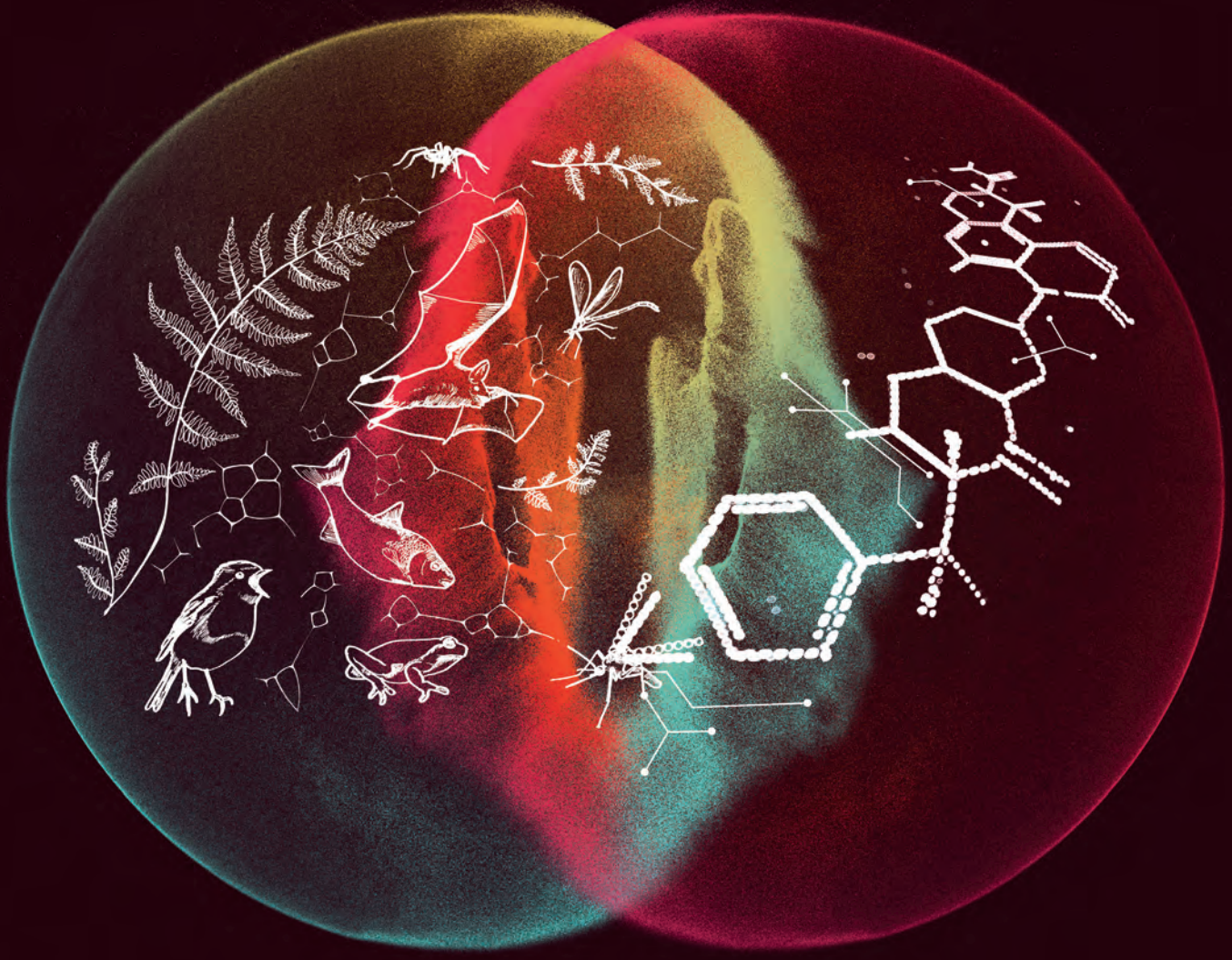

GENE DRIVE ORGANISMS: A NEW DIMENSION OF GENETIC ENGINEERING

Applications, risks and regulation

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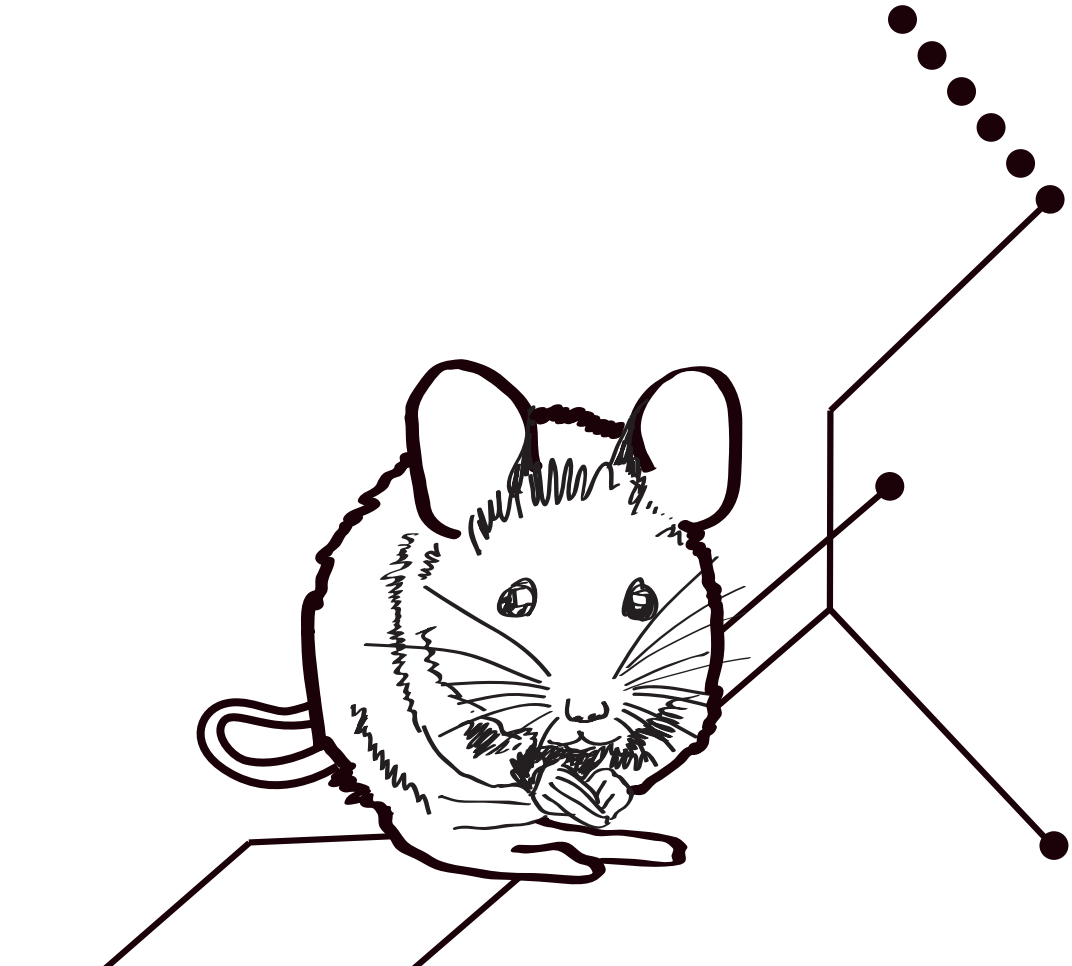
01

WHAT ARE GENE DRIVE ORGANISMS?



Enabled by new genetic engineering techniques such as CRISPR/Cas9, so-called gene drives have been developed in recent years that enable humans to spread new genes throughout the genome of wild animal populations. Gene drives force the inheritance of newly introduced genes to be inherited by all offspring, even if this lowers the survival chances of the affected species. In the most extreme case, gene drive technology could drive an entire species to extinction or replace wild populations with genetically modified organisms.

'Selfish' reproduction

In nature, the process of evolution is slow: It takes many generations before inherited changes take hold. In sexual reproduction, genetic material recombines in each generation. New traits are in constant competition with older ones. However, only one of the two is passed on to the offspring. Which one is determined by chance. According to Mendel's rules, the probability that a new trait will be passed on to the offspring is 50 percent. As a rule, a higher inheritance rate only occurs if the traits are associated with advantages for the survival of the species.

However, not all natural genetic traits follow these Mendelian rules of inheritance. In plants, animals and humans, there are genetic elements that copy themselves into other parts of the genome with the help of enzymes, spreading independently and thus increasing the frequency of their inheritance. They are often referred to as naturally occurring gene drives and have been termed 'selfish' genes because they can spread throughout the genome without benefiting the species. Examples are so-called 'jumping genes' (transposons). In the course of evolution, plants, animals and humans have found a way to deal with these genetic elements: Some gave rise to important functional, usually regulatory, units. In many other cases, mechanisms have been developed to silence the 'jumping genes' in the genome (for more information, see infobox).

Gene drives are based on a similar principle. In 2003, British researcher Austin Burt formulated the idea that genes can spread rapidly if they over-write competing variants. The natural evolutionary process then no longer applies.[1]

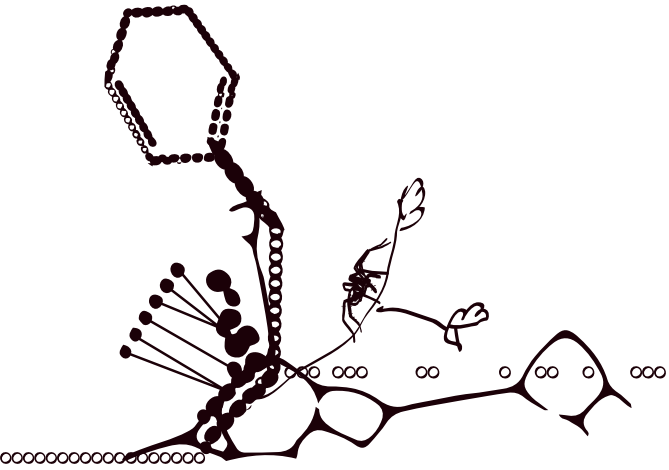
With gene drives humans can alter the genetic makeup of wild organisms and spread new characteristics that serve human purposes alone.

→ What are gene drive organisms?

CRISPR/Cas9 makes it possible

The realization of Burt's idea of repurposing 'selfish' genetic elements for human purposes failed for a long time due to technical hurdles. That changed in 2012, when Jennifer Doudna and Emanuelle Charpentier, now both Nobel laureates, recognized the potential of the CRISPR/Cas9 system for biotechnology.[2] In bacteria, it can serve as a kind of immune system to provide protection against viruses: The CRISPR sequence in the bacteria's genome recognizes the invader and activates enzymes that attack the virus and cut up its genome.

These two researchers were the first to realize that the combination of CRISPR sequences and Cas9 could be used to specifically alter the genome of many living organisms and introduce new segments into their DNA. It was the missing tool needed to turn Burt's idea into reality.[3] In 2015, a functional CRISPR/Cas9 gene drive in fruit flies was published for the first time.[4] In the years that followed, trials in mosquitoes[5] and mice[6] were also successful. Researchers now suspect that almost any animal species could be manipulated with a gene drive.



Difference between 'selfish' gene variants, 'natural' gene drives and engineered gene drives

So-called 'selfish' genetic elements are found in the genome of almost all living beings. Their reproduction seems to be of no consequence in the short term. However, they play an important role within longer periods of evolution. They contribute to the emergence of new gene variants and may well facilitate adaptation to changing environmental conditions. Numerous protective mechanisms limit the uncontrolled multiplication of these elements in the genome and limit the damage to the living being.

Transposons are among the most common 'selfish' elements.[7] They essentially consist of an enzyme that makes copies of the transposon and inserts them elsewhere in the genome. This is where the term 'jumping genes' comes from. They were originally discovered by Barbara McClintock, who was awarded the Nobel Prize in 1983.

In bacteria, a particular variant of 'selfish' elements called homing endonucleases has been discovered.[8] They, too, consist of only a single enzyme and can insert themselves precisely into specific DNA sequences. Synthetic homing gene drives based on CRISPR/Cas9 have been designed along these lines.

Engineered gene drives, on the other hand, are artificial genetic elements that come with specific human-determined purposes and functions. They have not evolved and adapted through evolutionary processes. They are designed to serve human interests. Evolutionarily established mechanisms that control the spread of 'jumping genes' are often ineffective here. Engineered or synthetic gene drives thus set in motion a 'mutagenic chain reaction'[9], the consequences of which cannot be controlled.

Some publications refer to Wolbachia bacteria as 'natural' gene drives. This is not quite correct: Wolbachia is a bacterial infection of insects that is heritable over generations.[10] Wolbachia bacteria occur naturally in the cells of certain insects, such as fruit flies. They reduce the reproductive capacity of infected insects. Therefore, with the hope of combating dengue fever, mosquitoes of the species Aedes aegypti were infected with Wolbachia bacteria in the laboratory. It was found that certain Wolbachia bacteria can block the transmission of dengue fever to humans.[11] Field trials with Wolbachia infected mosquitoes first took place in 2011 for testing purposes in Australia.[12] Unlike synthetic gene drives, this approach does not use genetic engineering. This means that the risks of genetic side effects associated with genetic engineering through cross-breeding and interaction with wild populations are not relevant in Wolbachia interventions.

The new dimension: The difference between genetically modified organisms and genetically modified gene drive organisms

For several years, release experiments with genetically engineered insects have been taking place in the environment for research purposes. For example, since 2011, the company Oxitec in Brazil has repeatedly released genetically. modified mosquitoes of the species Aedes aegypti. Their genetic modification was intended to render the offspring of the mosquitoes unable to reproduce.[13] The goal of these releases was to significantly reduce the tropical disease-carrying mosquito population. Whether the goal was achieved is debatable.[14] In any case, none of the past releases involved insects that inherit gene drives.

But what is the difference between genetically modified organisms (GMO) and genetically modified organisms that inherit a gene drive, making them a gene drive organism (GDO)?

The new dimension of genetically modifying wild populations with gene drives is in stark contrast to the previous goals, strategies, and possibilities of genetic engineering.

Until now, genetically modified organisms have not been expected to produce viable offspring, have not been expected to survive in the wild for long, or have been prevented from mating with wild conspecifics. Thus, so far, the spread of GMO should have remained limited in space or time outside of their point of origin in the laboratory. Neither these genetically modified organisms nor their modified genes were supposed to persist in nature.

