Gene Drives

Ethical considerations on the use of gene drives in the environment

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1 Subject of the report

A gene drive is a biological mechanism that accelerates the transmission of genes in organisms that reproduce sexually. Generally speaking, gene variants (alleles) have a 0.5 probability of being passed on to the next generation. Gene drives result in certain gene variants being passed on with a much higher inheritance rate than under Mendel's laws of inheritance.

A gene drive consists of a genetic element in an organism's chromosome. This genetic element codes for an enzyme that can cut the corresponding ('homologous') second chromosome at the same sequence site at which the gene drive is located on the first chromosome. The cell then repairs the cut in the second chromosome using a copy of the first chromosome. The genetic information with the gene drive is then found in both chromosomes. If this mechanism is fully effective, every descendant of a sexually reproducing organism will receive a chromosome that contains the gene drive. Thus, if this mechanism replicates in each generation, the new genetic information will spread very rapidly in a population.

Gene drives also occur naturally. The development of new genome editing techniques such as CRISPR-Cas systems makes it possible to create new gene drives faster and in a targeted way and to accelerate the propagation of specific genes in populations. These are known as genetically engineered or synthetic (as opposed to natural) gene drives. On the one hand, a gene drive can be used to introduce additional genetic information for new traits into a population. On the other hand, it can also be used to remove essential DNA sequences, thereby creating a lethal factor that causes the offspring to die during development. Such possibilities mean that gene drives are of interest for a variety of applications, including some that are morally laudable, such as combating malaria. While tackling malaria is something that most people would support, there is nonetheless a need for a differentiated, critical assessment of the possible side effects of the means used to achieve that goal.

The following short report by the ECNH provides an ethical assessment of genetically engineered or synthetic gene drives, i.e. an ethical assessment of the procedures and associated interventions on living beings as well as the consequences of gene drive applications in the environment. The report ties in with a number of previous ECNH publications and in particular, as regards applications in the environment, with the committee's fundamental considerations on the requirements for the regulation of new technologies in the environmental field, as set out in its May 2018 report 'Precaution in the environmental field'.[1]

1 ECNH, Precaution in the environmental field. Ethical requirements for the regulation of new biotechnologies, 2018.

2 Objectives of research and application

2.1 Conceptual approaches to gene drives

The possibility of using genetic drives to spread genetic information rapidly within a population could be harnessed for a variety of purposes. An overview of the latest developments in gene drive projects can be found in the ECNH-commissioned literature review by Anne Eckhardt (risicare GmbH),[2] which identifies three main focal areas:[3]

1. *Reducing or eliminating populations:* Gene drives could be used to reduce the fertility of living beings that cause disease or transmit pathogens, to the extent of destroying a population,[4] with a view to fighting pathogens or the carriers of pathogens for humans, animals and plants. In agriculture, they could provide a means to counteract pests. Other possible applications include the containment of invasive alien organisms or animal and plant pathogenic organisms that threaten native biodiversity.

2. *Changing traits within a population:* Another objective is to use gene drives to modify the characteristics of organisms within a population, reducing their ability to cause or transmit diseases or increasing or restoring their sensitivity to remedies such as antibiotics, both in human medicine and in livestock. Other goals include boosting resistance to viruses or bacteria and reversing the resistance of weeds to herbicides, as well as controlling pests by influencing populations through the use of external agents, e.g. to control the rate of female and male insects.

3. *Strengthening populations:* A third thrust of gene drive development is strengthening populations, for example by reducing their susceptibility to disease, and thereby conserving endangered species.

2.2 Examples of applications

As regards specific applications, the area currently receiving most attention in public debate and specialist literature is malaria control projects. One approach involves using gene drives to eliminate populations of Anopheles mosquitoes, which transmit the malaria plasmodium. Another research approach entails, not controlling the mosquitoes, but preventing them from transmitting the pathogen, i.e. the plasmodium. Similar projects aim to combat viral diseases such as Zika, dengue, chikungunya, West Nile fever and others transmitted by the tiger mosquito. Others are about containing infectious diseases such as Lyme disease, which are also transmitted to humans, other mammals and birds by blood-sucking insects such as ticks, horseflies or mosquitoes from infected host organisms (such as rodents).

