders to together find appropriate solutions to problems at hand. A precautionary approach to risk could warrant the active promotion of (alternative) research opportunities, paying attention to responsible business models. The furthering of an innovation-friendly research culture in the EU furthermore requires a realistic representation of innovation goals that account for such a precautionary approach.

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9 Appendix 1

Decision 14/19 of the Convention on Biological Diversity[15]

The Conference of the Parties:

"9. Recognizes that, as there could be potential adverse effects arising from organisms containing engineered gene drives, before these organisms are considered for release into the environment, research and analysis are needed, and specific guidance may be useful, to support case by case risk assessment"

"10. Notes the conclusions of the Ad Hoc Technical Expert Group on Synthetic Biology that, given the current uncertainties regarding engineered gene drives, 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;

"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 (14/19) 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 minimize 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"."

[15] See https://www.cbd.int/conferences/2018/cop-14/documents for the full report.