The gene drive approach breaks radically with these considerations. In contrast to conventional GMO, genetically modified organisms that inherit gene drives aim to spread genes synthesized in the laboratory into wild populations or to eliminate natural genes. And they do so even if this harms the species or offers it no survival advantage, which is why these genes would not prevail on the basis of natural selection.

Gene drives shift the locus of genetic modification from the genetic engineering laboratory to the wild: In the case of CRISPR/Cas9-based homing gene drives, the genetic engineering mechanism (CRISPR/Cas9) copies itself into the genome of wild offspring every time a GDO reproduces - over generations. The 'forced' inheritance of even harmful genes triggered by the gene drive sets in motion a theoretically unstoppable "mutagenic chain reaction"[15].

Thus, via gene drives, human-induced genetic modifications can spread through wild populations much faster than conventional GMO, based on natural selection mechanisms, could have done.[16]

Until now, all experiments with genetically engineered gene drives have taken place exclusively in the laboratory or in closed containers. But gene drives are actually intended for use in the wild. They are designed to introduce new genes into the genome of wild populations, even if these reduce the chances of survival of the species concerned.[16]

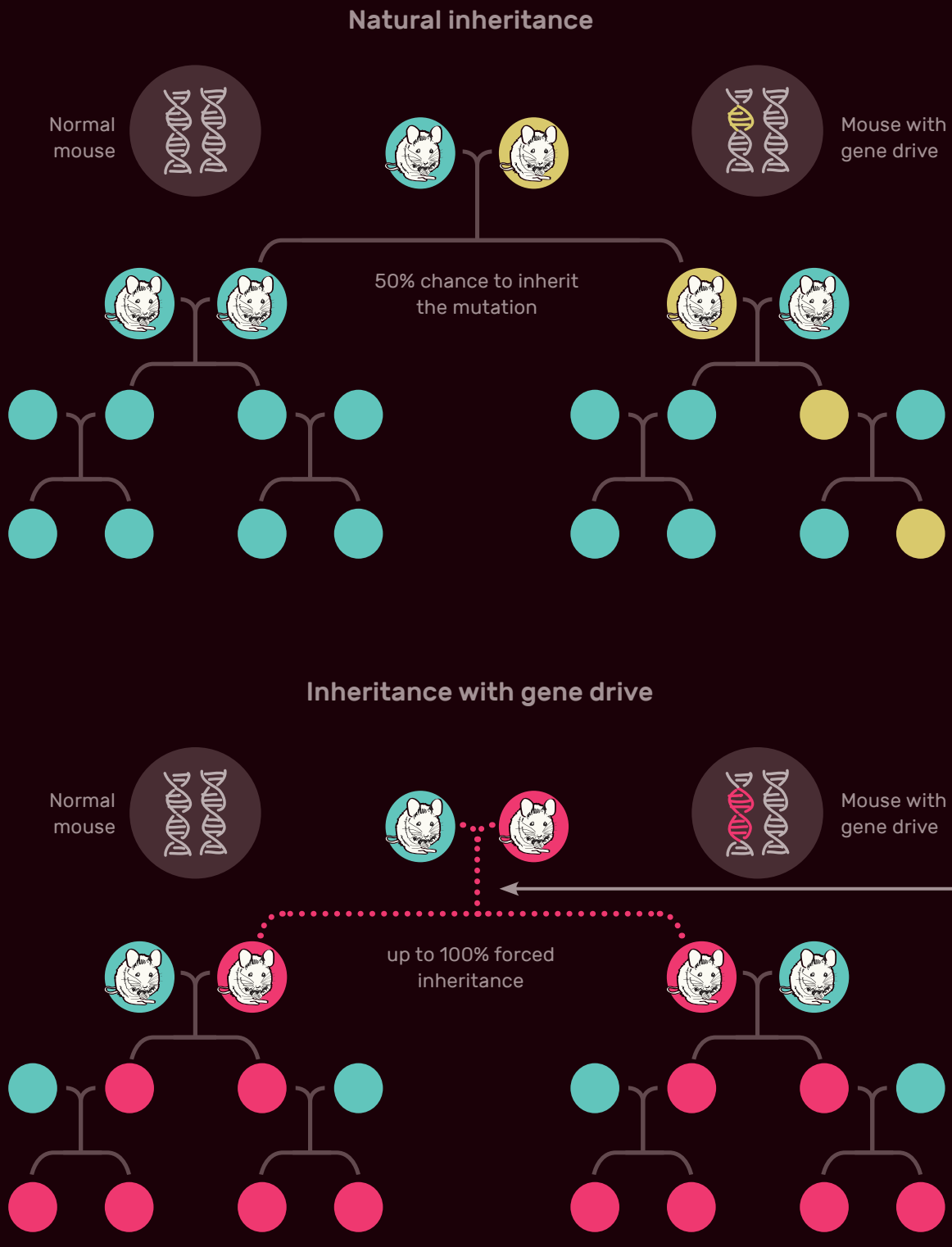
The goal of their use in the wild may be to replace the entire wild population with genetically modified gene drive organisms or to greatly reduce it. In the most extreme case, deployment could drive the entire species to extinction.

First field trials with gene drive mosquitoes could be carried out in Burkina Faso as early as 2024.[17] *This would be an experiment without any safeguards: mechanisms that effectively control a gene drive in nature only exist in theory.*

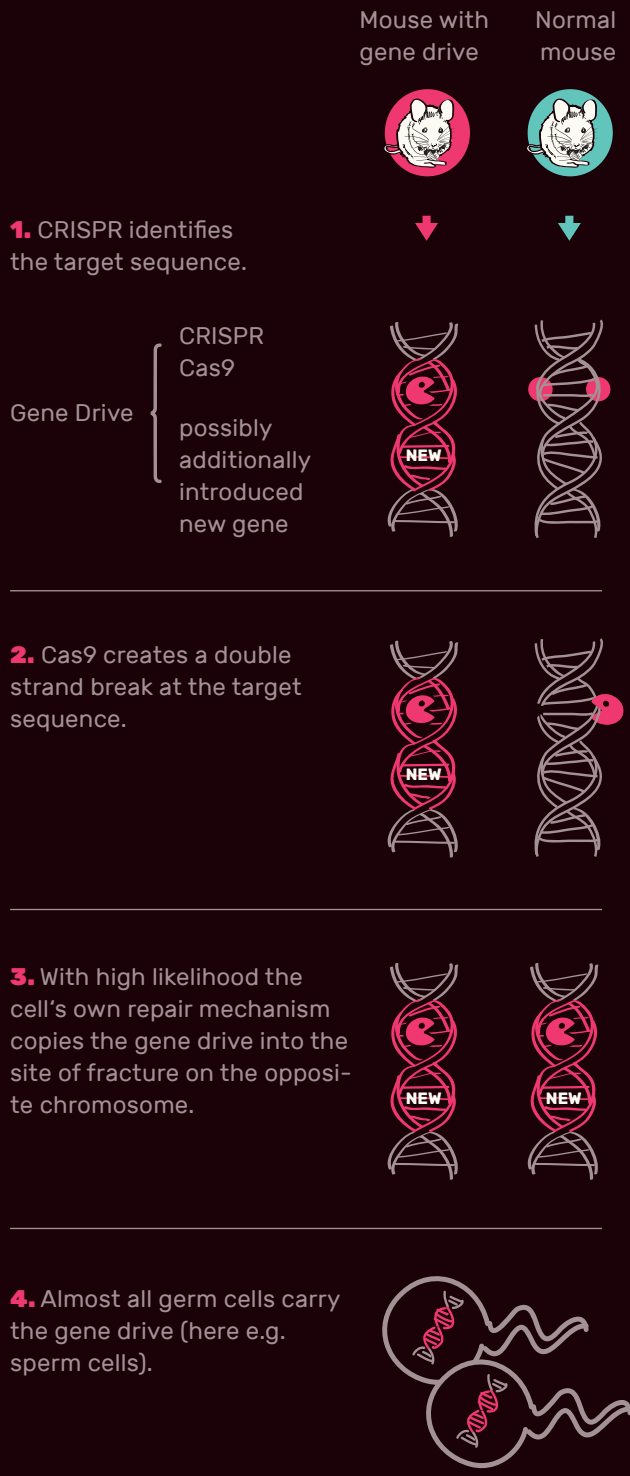
According to the current state of science, the outcome of the experiment would no longer be controllable by humans. All manipulations of this kind on animals, plants and entire ecosystems would be irreversible.

What are gene drive organisms?

How does a homing gene drive with CRISPR / Cas9 work?



Forced inheritance with gene drives

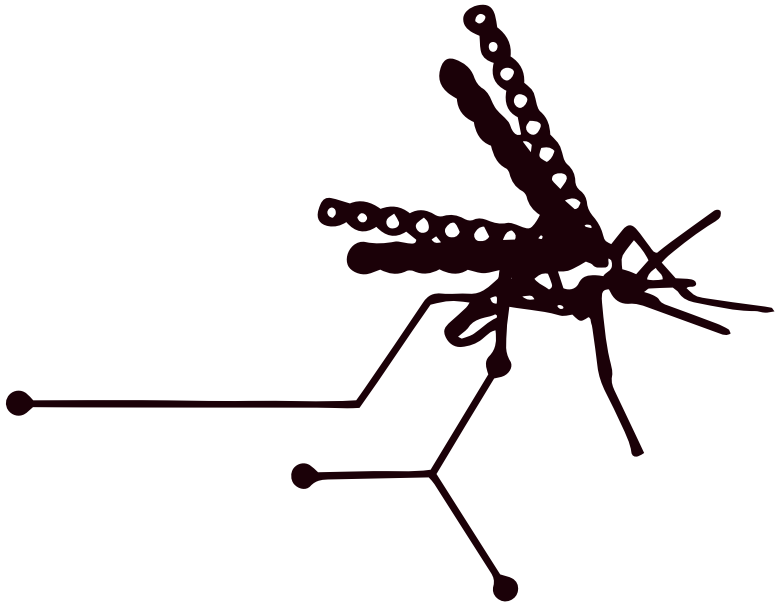


How does a CRISPR/Cas based or homing gene drive work?

So-called homing gene drives based on CRISPR/Cas9 are the most common variant of synthetic gene drives. Such a gene drive consists of at least two components: the Cas9 genetic 'scissors' and a messenger molecule. In addition, a new or modified gene can be introduced. The gene drive is first introduced into the genome of the target organism, e.g. a mouse, in the laboratory. This gene drive becomes active after fertilization of the egg cell and identifies a target sequence in the non-manipulated chromosome with the help of the messenger molecule. There, Cas9 induces a double-strand break. Natural repair mechanisms in the damaged cell then attempt to repair the break using a template. The gene drive on the genetically modified chromosome serves as a template: it is very likely to be copied completely and incorporated within the target sequence on the previously unmanipulated chromosome. This targeted process is called homing. In addition to the integration of the gene 'scissors' at the target site, existing gene sequences can be switched off and/or new ones can be additionally inserted. This process ultimately results in all offspring inheriting a copy of the gene drive. The gene drive mechanism is re-activated with each reproduction - and in all subsequent generations. It theoretically only comes to a halt when the target sequence has disappeared from the entire population.

02

POTENTIAL APPLICATIONS OF GENE DRIVE ORGANISMS



Gene drives could be applied in numerous fields. Currently, research is focused on three areas: the control of disease vectors, the removal of invasive species from sensitive ecosystems, and the control of so-called pests in agriculture.

GENE DRIVES FOR THE ELIMINATION OF DISEASE CARRIERS

Infectious diseases such as malaria, dengue fever and Lyme disease are transmitted to humans by mosquitoes or ticks. Controlling these vectors has long been part of disease prevention. Gene drives are expected to take these efforts to a new level.

Malaria

The malaria pathogen is spread by several species of Anopheles mosquitoes. A concerted global program of malaria control using mosquito nets, insecticides and medicines has helped push back the disease in many regions of the world, reducing deaths by about half between 2000 and 2015.[18] In 2016, the World Health Organization (WHO) identified 21 countries with the potential to reach the goal of zero indigenous malaria cases by 2020.

In the process, 39 countries have already been certified as malaria-free, most recently Sri Lanka (2016), Paraguay (2018), Algeria (2019) and El Salvador (2021).[19] China, Malaysia and Iran are also well on their way to achieving the three-year malaria-free status required for certification. Other factors for successful control of the disease include, above all, strong political will, a functioning health system, good training of medical personnel, national programs for education and prevention activities, medical surveillance programs, rapid and correct diagnosis and treatment, and rapid responses to outbreaks that do occur.[20] But there remain 87 countries where such measures have not been adequately implemented. In 2017, more than 200 million people contracted malaria, and more than 400,000 people died from it. Sub-Saharan Africa is the hardest hit, with mortality particularly high among children under five.[21] Gene Drives are intended to remedy this situation by massively reducing the number of Anopheles mosquitoes in Africa and thus also the transmission of malaria.

Target Malaria, an international research consortium, is playing a leading role in the development of such gene drives. The consortium has a budget of around 100 million U.S. dollars, most of which comes from the Bill & Melinda Gates Foundation and the Open Philanthropy Project.[22 23]

Target Malaria's plans have already reached the stage where the first model projects have been launched in Burkina Faso, Mali, Ghana and Uganda.

To control mosquito populations, Target Malaria is taking two different approaches:

One aims to create sterile female Anopheles mosquitoes by altering a gene called Doublesex. A CRISPR/Cas9 gene drive will be used to spread this genetic modification into the wild population. In 2018, experiments in large cages showed that this

approach works in principle: The gene drive caused the population to collapse after about ten generations.[24]

Target Malaria's second approach involves manipulating the sex distribution of mosquitoes so that only male mosquitoes are born. This approach is being tested in a project in Burkina Faso in three different phases, in which a gene drive will only be used in the third phase.

In the first phase, male mosquitoes were rendered unable to reproduce using genetic engineering.[25] Field trials with these sterile mosquitoes were conducted in Burkina Faso in 2019.[26] According to Target Malaria, these preliminary trials are aimed at gaining field experience and familiarizing the population in Burkina Faso with such trials. Although Target Malaria claims to have involved the local population in the decision-making process, these experiments caused protests both in Burkina Faso and internationally.[27] [28]

In the second phase the mosquitoes are to be genetically modified so that they produce predominantly male offspring.[29] The genetic modification introduced via a so-called X-shredder (see box) would be inherited according to Mendelian rules. Thus it is not yet a gene drive at this stage. In order to reduce the mosquito population with these releases, genetically modified mosquitoes produced in the laboratory would have to be released repeatedly in high quantities.