In the area of agricultural production, for example, research is under way to develop gene drives to combat pests such as the spotted wing drosophila *(Drosophila suzukii)* and psyllids, which damage fruit trees. Another objective is to restore herbicide sensitivity to herbicide-resistant weeds using gene drives.

Another area of application is the use of gene drives for military purposes. Here, the focus is on the research and development of 'anti-gene drives' to counter harmful gene drives should the need arise. Such harmful gene drives could be used to spread human diseases or to damage agriculture and local food production, for example. 'Dual use' research projects and the possible use of gene drives for terrorist purposes also need to be considered in this context.[5]

2 Risicare, Gene Drives. Kurzbericht, November 2018 (www.ekah.admin.ch)

3 It should be noted that there are currently no known instances of synthetic gene drives being actually used in the environment.

4 Parental generations of, for example, insects or rodents that are disease vectors are modified so that their progeny die at the development stage. One way of achieving this is for a gene drive to remove a gene sequence needed for survival on the second chromosome, thereby creating a lethal factor. A descendant carrying such a lethal factor cannot survive.

5 See also section 3.3.

3 Ethical assessment

3.1 Moral status of individuals, populations, species and biodiversity

Developing a gene drive to modify a population presupposes genetic intervention on individuals. The Swiss Federal Constitution requires the dignity of living beings to be taken into account when dealing with animals, plants and other organisms.[6] This constitutional requirement has been transposed into the Gene Technology Act (Art. 8 GTA) and, in the case of animals, the Animal Welfare Act (Art. 4 AniWA), for vertebrates in particular. The concept of the dignity of living beings relates to individuals. The interests of these individuals not to be harmed or distressed need to be weighed against human interests in a specific application of gene drives.[7]

Some species concepts, which among other things underpin the legal protection of species, assume that not only individuals but also species are morally relevant entities and that they can be harmed in a morally relevant sense. Similar concepts exist with regard to populations and biodiversity, which are also to some extent deemed to be moral entities. Such concepts are also used to justify gene drive projects in the fields of nature conservation, species protection and biodiversity protection. They are based on assumptions to which the ECNH raised critical objections in 2015.[8] Accepting the assumptions underlying these concepts, however, raises questions, for example regarding the criteria whereby a population or species is considered to be dispensable or may, or even must, be destroyed. It would also need to be spelled out at what point conspecifics whose traits are changed by gene drives are still considered members of the original species and what this means in terms of their moral status. If species are viewed as moral entities, this could also imply that, where a conflict arises, conserving a species is more important than conserving individual living beings.

3.2 Considerations relating to risk ethics

3.2.1 Some principles of risk ethics

The ECNH has set out its considerations on risk ethics in detail elsewhere and in particular discussed the various justifications for and implications of consequentialist and deontological risk ethics.[9] Essentially, a consequentialist risk theory requires an action to be judged only according to its consequences. According to the best known theory within this theoretical family, the utilitarian risk theory, the opportunities are weighed up against the risks and the action that is expected to generate the greatest possible benefits (or 'utility') *must* be chosen. According to deontological risk theories, opportunities (i.e. the possible benefits) of a gene drive application only come into play if the risks associated with the application are acceptable for the morally relevant entities. Risks to these individuals that exceed the acceptability threshold *must not* be weighed against the opportunities. These two theories are incompatible; one has to opt for either one or the other.[10]

An appropriate risk assessment presupposes sufficient risk data. In other words, information about the probability of occurrence of damage scenarios must be available. This raises three questions: Based on what data are the risks of specific gene drive projects currently assessed? Which plausible scenarios are investigated? What do we know about their probabilities of occurrence?

6 Article 120 of the Swiss Constitution.

7 For further ECNH reports on the moral status of individuals, see in particular: ECNH, The Dignity of Animals, 2001 and ECNH, The dignity of living beings with regard to plants, 2008.

8 ECNH, Stellungnahme zu Anhörungsvorlage 'Nationale Strategie invasive gebietsfremde Arten', 2015.

9 See in particular ECNH, Precaution in the environmental field. Ethical requirements for the regulation of new biotechnologies, 2018, section 3.5.

10 It should be noted that fundamental rights tend to follow a deontological logic, independent of any consideration of total utility.

If a consequentialist (utilitarian) risk assessment is deemed admissible, the risk data must meet additional requirements. It is not enough to highlight the benefits of an application as these benefits are not guaranteed but merely *possible*, with a certain probability of occurring. In other words they are an opportunity. In a utilitarian approach to risk, in order for risks to be weighed up against opportunities, additional information about the probability of occurrence of benefit scenarios is therefore required. Only then can the greatest possible net utility be calculated.

3.2.2 Specific risks of gene drives

Like all human interventions in the environment, the application of gene drives involves risks. Living beings with a synthetic gene drive have specific traits that distinguish them from other genetically modified organisms. The following must be considered in the risk assessment:

- Gene drives have the potential to change the gene pool of a population in such a way that certain genetic information prevails within the entire population.
- If this genetic information entails a lethal factor, there is a possibility that other populations beyond the target population will be eradicated.
- Where generations succeed each other rapidly, this can take place within a very short time.
- The explicit aim of a gene drive is not to modify selected individuals but to disseminate certain traits within a population. On the one hand, it is possible that the gene drive will propagate not only in the intended population but also in unintended populations of the same species. On the other hand, a gene drive may propagate in a closely related species if it transfers to that species as a result of hybridisation and spreads there thanks to an identical target sequence.

When it comes to risk assessment this raises the following issues, among others:

- *Outcrossing to unintended populations and species.* In previous applications of new biotechnologies in the environment, a key factor in the risk assessment has been the extent to which it is possible to prevent outcrossing of genetic modifications to wild populations. In the case of gene drives, the desired effect is precisely that: for a new genetically engineered or modified trait to prevail as quickly as possible within a specific (wild) population. Given the mechanisms by which gene drives operate, namely accelerating the inheritance of genetic modifications within a population, how is the probability of a gene drive being transferred to non-target populations to be assessed?
- *Possible consequences of optimising gene drive efficiency.* Laboratory experiments on mosquitoes have shown that populations develop resistance to a gene drive over time. To prevent this, researchers have developed a method whereby the gene drive for sterility is inserted in a gene whose DNA sequence is considered particularly 'stable' and thus protected from mutations. In these cases, there are no similarly constructed sequences within the organisms that could take over the unwanted fertility function and thus circumvent the gene drive.[11] The strategy of using such stable DNA sequences helps a gene drive to be more effective. However, it also increases the risk of other unintended effects. For if such a stable gene with a very similar sequence occurs in different species, there is a risk that all these species would become sterile and thus be wiped out if such a gene drive were to be released.

11 Kyros Kyrou et al., A CRISPR-Cas9 gene drive targeting doublesex causes complete population suppression in caged Anopheles gambiae mosquitoes, in Nature Biotechnology, volume 36, 1062–1066 (2018) (https://www.nature.com/articles/nbt.4245).

Other questions that the ECNH believes must be examined include: How likely is it that a pathogen combated by means of a gene drive would look for a new host? How likely is it that a gene drive would introduce a new invasive species into the environment, and how would this cause harm? What is the probability that the collapse of one population would deprive another population or species of its basis for survival?

3.2.3 Specific challenges involved in compiling risk data

The regulations prescribe a *step-by-step* approach to dealing with genetically modified organisms, with risk assessment data collected incrementally. Risk scenarios such as the development of resistance can be partly derived from the characteristics of an organism. Simulation models are also used to assess the probability of occurrence of such scenarios. In addition, impacts on populations can be modelled. However, there is little scope for modelling long-term effects.

Even with conventional genetically modified organisms, it is difficult to compile data for assessing long-term risks in particular. In the case of drive-containing organisms, collecting risk data poses additional challenges as this technology is specifically designed to bring about the rapid spread of traits and any containment measure is in principle contrary to this intention. To implement the required step-by-step approach from the laboratory into the environment, a number of strategies are therefore being discussed as to how the effect of gene drives could still be limited.