The goal of Target Malaria in the third phase is to produce mosquitoes that carry the X-shredder on the Y chromosome, which would make all offspring male for generations and all carry the X-shredder. The genetic modification thus spreads like a gene drive throughout the population.[30]

While Target Malaria focuses on reducing the number of mosquitoes, gene drive developers at the University of California in San Diego are taking a different approach. With a multi-million dollar grant from India's Tata Foundation[31], they are looking for a way to create resistance in Anopheles mosquitoes that kills the malaria pathogen and prevents the infection of humans.[32] However, such gene drive organisms had proven to have only limited viability in initial cage experiments.[33]

Lyme disease

In temperate climates, the use of gene drives against Lyme disease is being considered. In the U.S., Lyme disease spread rapidly in 2018, affecting about 300,000 people annually.[34] For Germany, according to a projection from 2017, the number of new cases is estimated at about 100 000 per year.[35]

The disease is triggered by Borrelia bacteria, which often infect wild mice and are transmitted to humans by ticks. If the infection is not detected in time, a chronic disease can develop that is difficult to treat.

On two islands in the northeastern United States, a project was launched in 2016 that aims to interrupt the transmission of the disease with the help of genetic engineering. The target of the genetic manipulation is not the ticks as carriers, but the native white-footed mice, which are the most important host for Borrelia in these regions. An intervention in the immune system is supposed to make the mice resistant and interrupt the transmission chain of Borrelia. According to a citizen survey on the islands of Nantucket and Martha's Vineyard in Massachusetts, USA, a majority rejected the use of gene drive. Instead, the release of genetically engineered mice is forseen. They are supposed to mate with their wild counterparts and crossbreed a resistance to Lyme disease into the natural population. However, should trials on larger land masses be planned for the future, the use of gene drive mice would again be up for debate.[36]

There are several alternative strategies to prevent the transmission of Lyme disease to humans apart from gene drives and other genetic engineering methods. Infection can already be prevented by simple means: by wearing suitable clothing, applying anti-tick medication and regularly scanning the body. For a short time in the past, a vaccine by the American company GlaxoSmithKline (GSK) was readily available, but it was taken off the market again due to lack of interest.

How does a gene drive with X-Shredder work?

Genetically modified mosquitoes that carry an X-shredder are supposed to only produce male offspring.

During the formation of the mosquito germ cells, an enzyme is produced that cuts the X chromosomes and thus destroys them. Therefore, only male germ cells that pass on a Y chromosome are produced. Up to 95 percent of the offspring are therefore male and can spread the X-shredder in the population.[37]

X-Shredder variant 1 - No gene drive – If the X-Shredder is inserted on a chromosome that does not determine the sex, it is inherited according to Mendelian rules and probably cannot be found in the genetic material of the population after a few generations.

X-Shredder variant 2 - gene drive – The X-Shredder only becomes a gene drive when it is inserted on the male Y chromosome. In theory, it could then spread through the population as aggressively as a CRISPR/Cas-based homing gene drive. However, the development of such a variant currently face biological hurdles: epigenetic regulation of gene expression in mosquitoes prevents the X shredder from being activated on the Y chromosome.[38]

X-Shredder variant 3 - gene drive – It is also possible to combine the X-Shredder (variant 1) with a CRISPR/Cas-based gene drive. This is then called Sex Distorter Gene Drive (SDGD): If females mate with males carrying the CRISPR/Cas gene drive with the coupled X-Shredder, the gene drive is integrated into the gene Doublesex, which prevents the development of fertile females. The additionally integrated X-Shredder causes the X chromosome to be cut during the formation of the germ cells. The overall result is predominantly male offspring[39] In the combination of CRISPR/Cas gene drive and X-Shredder, both systems mutually safeguard each other: Should one system fail, the other will function. According to model calculations, the number of (biting) female mosquitoes could be reduced much faster with the Sex Distorter Gene Drive than with an exclusive CRISPR/Cas gene drive.

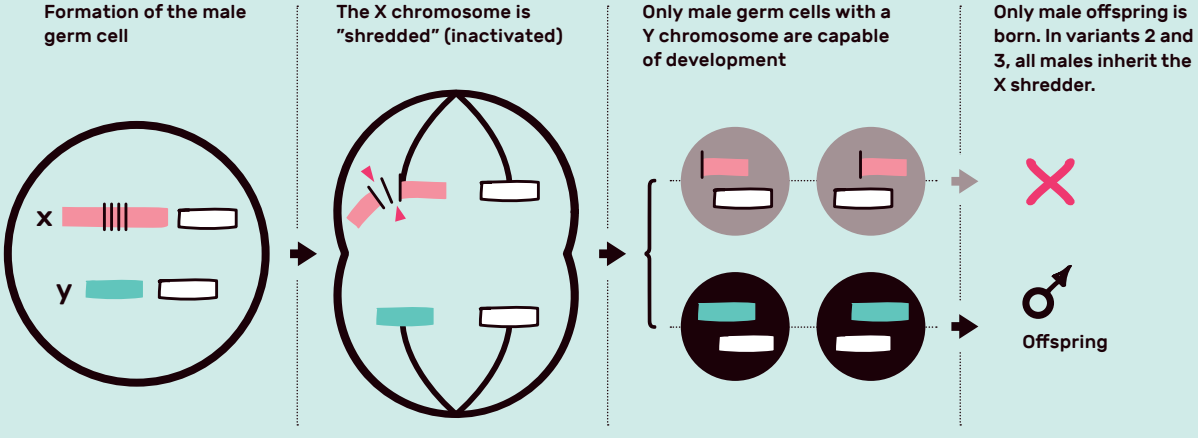


Illustration adapted from: Galizi, R., Doyle, L.A., Menichelli, M., Bernardini, F., Deredec, A., Burt, A., Windbichler, N., Crisanti, A., 2014. A synthetic sex ratio distortion system for the control of the human Malaria mosquito. Nat. Commun. 5, 3977. https://doi.org/1038/ncomms4977

USING GENE DRIVES TO COMBAT INVASIVE SPECIES

Humans have carried numerous animal species to foreign islands and continents, where they have become a serious threat to native flora and fauna. Major problems are caused, for example, by rats and mice, which significantly reduce populations of smaller animals and native birds. Conventional measures such as hunting, trapping, or poison baiting have been able to drive invasive species off small islands. On larger land masses, these measures reach their limits. Gene drives are intended to offer an alternative here.

The Genetic Biocontrol of Invasive Rodents (GBIRd) project, which is supported by seven universities, public authorities and non-governmental organizations from the USA and Australia, is investigating this approach.

GBIRd aims to address the question of whether mice can be eradicated through gene drives and under what conditions this intervention would be acceptable. The bulk of the project is funded by the U.S. military's Defense Advanced Research Projects Agency (DARPA) to the tune of $6.4 million.[40]

Among the most active members of GBIRd is the small conservation organization Island Conservation. It has been dedicated to the protection of seabirds for 25 years and says it has already rid 63 islands of rodents. So far, this has been done using conventional methods, but Island Conservation believes that further progress will require the use of gene drives.[41]

The first steps in this direction were taken at the University of California in San Diego, USA, when gene drives for mice were developed there for the first time in 2019.[42] However, the developers encountered an unexpected phenomenon: CRISPR/Cas9 was able to cut the DNA strand in all test animals, but only in females did the repair mechanism kick in, which activley spreads the new DNA segments in the genome. The gene drive was therefore only successful in one of the two sexes, and even there it only achieved an efficiency of about 70 percent. The gene drive in this form is probably not suitable for manipulating wild-living mammal populations.

New Zealand's former government also showed interest in using gene drives. The country's unique flora and fauna suffer great damage from introduced rats, stoats and the Australian fox cusu. With the Predator Free 2050 program, the New Zealand government pursued the goal of eradicating all invasive predators by 2050. The measures have already been successful on more than 100 smaller islands. To achieve success on the main islands as well, the use of gene drives was considered.

In light of the consideration of using gene drives for invasive species eradication in New Zealand, two gene drive developers published an article in 2017 warning against hasty releases and the use of gene drive organisms in conservation.[43]

Since the change of government that same year, there has been greater restraint in New Zealand in this regard. Before Predator Free returns to the topic, the many technical, social and ethical considerations and regulatory hurdles first have to be explored and overcome.[44]

The discussion on gene drives in the International Union for Conservation of Nature (IUCN)

In view of the possibility of using gene drives to remove introduced invasive species from sensitive ecosystems, the International Union for Conservation of Nature (IUCN), also known as the World Conservation Union, has also been discussing this technology since late 2015.

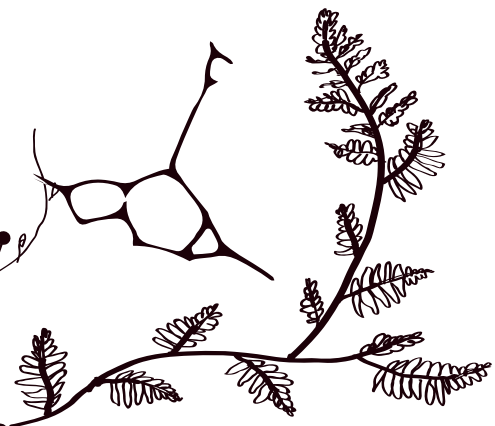
At its General Assembly in Hawaii in September 2016, IUCN adopted a resolution[45] that, among other things, mandated IUCN to prepare a scientific report on the implications of synthetic biology and gene drives for biodiversity conservation. Based on this scientific report, IUCN originally intended to take a position on the role of gene drive technology for nature conservation at its subsequent General Assembly in 2020.

In part through public protest and at the urging of global conservation luminaries[46] , IUCN committed in its 2016 resolution to refrain from any support or endorsement of research, field trials, or use of gene drive technology until this report would be available.

The report, entitled 'Genetic Frontiers for Conservation[47], was published in May 2019 and was met with harsh criticism from IUCN member organizations as well as conservation and development organizations around the world.

An analysis conducted by the research and advocacy organization ETC Group[48] concluded that a majority of the report's authors were known proponents of genetic engineering and should not have been engaged by IUCN, in part because of their economic self-interest in developing the technologies studied. In a subsequent open letter signed by 231 civil society organizations and several scientists, the report was criticized as "regrettably one-sided", "biased", and "inappropriate for the intended policy discussion". This report, they said, is not consistent with the precautionary considerations of the Hawaii resolution. The undersigned organizations therefore called on IUCN to commission another scientific report based on a precautionary analysis of the risks of the technology and to wait until such a counter-report is available before taking a decision on the issue.[49] In a similar vein was the request of an October 2019 letter from 23 IUCN members to the IUCN Council. According to its signatories, more time is needed for a fundamental, comprehensive, balanced discussion based on the precautionary principle, with greater involvement of IUCN members, prior to any IUCN decision-making.[50]

Confronted with this criticism, the IUCN Council withdrew its plan to adopt a position at its Members' Assembly, originally planned for June 2020. Instead, principles[51] for the discussion on the topic were defined in a consultation open to members. These are to be voted on at the IUCN World Conservation Congress in 2021 and will serve as the basis for a for discussions until a position will be voted on at the following Members' Assembly.



GENE DRIVES IN AGRICULTURE

In the long run, agriculture could become the most important field of application for gene drives - a fact that has hardly been discussed in public so far. Patents on CRISPR/Cas-based gene drives list hundreds of animals and plants whose containment or eradication could increase agricultural yields. However, a number of hurdles would still have to be overcome along the way.

Patent applications for agricultural applications

At least six patents on gene drives refer to specific applications in agriculture. The focus is on controlling pests and weeds and reversing herbicide resistance.

Two key applications come from leading developers of the CRISPR/Cas-based Gene Drive, the research groups led by Kevin Esvelt[52] and Ethan Bier[53]. Numerous claims are also filed in a patent by Bruce Hay's group.[54] Most of the claims are general, but one patent already contains detailed goals and methods that enable commercial use.

However, the commercialization of gene drives faces a fundamental problem: their spread cannot yet be contained, either spatially or temporally. Individual releases could result in the transboundary spread of GDO into neighboring ecosystems for decades. The classic business model of agribusinesses, which is based on continuous sales of the products, would be difficult to apply under these conditions.

In theory, its use appears commercially interesting in two scenarios: A gene drive could eliminate natural resistances that wild plants have developed to common herbicides. An agribusiness could then profit from increased sales of the herbicide because they would become usable again. Another scenario would be for large agricultural associations to fund the development of a gene drive that would benefit all association members.

Number of patent claims on possible agricultural gene drive applications

WO 2015/105928 A1

Titel: RNA-Guided Gene Drives
Assignee: President and fellows of Harvard College
Inventors: Kevin Esvelt, Andrea Smidler
International publication date: July 16, 2015

12 corn pests

9 cotton pests

13 small grain pests

10 soybean pests mentioned "within the scope of the present disclosure"

11 grape vine pests

13 palm tree pests

16 pests of nightshade crops, including peppers, tomatoes, eggplants, tobacco, petunias, potatoes

14 stone fruit pests

8 cyst nematode species

24 bark beetle species

11 pests of mollusc pests

186 name brand herbicides

11 pests of moth species

27 agribusinesses named

112 noxious weed varieties (**19** aquatic weed species, **5** parasitic weed species, **88** terrestrial weed species)

52 "additional weeds within the scope of the present disclosure" (e.g., ragweed, poison ivy, goldenrod)

46 pesticide species, e.g., atrazine, glyphosate, napthalene, copper hydroxide

Infographic adapted from: ETC Group, Heinrich Böll Foundation (2018). Forcing the Farm. How Gene Drive Organisms Could Entrench Industrial Agriculture and Threaten Food Sovereignty.

WO 2017/049266 A2

Title: Methods for Autocatalytic Genome Editing and Neutralizing Autocatalytic Genome Editing and Compositions Thereof

Assignee: The Regents of the Univeristy of California

Inventors: Ethan Bier, Valentino Gantz, Stephen Hedrick

International publication date: March 23, 2017

301 agricultural insect pests

20 agricultural pest mites

96 agricultural pest nematodes

68 plant pathogenic nematodes

48 insect vectors of plant pathogens

27 ornamental insect pests

6 mollusc pests

18 grape pests

6 strawberry pests

8 honey bee pests

34 mentioned weeds resistant to pesticides or herbicides

Infographic adapted from: ETC Group, Heinrich Böll Foundation (2018). Forcing the Farm. How Gene Drive Organisms Could Entrench Industrial Agriculture and Threaten Food Sovereignty.