One idea is to conduct field trials in places where the host organisms do not naturally occur. Another strategy involves using gene drives whose impact is limited in space or time. Such gene drives are known as 'local drives', as opposed to 'global drives', which in principle are passed on without limitation and could spread worldwide. Another attempt at *spatial* containment entails deploying gene drives on an island, whose physical isolation would limit their impact. *Temporal* limitation at molecular level involves designing gene drives in such a way that they could not replicate endlessly but would end after a set number of generation cycles.

However, testing gene drives in locations where no host organisms are present has the disadvantage that the gene drive organisms are not exposed to their competitors and predators. It is therefore not possible to test how effective a gene drive is under natural conditions. But if the risks of a 'next step' cannot be limited, the step-by-step principle is violated. Whether the terms 'local drive' and 'global drive' adequately describe the mechanisms is also questionable. From a biological point of view, islands are not spatially isolated in the way that would be required to mitigate the risks posed by a gene drive. And gene drives designed to be 'time-limited' by molecular biological design could turn into global drives if the mechanism failed to work as expected due to spontaneous mutations or for other reasons.

In cases where a gene drive does not work as the developers expect, for example if spontaneous mutations alter the gene drive's impact, another idea being discussed is that of 'reversal drives' or 'immunisation drives'.[12] This idea must also be questioned critically as it relies on the same risky technology whose risks it is intended to mitigate. The effectiveness of using one such drive to mitigate another is questionable.

3.2.4 Factoring in opportunities

If a consequentialist risk assessment is considered admissible, i.e. if opportunities are to be weighed up against risks to achieve the greatest possible benefit, such a calculation requires the necessary data on opportunities as well as risks. The opportunities of using gene drives to combat a problem cannot be assessed in relation to a control organism, but must be judged in comparison to existing control strategies. Examples of such strategies include the use of insecticides or mosquito nets to combat malaria and the use of poisons or traps to control mice or mouse-borne diseases.

It should be noted that opportunities in general, and those of gene drives in particular, also have to be considered from the point of view of deontological ethics. Thus, there are obligations in terms of solidarity and assistance, such as the duty to help people suffering from malaria as much as possible. If these positive obligations collide with negative obligations, a conflict of obligations arises which requires a weighing of interests. On the other hand, opportunities must not be taken into account if those affected are exposed to an unreasonable risk.

3.2.5 Challenges associated with great opportunities

- The greater the risks of using gene drives, the more critical it is to examine the objectives as a whole. The goals pursued must be of sufficient moral importance to justify the risks associated with gene drives. For example, the prevailing view among ECNH members is that this is not the case with the eradication of invasive alien living beings to protect native fauna and flora. By contrast, the ECNH sees the fight against diseases such as malaria as a high-priority objective. However, this does not mean that *any means* of achieving this objective are justified.

- Some people consider that gene drives provide very great opportunities to tackle what are recognised as being major problems. However, where the suffering of those affected is great, there is a fear that gene drives could be used without sufficient prior risk assessment.

- An exceptional situation, such as an acute emergency that requires intervention, makes it harder to lay down decision-making criteria. Nevertheless, even when under pressure, it is important to be aware that the benefits are not assured but are opportunities (i.e. positive effects that only have a certain probability of occurring). Even in such circumstances, a scientific basis is needed to estimate in advance the probability that these opportunities will occur. As a general rule, the *criteria for using new technologies in exceptional cases* should, whenever possible, be discussed and determined *before* the exceptional situation arises (e.g. an outbreak of a serious illness). Such special criteria for exceptional cases are also applied in other areas of risk.

- On the other hand, alternatives should always be considered. It may be that the chosen gene drive method will generate even greater risks, for example because organisms will adapt over time or because the use of gene drives causes pre-existing control measures such as the use of insecticides and mosquito nets against malaria to be neglected. In addition, a high-risk control method can divert attention away from the causes of a problem, which could be counteracted more efficiently, on a longer-term basis or with less risk using other means.

3.2.6 Challenges in relation to the decision-making process

Gene drives released into the environment have the potential to cause an impact that is not limited in time or space. While the risk assessment must be based on scientific data, the question remains open as to who decides which scientifically determined potential effects are to be considered positive or negative and what risk is ethically acceptable and therefore tolerable for all concerned.

3.3 Biosecurity risks

Gene drives could conceivably be used as biological weapons, for example by deliberately transmitting pathogens to humans and animals or damaging food sources. It is therefore important to examine to what extent the development and application of gene drives would create new biosecurity risks.

Biosecurity risks arising from 'garage' or 'do-it-yourself' biology, as a result of gene drives being produced inadvertently, are generally considered to be low at present. This is because producing gene drives is complex and requires a high level of specialist and technical knowledge, so the probability of gene drives being created in this way is small. That said, these biosecurity risks will need to be borne in mind as gene drives and their applications develop further, as the technical barriers to their production will presumably decrease.[13]

12 This would involve superimposing a 'reversal drive' on an existing gene drive to correct its effect. An 'immunisation drive' would protect carrier organisms from the effects of another gene drive.

13 For further considerations by the committee on biosecurity, see: ECNH, Freedom of research and biosecurity. Ethical considerations by the example of dual use research of concern, 2015. (Available in German and French only)

4 Recommendations

Recommendations on regulation

1.

Dealing with gene drives on the basis of an appropriate risk assessment. The rapid development of new techniques, including synthetic gene drives, and their use in the environment present regulatory challenges. The potential opened up, or at least promised, by the use of gene drives comes with risks attached. Consequently, the way that gene drives are managed and used must be determined by an appropriate risk assessment.[14]

2.

Consistent strengthening and application of the idea of precaution. In cases where data is lacking for an appropriate risk assessment, from an ethical perspective the concept of precaution comes into play. This is reflected in the precautionary principle under environmental law. In its 2018 report 'Precaution in the environmental field. Ethical requirements for the regulation of new biotechnologies', the ECNH examined in detail the conditions for decision-making in precaution situations (see Recommendations 1–4 of that report).

3.

International regulation. Given the specific mechanisms associated with gene drives and the resulting risks, regulation applying to Switzerland alone would be of limited effectiveness. The ECNH recommends that Switzerland systematically raise and champion the ethical requirements associated with gene drive use in international regulatory discussions. This includes enshrining participatory decision-making processes (see also Recommendation 8).

4.

Decision-making criteria for exceptional situations. The criteria governing the use of gene drives in exceptional situations, such as the outbreak of a major epidemic, need to be discussed as a matter of urgency. In such situations, decisions are taken under great pressure. It is therefore all the more important to define the criteria for exceptional cases before they occur.

Recommendations on implementation

5.

Compiling risk data. Given the way gene drives work, designing a step-by-step approach to this technology poses a major challenge for researchers and potential users. Without suitable concepts, the considerations for dealing with precaution situations will apply, along with the associated consequences. If suitable concepts are in place, an appropriate risk assessment is required. For this to take place, relevant scientific risk data must be collected. In keeping with the step-by-step approach, it is important not only to investigate the efficiency and effectiveness of gene drives but also to collect risk data in such a way as to enable the risks of the next step to be adequately assessed.

6.

Enable monitoring. From an ethical point of view, it is important to have systematic monitoring that can be overseen by independent bodies. To enable such monitoring of gene drives, the sequence of the gene drive must be accessible to any institution that carries out monitoring.

14 See ECNH, Release of genetically modified plants – ethical requirements (2012) and ECNH, New Plant Breeding Techniques – Ethical Considerations (2016).

7.

Reporting body to gather information. Another challenge lies in gathering the required risk information. The ECNH recommends setting up an international body to which gene drive developments can be reported. This body would pool risk information and make it available to decision-making authorities.

Recommendations on participation

8.

Establish and adhere to appropriate decision-making processes. At national level, decisions concerning the use of gene drives should be based on democratic decision-making processes. In view of the potential transnational impacts of gene drives, there should be cooperation with the countries concerned, including efforts at this level to promote compliance with democratic decision-making processes.

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