Examples of gene drive applications in agriculture

The use of gene drives would be conceivable for almost every field crop and for numerous farm animals or so-called pests. In three cases, there are already concrete plans.

Spotted wing drosophila

Originally native to Southeast Asia, the spotted wing drosophila (Drosophila suzukii) is a fruit fly that has spread worldwide and causes significant crop losses in numerous fruit varieties. It lays its eggs in nearly ripe, undamaged fruit with thin skins. In 2008, the spotted wing drsophila reached California and caused more than $38 million in damage to cherry orchards the very next year. According to calculations, these losses can rise to over $500 million annually in the western United States.[55] Since 2011, it has also appeared in Germany, jeopardizing the harvest of cherries, grapes, raspberries, blackberries and strawberries.[56]

In 2013 the California Cherry Board, an association of California cherry growers, began funding research on a gene drive with $100,000 annually.[57] A group of researchers at the University of San Diego, USA, developed a so-called Medea Drive.

The flies' offspring are not viable. This can affect one or both sexes (for more information, see infobox).

In initial laboratory experiments, a high number of modified flies was necessary to establish the Medea Drive in the population. In addition, many fly populations in the wild have natural resistances that would probably strongly hinder the spread of the Medea Drive. The researchers therefore suspect that a very large number of modified spotted wing fruit flies would have to be released to keep the Medea Drive in the population for several years. No field tests have been planned yet.[58] The patent applied for in 2017 on this Medea Drive also covers other species of tropical fruit flies as well as mosquitoes of the genera Anopheles and Aedes, which transmit malaria and numerous viral diseases.[59]

Psyllids

Other potential target organisms for a gene drive are psyllids. In 2005, bacteria that infect citrus trees and render their fruit inedible were detected for the first time in the USA. It is spread by introduced Asian citrus psyllids (Diaphorina citri), which ingest the bacteria while sucking plant sap and can then infect other trees. Within three years, the disease, called Huanglongbing, spread across most of Florida's cultivation regions, with citrus production plummeting by 70 percent.[60] Europe has so far been spared from the disease, but spread cannot be ruled out.[61]

Citrus growers in California are considering the use of gene drives to protect their plantations.[62] One option would be to release gene drive psyllids that cannot transmit the bacteria. A research project on this was completed in 2017 and identified a number of genes that could prevent transmission.[63] However, a gene drive has not yet been developed from this.

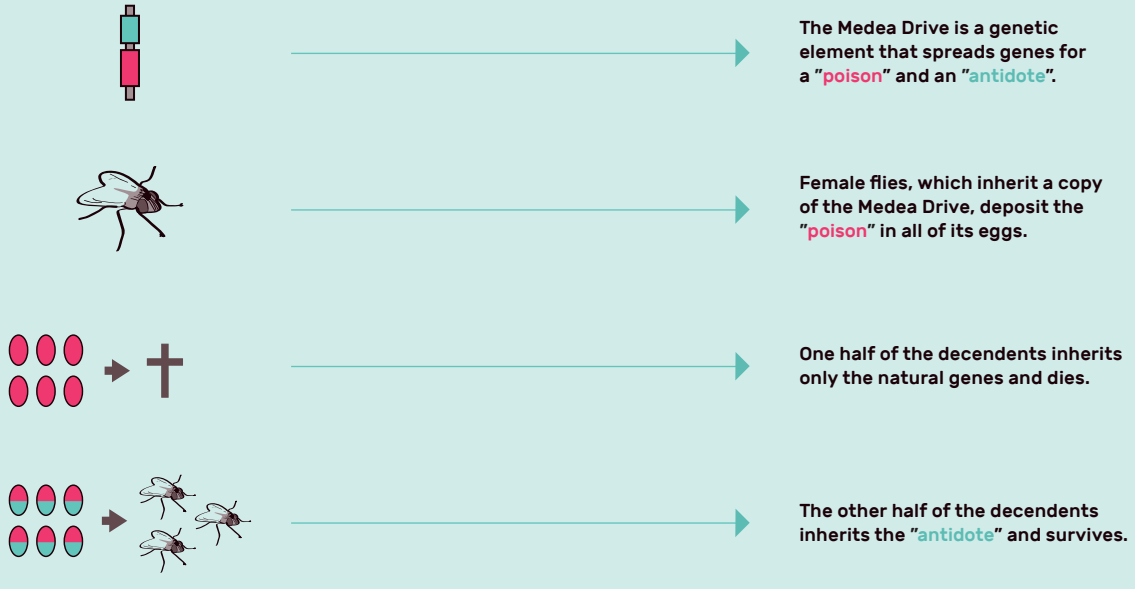
The New World screwworm fly

The New World screwworm fly (Cochliomyia hominivorax) is found primarily in the Americas and lays its eggs near body cavities or open wounds of mammals and birds. The hatching larvae burrow deeply into the tissues of infested animals, causing severe inflammation. The New World screwworm fly also infests livestock such as cows, sheep, and goats, which can die from the inflammation without veterinary treatment.[64] The screwworm fly was eradicated from the continental United States and Central America in the 1960s by releasing sterile male flies. To prevent new introductions from South America, a protected zone was established in Panama, but it is very costly to maintain. Scientists at the University of North Carolina, USA, therefore proposed the use of gene drives.[65] It could also be used to eradicate the screwworm fly in South America. In 2019, an international group of researchers was able to apply CRISPR/Cas9 in the screwworm fly for the first time, altering a gene in the fly that is crucial for the development of the fly's sex. This resulted in females that had male sexual characteristics and were presumably sterile.[66] This intervention is a first step toward developing a CRISPR/Cas-based gene drive that would aim to completely eradicate the screwworm fly.

How does a Medea Drive work?

The goal of a Medea Drive can be to replace or decimate a wild insect population. The Medea Drive consists of two genetic components that act according to the principle of poison and antidote. A new gene variant can be inserted as the third component, which is inherited by all surviving offspring. Both males and females can inherit the Medea Drive. But the toxin is produced only by the mother and is deposited in all eggs. The antidote, on the other hand, is not deposited in the eggs but is formed in the fertilized embryos. For embryos to develop in the poisoned eggs, the genetic information for producing for the antidote must also be anchored in their genome. The offspring are therefore only viable if they carry the Medea Drive in their genome, which also produces the antidote. Since the female fly carries only one copy of the Medea Drive, only half of her offspring inherit a Medea Drive. Thus, only half of the offspring can produce the antidote. The Medea Drive is available with and without CRISPR/Cas based homing gene drive.[67] The gene drive version without CRISPR/Cas probably spreads less invasively.[68]

Medea Drive: Poison and antidote



Quelle: Volker Henn. https://www.wissensschau.de/synthetische_biologie/gene_drive_medea_daisy_x-shredder.php

The Gene Driven Farm

This picture illustrates the areas in which gene drive organisms are being developed or considered for agricultural use.

Gene drives to eradicate, for example, **psyllids** that spread Citrus greening disease (Huanglongbing in Chinese) in citrus fruit.

Gene drives to eradicate the spotted wing drosophila, a **fruit fly** which lays its eggs in ripe fruit, such as cherries.

Illustration adapted from "The Gene Driven Farm" in ETC Group, Heinrich Böll Foundation (2018). Forcing the Farm. How Gene Drive Organisms Could Entrench Industrial Agriculture and Threaten Food Sovereignty.

Gene drives to eradicate, for example, **rats, mice, flour beetles and moths** that infest grain silos.

Gene drives to eradicate, for example, the **screwworm fly**, which lays its eggs in the wounds of cattle.

Gene drives to eradicate **nematodes** that cause plant diseases.

Gene drives to decimate **cabbage moths**.

Open questions regarding applications in plants

Theoretically, gene drives could also be used in plants. The U.S. National Academies of Science identified as one of the possible targets the foxtail plant Amaranthus palmeri[69], which has become a resistant superweed in the United States since the 1990s due to the overuse of herbicides such as glyphosate.[70] Amaranthus palmeri is a dioecious plant that produces either male or female flowers. Researchers have identified a gene that controls the formation of female flowers.[71] If it were possible to switch off this gene by means of a gene drive, only male plants could be formed, making natural reproduction impossible.

Another theoretical possibility would be to reverse resistance to common pesticides that dozens of plant species have developed and that pose major problems for industrial agriculture. These resistances caused by genetic changes that are often well researched and could theoretically be reversed by a gene drive.[72]

Several technical hurdles must be overcome before gene drives can be applied in plants.

Double strand breaks caused by CRISPR/Cas9 in the genome of plants are often repaired using error-prone mechanisms.[73] This prevents the gene drive from taking hold in plants. To inherit the gene drive to all offspring, another type of repair mechanism would have to repair the double-strand break using a template. In addition, many plants have significantly longer generation times than insects. The effect of a gene drive would only take effect after many years. And ultimately, the seeds of some plants can persist in the soil for years, significantly delaying the breakthrough of the Gene Drive.[74]

The implementation of a gene drive in plants is not yet possible with the current state of knowledge.

Gene drive organisms as bioweapons

A release of gene drive organisms could, in theory, have large-scale and long-lasting negative effects on ecosystems and societies. The release of gene drive organisms for civilian purposes could therefore cause conflict or lead to misuse. The targeted development of gene drive organisms for hostile purposes is also conceivable.[75]

One way that gene drive organisms could be used as bioweapons would be to use them to eradicate important beneficial insects for agriculture in a particular region.

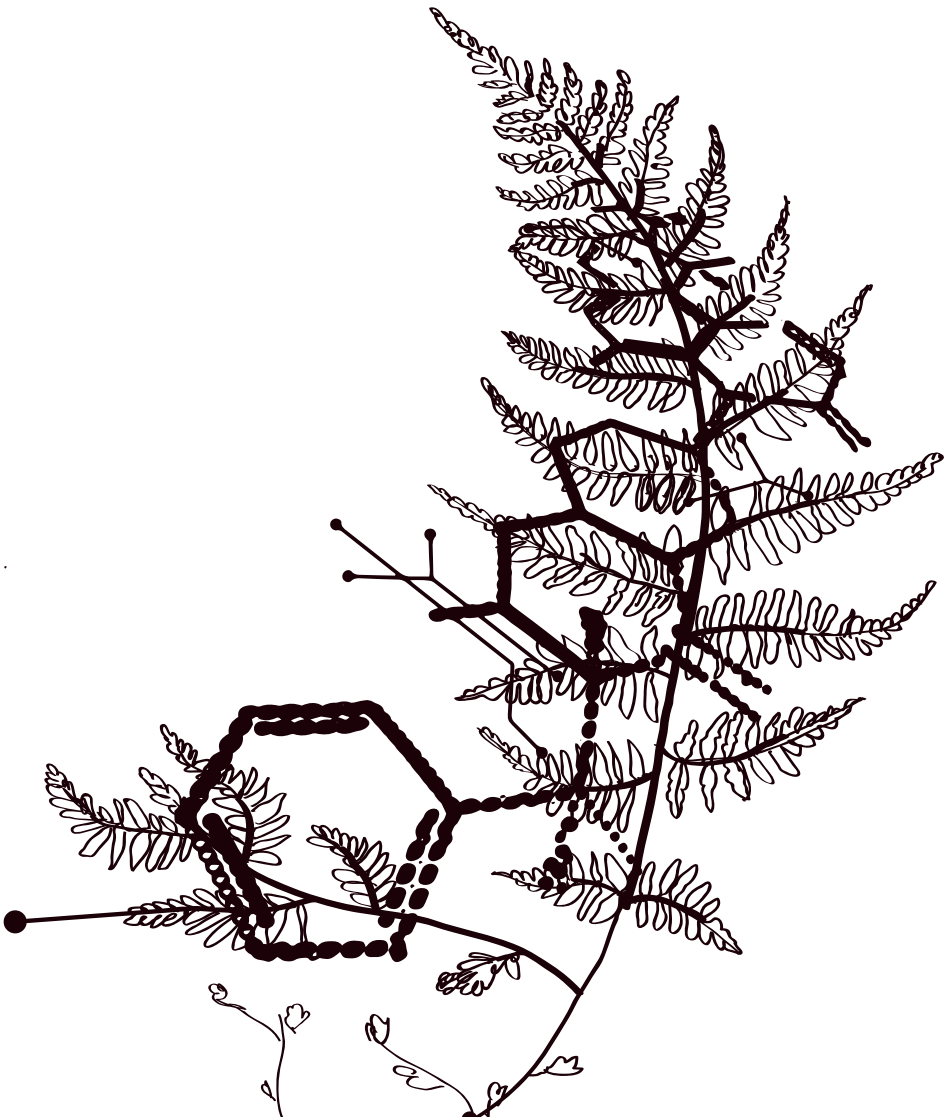
However, until gene drive organisms and their harmful effects can be limited both spatially or temporally, there are few convincing scenarios for government gene drive weapons programs.[76]

Despite these challenges, **the U.S. military's Defense Advanced Research Projects Agency (DARPA) is one of the largest funders of gene drive research and is financially involved in almost every gene drive research project.**[77]

The DARPA research program, titled Safe Genes, sets out to control, limit, or recover GDO from the environment. There are numerous gray areas in the spectrum between unexpected negative effects of gene drive organisms in nature, their misuse, and the deliberate development of gene drives for hostile purposes.

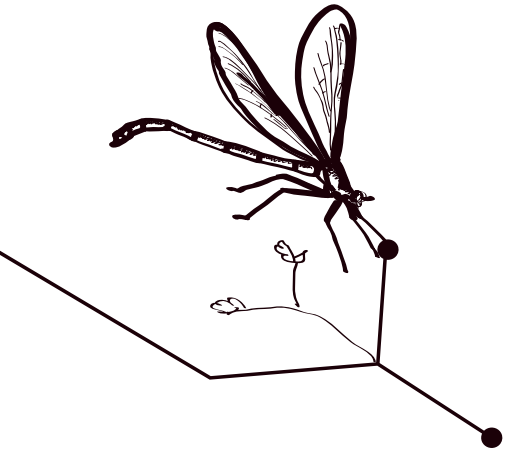
While the effect of a gene drive organism might be considered positive in a particular region, its consequences might be considered undesirable or negative in other affected regions, leading to insurgency or conflict.

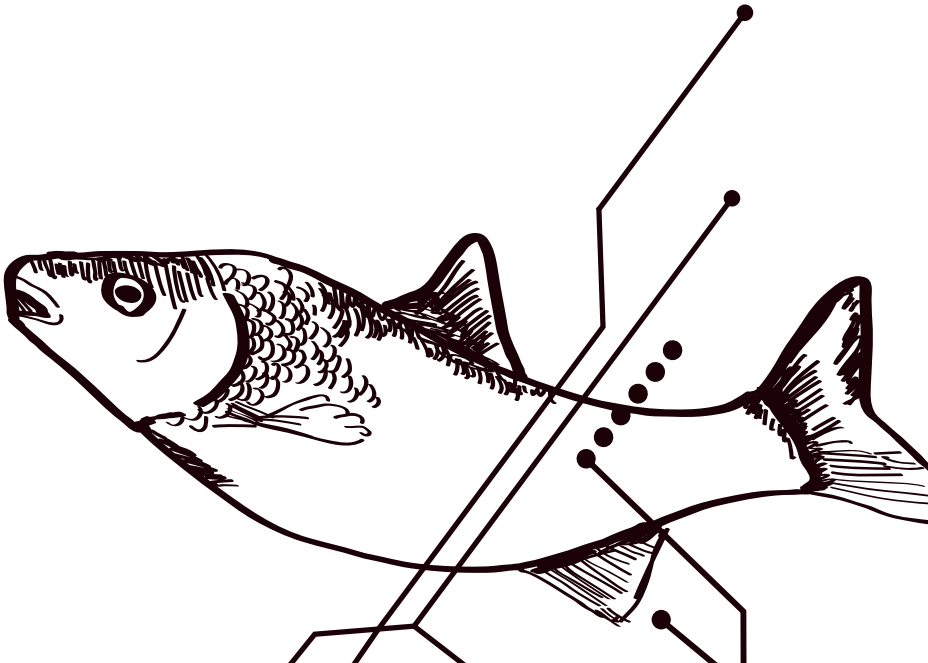
Conflict from the use of gene drive technology in the environment could also be triggered by a lack of public (or international) consensus on a release of gene drive organisms in one's own or neighboring countries. Resulting damages, such as crop loss, biodiversity loss, or unintended health, social, or economic effects, can lead to conflict if there is no adequate compensation for them. Even the unintended presence of a GDO in a country that has not consented to a release can lead to interstate conflict or diplomatic crises.[79] For these reasons, experts at the UN Biological Weapons Convention have been monitoring and discussing the issue for years.[80]



03

ECOLOGICAL RISKS





Gene drives are at an early stage of development. The discussion about possible consequences and risks is therefore still largely speculative. However, numerous critical points are already emerging that must be taken into account before considering a release.

Uncontrollability

The vast diversity of natural habitats and ecosystems affected will make the prediction and control of potential risks much more difficult.

In 2016, the U.S. Academy of Sciences recommended that gene drive organisms first be tested on small and remote islands.[81] However, calculations using models show that this would not provide sufficient containment as individual GDO can reach other regions through water, wind or unintentional transport and spread the gene drive further.[82] Moreover, GDO could be spread deliberately.

A group of researchers led by gene drive developer Kevin Esvelt at the Massachusetts Institute of Technology (MIT) in Boston, USA, is working on a gene drive variant that can be limited in its spatial spread. They call this gene drive the Daisy Chain Drive.[83] So far, however, this gene drive variant exists only in theory (for more information, see infobox).

Once released into nature, a gene drive organism actively propagates in wild populations and can spread rapidly over large distances.

What is a Daisy Chain Drive?

The Daisy Chain Drive is a variant of gene drive based on CRISPR/Cas9 that has not yet been implemented. In theory, the CRISPR/Cas-based gene drive would consist of individual elements located on different chromosomes.[84] Element C consists of the gene 'scissors' and a guidepost for B. Element B is the gene 'scissors' Cas9 plus guidepost for C. C is the target site of the gene drive, an essential gene that is knocked out by the DNA double-strand break and replaced by a new gene if necessary. Component C is inherited according to Mendelian rules. Therefore, the process should stop on its own at a certain point, which could limit its spatial and temporal distribution.

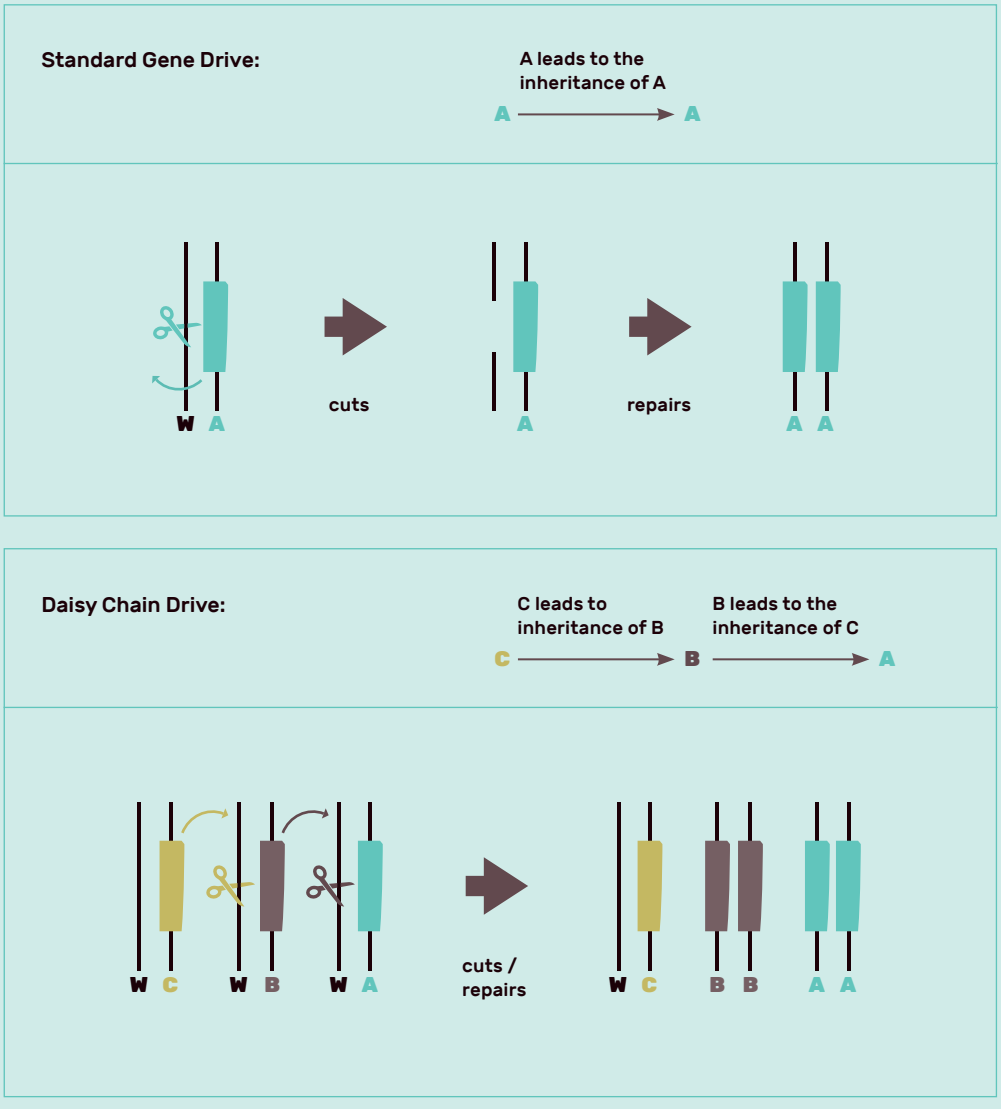


Illustration adapted from: Noble C, Min J, Olejarz J, Buchthal J, Chavez A, Smidler AL, DeBenedictis EA, Church GM, Nowak MA, Esvelt KM (2019). Daisy-chain gene drives for the alteration of local populations. Proc Natl Acad Sci USA 116:8275.

Irreversibility

A gene drive causes a permanent genetic modification of the genetic material, which is passed on to all subsequent generations. Even if a gene drive encounters resistance and no longer spreads on its own accord, these changes can continue to be inherited according to Mendelian rules and persist for a long time in the genome of the population. Only if the deactivated gene drive severely impairs the survivability of the individuals do the mechanisms of natural selection take effect, eliminating the change in the natural populations.

As early as 2014, a discussion started about the need for a so-called Reversal Drive, which would be intended to reverse the changes caused by a gene drive in the manipulated populations. In principle, this is a modified version of the original gene drive that overwrites the previous genetic manipulations and prevents their further spread. However, even such a Reversal Drive can not restore the original genetic state of the population, but only introduce further genetic modifications into the genome of these populations.

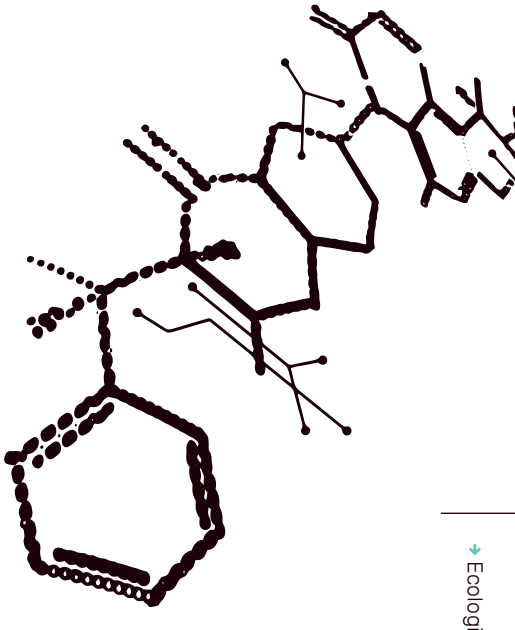
In a study on fruit flies, genetic elements were presented that were designed to switch off or completely remove CRISPR/Cas-based gene drives from the genome. Specific signposts of the CRISPR/Cas9 'gene scissors' are used to terminate the chain reaction of a CRISPR/Cas-based gene drive. The result: the 'gene scissors' paralyze themselves. Results from cage experiments show that these elements can prevail for 10 generations. However, synthetic genetic elements remain in the genome and are inherited according to Mendelian rules. In addition, unintended changes to the genome occur. It is difficult to estimate how these remaining genetic changes will behave in the wild populations in the long term and whether they will be influenced by external factors.[85]

According to current knowledge, any release of a gene drive carries the risk of irreversibly and uncontrollably altering the genetic material of a natural population.[86]

Outcrossing across species boundaries

Gene drives are tailored to the genome of a single species, but in many cases outcrossing across species boundaries could be inevitable. For example, the malaria-carrying mosquito Anopheles gambiae belongs to a complex of seven different subspecies that are genetically very similar and can produce fertile offspring with each other.[87] A gene drive by Target Malaria targets disruption of the Doublesex gene, which has undergone little change during the evolution of the mosquito species. This approach could drive all seven related mosquito species to the brink of extinction, although at least one species does not transmit malaria.[88]

A similar risk exists in fruit flies of the genus Drosophila, which have played a central role in the development and application of gene drives. It has been known for over 90 years that different species of Drosophila can interbreed and produce fertile offspring.[89] Thousands of other animal and plant species form natural hybrids, so the spread of gene drives would not be limited to one species but could also extend to its closer relatives.



Unexpected effects of CRISPR/Cas9

Many engineered gene drives use CRISPR/Cas9 to create a double-strand break at defined locations in the genome. However, this tool does not work flawlessly.[90]

CRISPR/Cas9 can change the activity of the target gene in unpredictable ways, increase the mutation rate in the genome, lead to unexpected mutations, or be disrupted in its function by emerging resistances. For example, there are increasing reports of so-called off-target effects, unintended changes to non-target sequences that can occur when the CRISPR/Cas system is applied.[91]

Moreover, the genetic modifications not only affect the target area, but often also other areas in the genome.[92] One of the reasons for this is that in wild populations there are more sequences in the genome to which CRISPR/Cas9 can dock than the computer programs used for this purpose were able to determine in the laboratory. Gene drives can therefore lead to the development of organisms with unpredictable characteristics.[93]

Resistances

CRISPR/Cas-based gene drives search for a clearly defined DNA sequence at which they are to cut the genetic material. Even single mutations to this sequence can therefore render the target unrecognizable to them. The organism thus becomes resistant to the gene drive. Such resistance can arise if the DNA double-strand break generated by CRISPR/Cas9 is incorrectly repaired by the cell and alters the target sequence. However, resistance could also occur naturally, especially in populations with high genetic diversity.

If a gene drive encounters resistance, it will break off at this point and only change part of the population. Whether it disappears again completely, however, depends on the number of individuals already changed and the disadvantages that the gene drive brings for their survival. It is therefore entirely possible for the gene drive to persist for a long time in an animal species despite resistance.

Unpredictable impacts on ecosystems

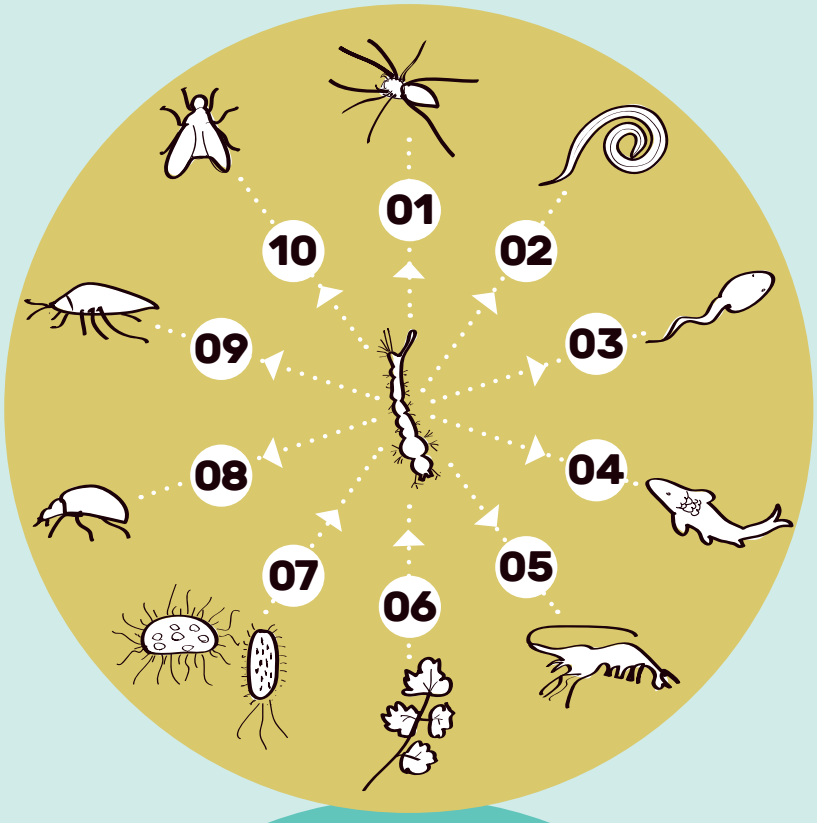
Every living creature, even if it appears dangerous or harmful to humans, performs important tasks in its habitat. The extinction or even manipulation of one species will therefore have consequences for the entire ecosystem.

This can be well illustrated by the example of mosquitoes. In the course of their life cycle, they form important food sources for various animals. For example, mosquito larvae living in water are a food source for water bugs, beetles, flies, spiders, flatworms, tadpoles, fish and crustaceans. It is assumed that 95 percent of the larvae of the African malaria mosquito Anopheles gambiae are being eaten before becoming adults.[94] Adult mosquitoes are also an important food source and are consumed by dragonflies, spiders, bats and birds, among others. In the Camargue, a nature reserve in southern France, reduction of mosquito populations with a biological control agent has also led to a reduction in the number and diversity of birds and dragonflies.[95] A role in plant pollination also cannot be ruled out, as adult mosquitoes feed on nectar, among other things.[96] The role of mosquitoes in their tightly interwoven ecosystem has hardly been studied so far, so the consequences of a possible extinction are not foreseeable.

These consequences can also affect humans: If one mosquito species is displaced, other species, which may transmit even more dangerous diseases, can spread more widely. Such risk scenarios are known with regard to the control of the dengue fever-transmitting yellow fever mosquito (Aedes aegypti) in North America and Brazil, which competes with the invasive Asian tiger mosquito (Aedes albopictus).[97] If the yellow fever mosquito disappears, this could further promote the spread of the tiger mosquito, which is no less dangerous and also transmits dengue fever.[98]

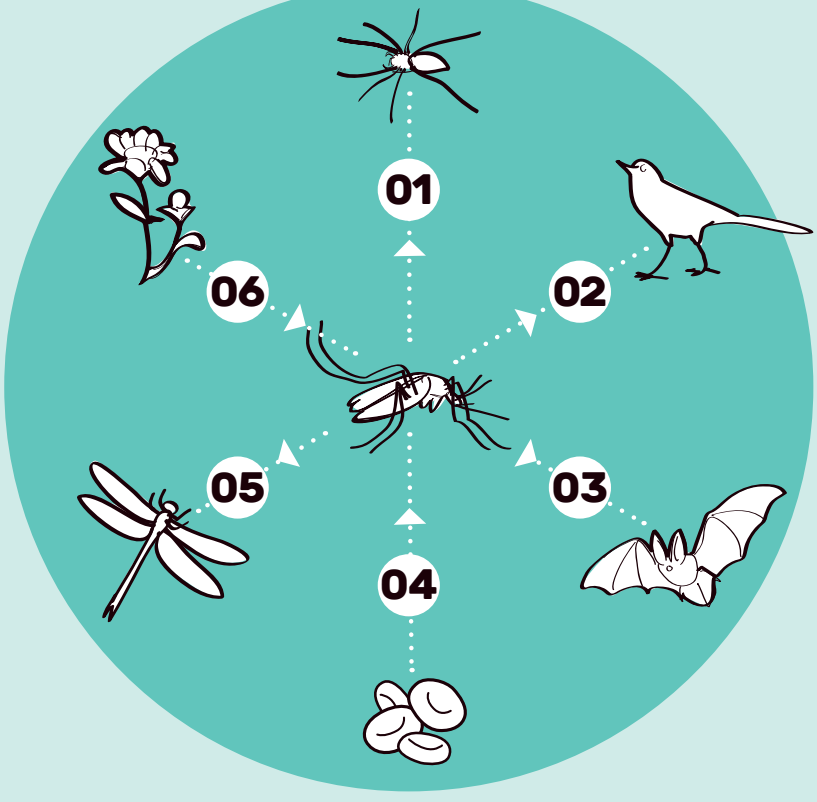
But even if a species is not wiped out, gene drives harbor considerable risks: If the characteristics of the organisms change unintentionally, they can, for example, change their behavior, transmit more diseases, or even disturb or destroy the habitat of other species. Because the respective species are closely linked to their ecosystems, the effects of uncontrolled spread cannot be predicted reliably.[99]

Food web of mosquitoe larva and mosquitoe



Mosquitoe larva

1. spiders
2. flatworms
3. tadpoles
4. fish
5. crustaceans
6. decaying detritus
7. aquatic micro-organisms
8. beetles
9. water bugs
10. flies

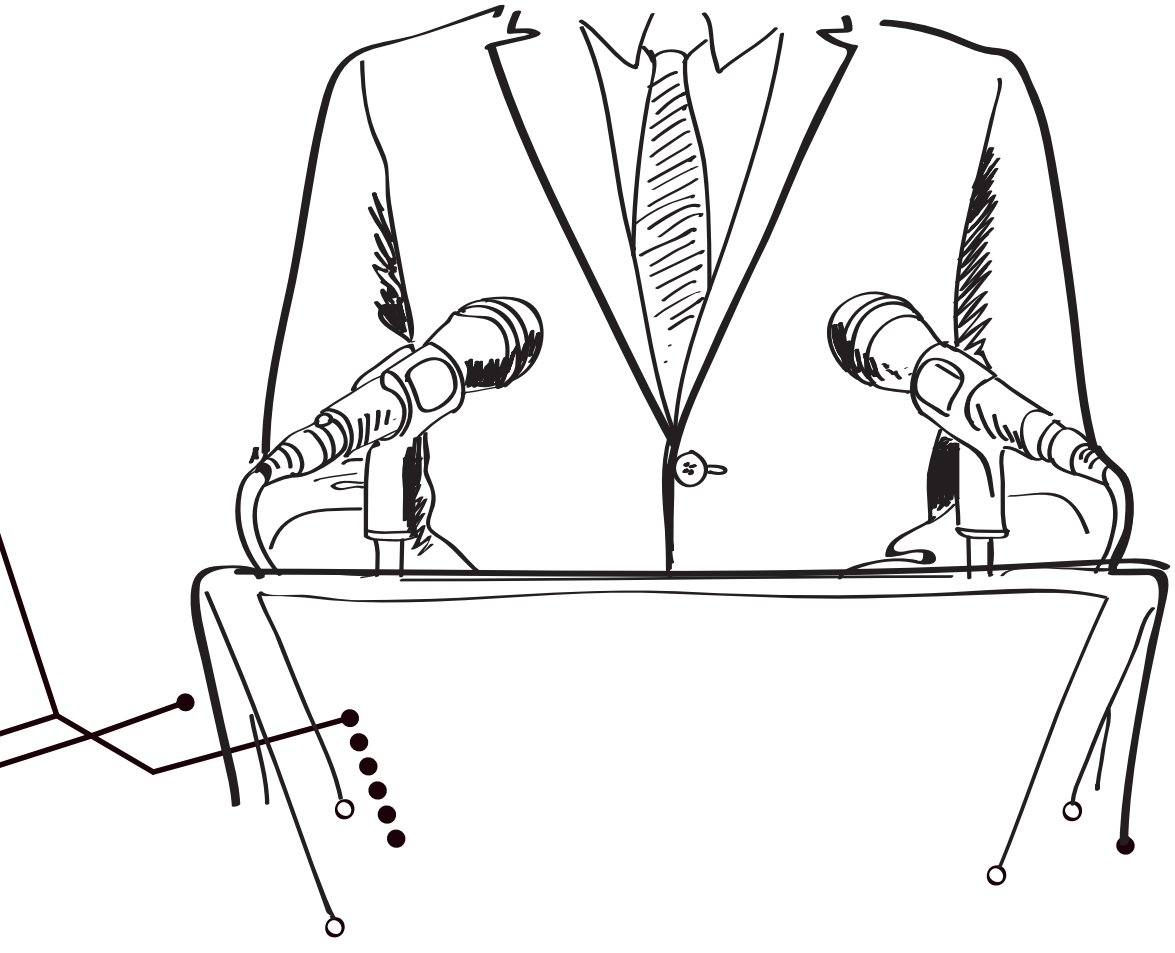


Mosquitoe

1. spiders
2. birds
3. bats
4. blood (only female mosquitoes)
5. dragonflies
6. nectar

04

GENE DRIVE REGULATION



The political debate on the regulation of gene drive technology is still in its infancy, both in Germany and Europe, as well as internatonally. There is no specific and binding regulation for handling this new technology.

REGULATION OF GENE DRIVE ORGANISMS IN GERMANY

In Germany, the political discussion and regulation of gene drives is still in its infancy. An official position of the German government on the evaluation and regulation of gene drive organisms is not yet available.

Genetic Engineering Safety Ordinance: safety standards for gene drive research

In March 2021, gene drive organisms have been included in federal genetic engineering legislation for the first time. The Genetic Engineering Safety Ordinance (GenTSV) sets safety standards for handling GMO in research laboratories.

In this context, laboratory work with genetically modified organisms is assigned to one of four safety levels depending on its hazard potential for humans, animals and the environment. Safety level 1 applies to work with no hazard potential, while safety level 4 applies to work with a high hazard potential. Depending on the safety level, different safety measures must be upheld during experiments.

According to the Genetic Engineering Act (GenTG), the approval of a research project with GMO, its classification by safety level and monitoring of safety requirements is the responsibility of regional authorities. According to §10 paragraph 7 of GenTG, these authorities are obliged to obtain an opinion from the Central Commission for Biological Safety (Zentrale Kommission für die Biologische Sicherheit, ZKBS) in this process.

In 2016, in the absence of a uniform regulation by the Genetic Engineering Safety Ordinance, the ZKBS had defined safety level 2 as sufficient for the work with gene drive systems in the laboratory.[100] This was changed when the new version of the GenTSV came into force on 01.03.2021.

In the revised Genetic Engineering Safety Ordinance, laboratory work with genetically engineered organisms containing gene drives is assigned to safety level 3 as a precautionary measure[101]. This ensures that every research project involving gene drives is reported to a supervisory authority and that a case-by-case risk assessment is carried out by the ZKBS before experiments begin. In order to reliably prevent the escape and spread of GDO into wild populations, Article 1, §11, 6 stipulates that the ZKBS has to recommend specific safety measures to

the regional authority. Based on this recommendation the regional authority can then proceed with the authorization of the experiments and is then allowed to even change the required safety level on its own accord.[102]

These amendments had been requested by the Bundesrat (a federal constitutional organ which represents the German federal states in federal decision-making) in summer of 2019. The German federal government had originally only envisaged a classification of gene drive projects into safety level 2. The necessity for amendments had been brought to the attention of the German federal states via an open letter by environmental and agricultural organizations.[103] They argued that safety level 2 would not do justice to the potential threat posed by GDO to biodiversity.

Positioning of the German Bundesrat

In its resolution on the amendment of the Genetic Engineering Safety Ordinance of June 2019, the Bundesrat (a federal constitutional organ which represents the German federal states in federal decision-making) acknowledges that the release of gene drive organisms carries the risk of "irreversibly altering or wiping out entire populations of plants or animals." Furthermore, it refers to the declaration of the Network of GMO-Free Regions of Sept. 7, 2018, which expresses "the greatest reservations about the release of organisms that have so-called 'gene drives' that aim to alter the genetic characteristics of entire populations of plants and animals" and calls for "taking all necessary measures to prevent the release of gene drives into our environment."[104] In this context, the Bundesrat calls on the German government to take into account the precautionary principle and to give particular weight to nature conservation in the future design of specifications for the risk assessment and safety classification of gene drive organisms."[105]

Positioning of the German federal states

At its 9th conference in September 2018, the European network of the then 64 GMO-free regions in Europe, including 11 German federal states, adopted a declaration which called on national governments and the European Union to ban the release of gene drives in the European Union and to advocate at international level, in the context of the UN Convention on Biological Diversity (CBD) and the IUCN, for a moratorium on the release of gene drive organisms.[106]

At the Conference of Agriculture Ministers (AMK) in September 2019, the agriculture ministers of the German federal states called on the German government to put gene drive organisms back on the agenda of the Conference of the Parties to the UN Convention on Biological Diversity (CBD) and its Biosafety Protocol at COP 15 in China on the occasion of the six-month EU Council Presidency in the second half of 2020.[107]

Positioning of the German Federal Ministry for the Environment

The German Federal Ministry for the Environment has been critical of the use of gene drive technology in nature. In response to an open letter from environmental and nature conservation organizations in the run-up to the CBD's COP 14, a senior ministry official responded in September 2018 that **the ministry would strive to prevent the release of gene drive organisms in Germany or Europe as long as negative effects on the environment could not be ruled out.** Furthermore, the ministry would advocate for the application of the precautionary principle in international negotiations within the framework of the CBD. The official also saw a great need for research with regard to the environmental risk assessment of gene drive organisms.[108]

Process in the German Parliament

The German Bundestag (i.e. the German parliament) has commissioned its office for technology assessment (Büro für Technikfolgenabschätzung beim Deutschen Bundestag, TAB) on a cross-party basis to assess open ecological, ethical and regulatory questions surrounding the risks and options for action as well as alternatives to gene drive technology. The report is due by the end of 2021 and is supposed to help the German Bundestag find a position on the subject.[109]

Positioning of the German parties

At the request of an alliance of environmental and agricultural associations in spring 2019, the Social Democratic Party of Germany (SPD)[110], Bündnis90/ Die Grünen (the Green Party)[111] and Die Linke (Left party)[112] declared their support for an international gene drive moratorium. The Christian Democratic Union of Germany (CDU)[113] described this idea as worthy of consideration. The Liberal Democratic Party (FPD) and Alternative for Germany (AfD) did not take a position on this.

Research project on risk assessment & monitoring of gene drive organisms on behalf of the German Federal Agency for Nature Conservation (BfN)

Risk assessment and monitoring plans for the release of genetically modified organisms into the wild, which include gene drive organisms, are based on European Union laws, principles, procedures and requirements. However, the implementation of the approval and the execution of the monitoring is up to the EU member states.

For this reason, the German Federal Agency for Nature Conservation (BfN), which is responsible for the environmental risk assessment of GMO in Germany, initiated a research project at the end of 2018 to identify potential risks and fundamental challenges for the risk assessment of gene drive organisms before the first field experiments with GDO take place. The research project conducted at the University of Natural Resources and Applied Life Sciences, Vienna, aims to identify, among other things, the new challenges that gene drive technology poses to risk assessment and how the ecological consequences of gene drives can be recorded and evaluated. To this end, the project will also examine the extent to which gene drives can be contained spatially and temporally and what role computer-based modeling can play in the assessment of environmental risks. In addition, the project will analyze how the EU-mandated monitoring of GMO for gene drives would need to be adapted to capture and assess their environmental impact after a release. Results of the project are expected to be available in autumn 2021.[114]

REGULATION OF GENE DRIVE ORGANISMS AT EU LEVEL

The political debate surrounding the regulation of gene drive technology at the European level has only just begun.

In July 2018, the European Commission commissioned the European Group on Ethics in Science and New Technologies (EGE) to develop an opinion and policy recommendations around the ethical, social and legal implications of new genetic engineering techniques (genome editing) on humans, animals and plants.[115] It was published in March 2021.[116] In preparation, a roundtable was held in Brussels in October 2019, where participants from science, industry, politics and civil society discussed the ethical issues around new genetic engineering applications, including gene drives.[117]

As concrete environmental applications for the use of gene drives in the EU are still a thing of the future, the political debate has so far focused on the EU's positioning in the negotiations of the UN Convention on Biological Diversity (CBD). Prior to the 14th Conference of the Parties (COP) to the CBD in Egypt, the EU Council of Ministers recognized "potential adverse effects on biodiversity" from gene drive organisms and considered it necessary to apply the Convention's precautionary approach.[118]

In January 2020, the European Parliament adopted a resolution calling on the European Commission and the EU Council of Ministers to advocate for a global gene drive moratorium at the upcoming Conference of the Parties to the UN Convention on Biological Diversity (COP 15) in China.[119]

In addition, MEPs called for the new Post-2020 Global Biodiversity Framework to be based on the following core principles: the precautionary principle, a rights-based approach to involve rights holders in the development of legislation affecting them, and mandatory prior technology assessment of new technologies that could have a negative impact on biodiversity. In doing so, MEPs responded to a joint call from 50 European NGOs, experts and foundations.[120]

The European legislation on genetic engineering

In the EU, Directive 2001/18 regulates the conditions under which genetically modified organisms (GMO) may be released into the environment.[121] There is no dispute that gene drive organisms are forms of GMO.

The transposition of the requirements of the EU Directive into national law is mandatory for all member states. Only EU institutions can make changes to the directive. Since 2015, however, member states have been able to prohibit the cultivation of genetically modified plants on their territory even if approval has been granted for them at EU level called opt-out. In theory, this also applies to gene drive organisms.

Directive 2001/18 obliges member states to take all necessary measures to avoid adverse effects on the environment and human health that could arise from releases of GMO into the environment. Both protection goals are of equal importance: It is therefore not possible to trade off conceivable advantages for human health against possible disadvantages for the environment. The precautionary principle obliges the competent authorities to take measures to prevent negative effects even if full scientific or technical certainty and knowledge has not yet been obtained.[122]

Legal interpretation of the EU Directive 2001/18 with regard to gene drive organisms

According to the EU's genetic engineering Directive 2001/18, any release of a GMO requires approval. It may only be granted if it has been established, on the basis of a prior risk assessment involving the member states and the European Commission, that the release will not have any adverse effects on human health or the environment. The protection of the environment and human health must be ensured in accordance with the precautionary principle. The period of validity of the authorization must not exceed ten years. The released GMO and its potential effects must be monitored throughout the entire period according to a monitoring plan to be submitted.

The aim of Directive 2001/18 is to prevent the uncontrolled spread of GMO into the environment and their outcrossing to other organisms.

Even the spread of a GMO in the environment beyond the planned site of release will be evaluated as an adverse effect in this context. If there is a risk to the environment or human health, approval for a release may not be granted.

Recital 4 of the directive underlines the specific problem of deliberate release of GMO into the environment: "Living organisms released into the environment in large or small quantities for experimental purposes or in the form of commercial products may reproduce in the environment and spread beyond national borders, thereby affecting other member states. The effects of such releases may be irreversible."

To identify and assess risks to the environment and human health, a risk assessment must identify any new risks prior to any release of a GMO into the environment.[123] Annex II of the directive sets out the requirements for this risk assessment. It requires that all intended and unintended, direct and indirect, immediate and delayed, long-term and cumulative long-term effects of the release be examined.[124] Cumulative long-term effects include, among others, effects of the released GMO on food chains, flora and fauna, and biodiversity. The effects on altered population dynamics and genetic diversity of target species, as well as their competitors, prey, hosts, symbionts, predators, parasites and pathogens must also be covered by the risk assessment.[125]

Furthermore, it is specified that possible negative effects are not to be excluded from the assessment of risks because they are unlikely to occur. Furthermore, it is stated that there is no distinction between significant and other (negligible) negative effects.[126] **The directive thus prescribes a worst-case scenario as the basis of the risk assessment and requires that it be assumed that every potential adverse effect will actually occur.**

For safety reasons, the directive recommends that the release of a GMO should be carried out step by step and that each subsequent step should only be taken if the assessment of the previous steps did not indicate any adverse effects on human health or the environment. However, a step by step procedure will not be possible due to the nature of gene drive organisms. Sufficiently reliable proof of the harmlessness of a GDO can only be provided if the GDO has been released into the environment and there has been no evidence of hazards to the environment or human health over several generations. However, the release of even just a few gene drive organisms results in their possibly irreversible spread in the environment. According to the current state of research, once GDO have been released, their spread cannot be limited or be recovered with certainty, and their effects in nature cannot be reversed.

In order to take into account the particular risk posed by a self-replicating spread into the environment, the approval of a GMO can be granted for a maximum of 10 years. After that, it must either be renewed or it expires. Once the approval has expired, the GMO should not be found in the environment any longer. It is not apparent how this provision would be complied with in relation to GDO.[127]

Directive 2001/18 was designed and enacted to regulate the release of genetically modified crops. It assumes that the effect and spread of GMO in nature can be limited in space and time. However, according to the current state of research, this assumption does not hold for gene drive organisms.

Conclusion: The release of gene drive organisms is unlikely to be permissible under current EU legislation.

The purpose of gene drive organisms is to spread independently in the environment, to interbreed with wild conspecifics and to pass on their modified genes to as many offspring as possible in order to spread them throughout the entire population of a species. Because this is clearly contrary to the current provisions of Directive 2001/18 with regard to the protection of the environment, it is not possible to authorize the release of a gene drive organism into the environment under European law.

Member states of the EU are therefore legally obliged to ensure that no GDO would be found within their political borders. Article 4 of Directive 2001/18 also requires that "in the case of an unauthorized release (...) the member state concerned shall ensure that the necessary measures are taken to terminate the release or placing on the market, to initiate countermeasures if necessary and to inform the public of the respective member state, the Commission and the other member states."

For this reason, it is in the self-interest of the EU and all EU member states to prevent the release of GDO that can reach their territory, including territory outside the EU.

Risk assessment by the European Food Safety Authority

The risk assessment, which is carried out as part of the approval review of a GMO, is carried out by the European Food Safety Authority (EFSA). It develops specific guidelines for its implementation.

Both the guidelines for environmental risk assessment[128] and the guidelines for risk assessment of genetically modified animals[129] are relevant for gene drive organisms. Should plants also be modified by gene drives in the future, the guidelines for the risk assessment of food and feed from genetically modified plants would also be relevant. For genetically modified plants only, there are also post-market environmental monitoring (PMEM) guidelines that govern the management and monitoring strategies for released genetically modified plants.[130]

At the time this publication went to press, no genetically modified animals or products derived from them had been approved for marketing in the EU. Neither have there been any applications for approval. Nevertheless, guidelines for the risk assessment of genetically modified animals exist as an aid for future applications.

These guidelines for the risk assessment of genetically modified animals published by EFSA in 2013 already contained considerations on horizontal gene transfer through gene drive systems in the section on insects.[131] Since 2013, several scientific bodies had been looking at the risk assessment of synthetic biology applications and had seen a need for action with regard to gene drives.[132] The scientific committee of the French High Council for Biotechnology (Haut Conseil des Biotechnologies, HCB) concluded in a May 2017 opinion that the risk assessment criteria of Directive 2001/18 were applicable to gene drive organisms. However, it noted that GDO introduce new elements and objectives that require adaptation of the existing risk assessment.[133]

In June 2018, the European Commission mandated the EFSA to consider whether existing guidance on the risk assessment of GM animals was sufficient to identify potential new risks to the environment, human and animal health, or whether it needed to be adapted. However, this did not include a mandate to develop new guidelines for the risk assessment of GDO. Nonetheless, the technical and scientific expertise on GDO risk assessment developed through this mandate is intended to inform the consideration of guidelines for the risk assessment of gene drive organisms under the Convention on Biological Diversity and its Cartagena Protocol on Biosafety.[134]

In May 2019, EFSA organized a stakeholder workshop to discuss this topic.[135] The final report was presented in November 2020.[136] The composition of the scientific working group, which had been commissioned to draft the report however,, has been criticized for being biased.[137] According to research by the Brussels-based non-governmental organization Corporate Europe Observatory (CEO), all six members of the working group have conflicts of interest related to the development of GDO, as they work in companies or research groups whose activities fall under the EFSA's remit. Three of the experts have financial ties to organizations developing gene drives, including Target Malaria and the U.S. military agency DARPA.[138]

Recommendation: Strengthen the precautionary principle in the risk assessment of genetically modified organisms in the EU through cut-off criteria.

A contribution by Dr. Christoph Then

The precautionary principle, as enshrined in EU Directive 2001/18, can only work if effective measures can actually be taken to protect the environment and human health in cases where this appears necessary. Retrievability (i.e. controllability in time and space) is a crucial prerequisite for this.

"Member states shall ensure, in accordance with the precautionary principle, that all appropriate measures are taken to avoid adverse effects on human health and the environment which might arise from the deliberate release or placing on the market of GMO" (EU Directive 2001/18, Article 1). As soon as evidence emerges for an actual risk to humans and the environment, emergency measures must be taken: "Member states shall ensure that emergency measures, such as suspension or termination of the placing on the market, are taken in the event of a serious risk [...]" (EU Directive 2001/18, Article 23). In addition, there is the provision from Article 13 of the directive that marketing authorization may only be granted for ten years. Thereafter, the approval must be reviewed again on the basis of monitoring. If the genetically modified organism loses its approval, it must be removed from the environment again.

The release or placing on the market of genetically modified organisms whose spread cannot be controlled is fundamentally in conflict with these provisions. ***If a GMO can no longer be retrieved from the environment, the enacting of the precautionary principle becomes impossible.***

In this context, the GeneTip project, funded by the German Federal Ministry of Education and Research (BMBF), was the first research project in Germany to address the prospective technology assessment of gene drive organisms.[139] *One result of the project is the recommendation to introduce a new central mechanism for the risk assessment of GMO: the designation and definition of so-called reasons for concern (in simple terms, factually justified risks). Such reasons for concern are often identifiable at an early stage of research and development and could lead to the characterization of a GMO as "of particular concern".*

To this end, the authors propose, among others, the following criteria for the identification of reasons for concern:

- Impossibility of making reliable forecasts
- Interventions in systems that are particularly critical for human health
- Interference with ecological systems that are pre-stressed or have tipping points
- Lack of technical maturity and reliability
- Particularly wide reach, to the point of global and irreversible spread of GMO
- The ability to spread in natural populations

According to the report of the GeneTip project, a characterization as a 'GMO or construct of very high concern' could lead to the same consequences as stipulated for substances regulated under the EU chemicals legislation REACH and the EU pesticides legislation, respectively. Here, the estimation of the spatial-temporal complexity or controllability plays an important role.

The REACH regulation states that "experience at international level shows that substances with persistent, bioaccumulative and toxic properties or with very persistent and very bioaccumulative properties are of particular concern."[140] with very persistent and very bioaccumulative properties are of particular concern." Therefore, REACH established appropriate criteria to define persistent, bioaccumulative and toxic substances, as well as substances that are particularly bioaccumulative and persistent.

The EU regulation on the authorization of pesticides integrates these criteria for POP (persistent organic pollutant), PBT (persistent, bioaccumulative, toxic) and vPvB (very persistent, very bioaccumulative) into the decision-making process as exclusion criteria, which mean that authorization can generally be refused and the authorization process is not continued.[141] The decisive factor is not only the toxicity of a substance, but also its behavior and fate in the environment. If a substance is classified as vPvB, it cannot be approved under this EU regulation, even if long-term damage has not been proven.

According to the final report of GeneTip, such cut-off criteria could also be helpful in the approval of GMO and gene drive organisms. If genetically modified organisms escape spatiotemporal controllability because they can replicate in natural populations without effective control of their persistence and spread, a sufficiently reliable risk assessment would not be possible. The approval process cannot continue and a release of the GMO cannot be authorized.

The results of GeneTip were taken into account by the expert group (AHTEG) advising the Conference of the Parties to the UN Convention on Biological Diversity. Among other things, unforeseen effects that occur only after several generations are named as a specific challenge for risk assessment.[142] In contrast, the European Food Safety Authority (EFSA) largely ignores these challenges in its report submitted in November 2020.

Dr. Christoph Then head of the Institute for Independent Impact Assessment in Biotechnology (TestBiotech) and co-author of the GeneTip project. Testbiotech is concerned with impact assessment in the field of biotechnology, calls for and promotes independent research, examines ethical as well as economic consequences, and tests risks to humans and the environment. Testbiotech provides industry-independent expertise and thus aims to strengthen the decision-making competence of society.

REGULATION OF GENE DRIVE ORGANISMS AT THE INTERNATIONAL LEVEL

The topic of gene drives has been discussed within the framework of international agreements since the development of the first gene drive organisms in 2014/2015. Initial recommendations have been adopted within the framework of the UN Convention on Biological Diversity (CBD). However, from a legal point of view, such recommendations of the Conferences of the Parties to the Convention on Biological Diversity or even other international organizations are not binding for the Parties to the convention or for other states. Guidance documents are also not legally binding. In this respect, there currently exists neither legally binding international agreements nor specific internationally binding provisions on the release of gene drive organisms into the environment.

Discussions about gene drive organisms in the UN Convention on Biological Diversity (CBD)

Since 2015, gene drives have been discussed within the UN Convention on Biological Diversity pertaining to its work on synthetic biology and in the context of discussions on risk assessment of living modified organisms (LMOs) as part of its Cartagena Protocol on Biosafety. The convention treaty was concluded in 1992 and entered into force in 1993. Currently, 195 countries are parties to the convention, with the notable exception of the United States. The EU became a party to the convention in 1993.[143] All EU member states and the United Kingdom are also parties to the convention.

At the 14th Conference of the Parties to the UN Convention on Biological Diversity (CBD COP 14) in late 2018, delegates discussed a decision on synthetic biology, which should also include regulations on gene drive organisms.[144] Some parties introduced a call for a moratorium on the release of gene drive organisms into the environment.

In the run-up to the conference, more than 160 civil society organizations, mainly from the alternative agriculture movement and the global South, had called for this in an open letter.[145] However, the proposal failed to gain the necessary consensus, as African countries in particular, led by Nigeria and South Africa, opposed such a moratorium.

Research based on documents requested under U.S. Freedom of Information regulations concluded that this vote was due to the influence of Target Malaria, a project funded by the Bill & Melinda Gates Foundation. **Internal correspondences and documents released as 'Gene Drive Files' brought to light that Target Malaria had funded an agribusiness public affairs firm called Emerging AG. It recruited and coordinated about 65 scientists who became members of expert panels (Open-ended Online Forum on Synthetic Biology / Ad Hoc Technical Expert Group (AHTEG)) of the CBD.[146]**

Decision 14/19 on synthetic biology, finally adopted at CBD COP 14[147], argues that further research on gene drives is needed and that the development of specific guidelines for the risk assessment of gene drive organisms could be helpful. Further, the resolution stated that the "free, prior and informed consent" of indigenous peoples and local communities "may be warranted" when considering the release of gene drive organisms. As a compromise to the call for a moratorium, the parties agreed on non-binding precautionary considerations related to the release of gene drive organisms into the environment.[148]

Decision 14/19 calls on parties and other governments to apply a precautionary approach consistent with the objectives of the convention, taking into account the current uncertainties regarding gene drives.

Finally, it calls on parties and other governments to consider the introduction of gene drive organisms into the environment, including for experimental, research and development purposes, only if the following conditions are met:

a) **scientifically sound risk assessments on a case-by-case basis**

b) **existence of risk management measures to avoid or minimize potential adverse effects, if any**

c) **where appropriate, "prior and informed consent," "free, prior and informed consent," or "approval and participation" of potentially affected indigenous peoples and local communities is to be obtained, to the extent possible in accordance with national circumstances and legislation.**[149]

In addition, Decision 14/19 considers the recommendations of the CBDs Subsidiary Body on Scientific, Technical and Technological Advice (SBSTTA) on synthetic biology - including on gene drives - for discussion at the next COP.

Provisions on gene drive organisms under the Cartagena Protocol

The Cartagena Protocol on Biosafety is a legally binding protocol under the CBD. It has been ratified by 170 countries, including all EU member states, as well as the EU. The USA, Australia, Canada and Argentina are not parties to the protocol

The protocol aims to ensure the safe handling, transport and use of living modified organisms (broadly in line with the EU definition of GMO) and to minimize adverse effects on biodiversity and risks to human health. Decisions of the protocol must be implemented into national law by signatory countries.

Currently, Article 17 of the Cartagena Protocol requires signatories to inform the CBD secretariat and all affected or potentially affected states (parties and non-parties) of any occurrence under their jurisdiction that results or may result in the unintended transboundary spread of living modified organisms (i.e., genetically modified organisms, and thus also gene drive organisms).[150] This is also required by EU Regulation 1946/2003, which implements the Cartagena Protocol.[151] It stipulates that EU member states should prevent the unintended transboundary spread of GMO. In this way, the EU goes further than the provisions of the Cartagena Protocol, which only suggests the start of mutual consultations in such a case.

At its ninth session, the conference of the parties to the Cartagena Protocol (COP-MOP9) recognized in its **Decision 9/13 on risk assessment and management**, in paragraph 3, the potential adverse effects of gene drive organisms on the environment. This decision reiterated the need to consider, in advance of any release of such organisms into the environment, the need for research and (risk) assessment and whether specific guidance on this might be helpful in order to conduct a case-by-case risk assessment. International cooperation, knowledge exchange and capacity building should serve to better assess the potential adverse effects of gene drive organisms.[152]

At the tenth meeting of the Cartagena Protocol (COP-MOP 10), the member parties will discuss whether to develop guidance for the risk assessment of gene drive organisms.

In the run-up to the meeting, a panel of experts called the Ad Hoc Technical Expert Group (AHTEG) to the CBD had recommended the development of such specific guidance materials. According to their report, it is necessary to assess the impacts of gene drive organisms on ecosystems as a whole, because irreversible impacts on biodiversity are identified as possible consequences of releasing gene drive organisms into the environment. Among other issues, the spatial and temporal controllability as well as unforeseen effects that occur only in following generations are highlighted as challenges for the risk assessment of gene drive organisms.[153]

Provisions on gene drive organisms under the Nagoya-Kuala Lumpur Supplementary Protocol on Liability and Redress to the Cartagena Protocol

The Nagoya-Kuala Lumpur Supplementary Protocol on Liability and Redress is a sub-protocol of the Cartagena Protocol on Biosafety. It entered into force in 2018 and has 46 signatories, including 21 EU member states and the EU. The protocol provides liability rules for cases where the provisions of the Cartagena Protocol have not been followed. Like the Cartagena Protocol itself, this supplementary protocol applies to gene drive organisms. However, there are currently no provisions tailored specifically to gene drive organisms.

Under **Article 3** of the protocol, provisions on liability and redress apply when damage results from the transboundary movement of living modified organisms (LMOs), i.e. genetically modified organisms; no matter whether they were deliberately, unknowingly or illegally introduced into the environment[154] According to Article 2, damage is defined as a negative effect on the conservation and sustainable use of biodiversity.

Article 2 also states that response actions can only be taken if the harm is measurable, observable and significant. The significance of the damage is measured by the following criteria[155]:

- Whether they result in long-term or permanent changes that cannot be remedied by natural recovery within a reasonable period of time
- The extent of qualitative or quantitative changes that adversely affect components of biodiversity.
- Whether they reduce the ability of biodiversity to provide goods or services
- The magnitude of the adverse effect on human health.[156]

Problematically, there are neither financial guarantees provided by the protocol nor enforcement mechanisms for the protocol.

Regulations of the World Health Organization (WHO)

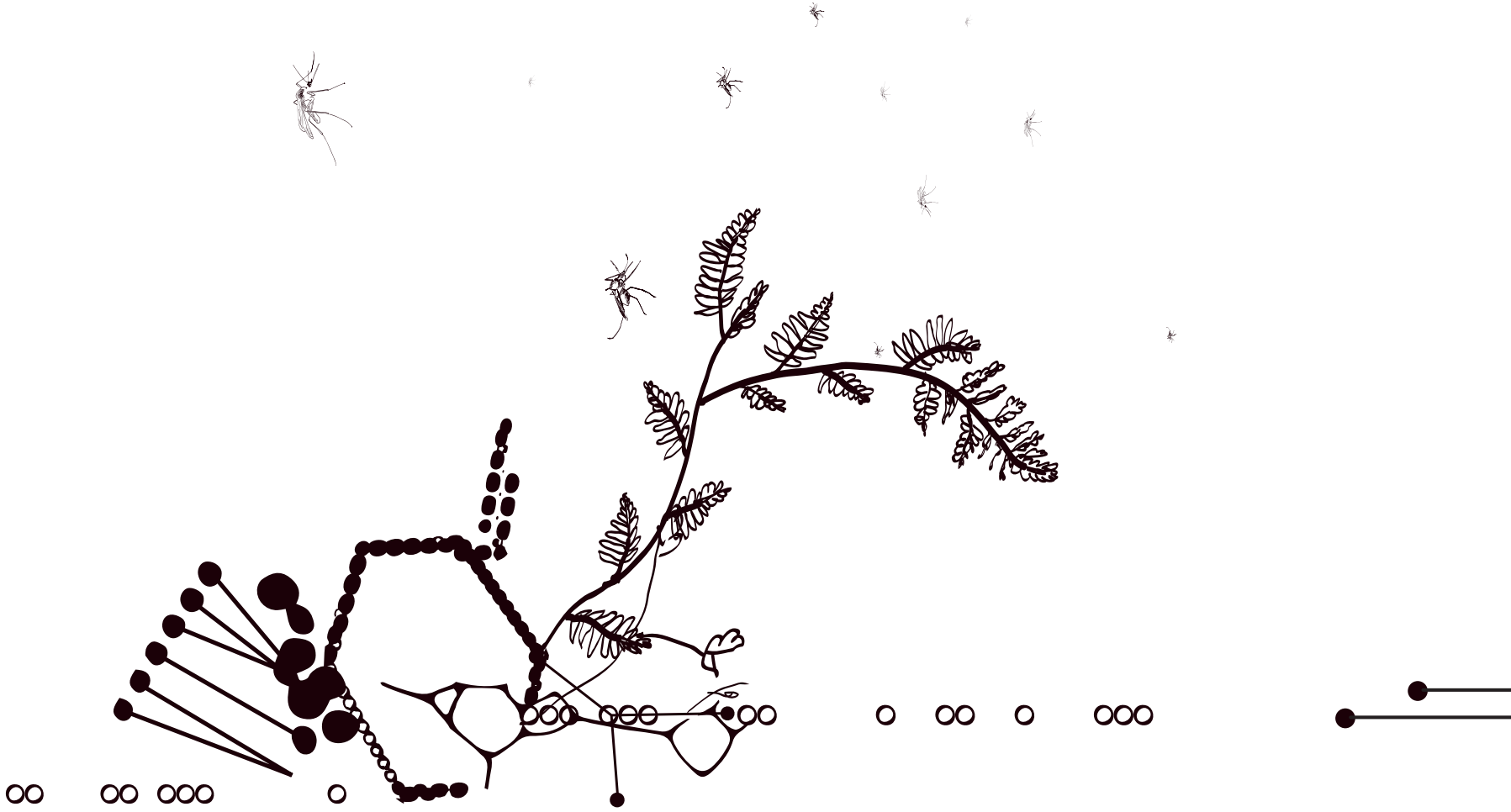
In 2014, an expert group established under the auspices of the World Health Organization (WHO) published a guidance framework for testing genetically modified mosquitoes.[157] However, the guidance has never been approved or adopted in any form by the WHO itself. Because the first publications on gene drive technology did not appear until 2015, the specific problems of this technology were not discussed in this guide. A revised version is expected by spring 2021, which should also include statements on gene drives. In October 2020 the WHO published a position statement, which clarifies the WHO's stance on the use of genetically modified mosquitoes for the control of vector-borne diseases, including the use of gene drives.[158] Along with this the WHO published guidance on ethics and vector-borne diseases, which includes a chapter on gene drive organisms.[159]

Provisions of the UN Biological Weapons Convention

The Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction prohibits the development, production and stockpiling of biological weapons for military use. The convention was adopted by United Nations member states in 1971 and entered into force in 1975. 183 state parties have signed the convention, committing themselves to destroy all stockpiles of biological weapons. However, there are no agreements on controls in this regard. Disclosure obligations and controls have not yet been integrated by an additional protocol.

Gene drives are prohibited under Article 1 of the Biological Weapons Convention if they are used for hostile purposes. This would also be the case, for example, if they were used as a means of delivering poisons or pathogens.[160] Likewise, any use of gene drives is also prohibited if there is no justification for their use for peaceful purposes or if they are otherwise inconsistent with the purposes and provisions of the UN Biological Weapons Convention.[161]

However, there are few convincing scenarios for gene drive weapons programs unless gene drives and their harmful effects can be spatially or temporally contained.[162]



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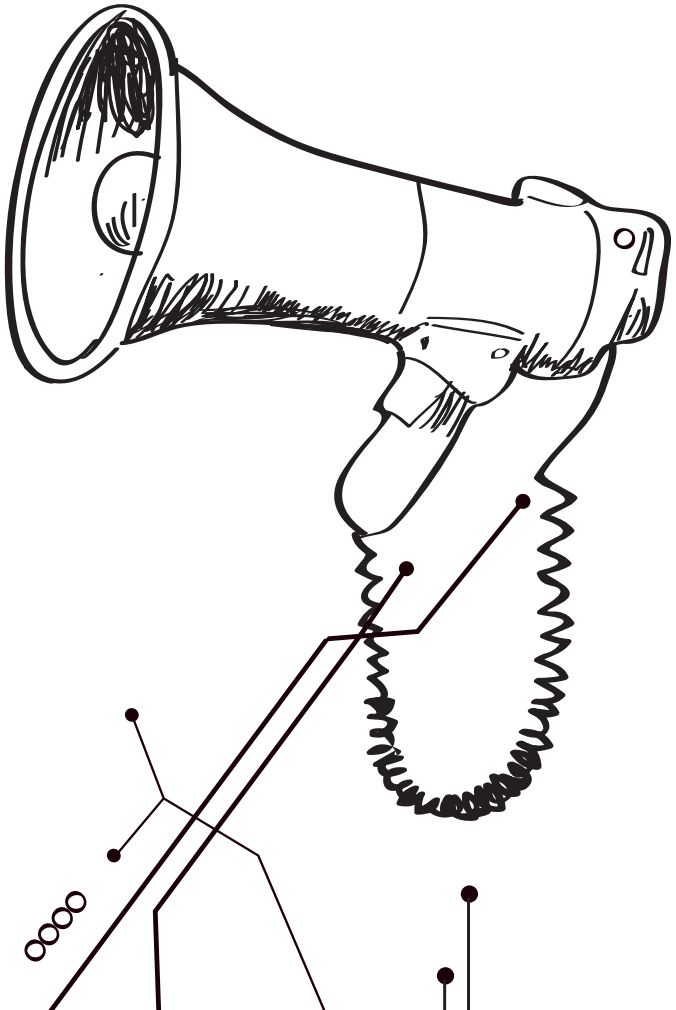
POLICY RECOMMENDATIONS

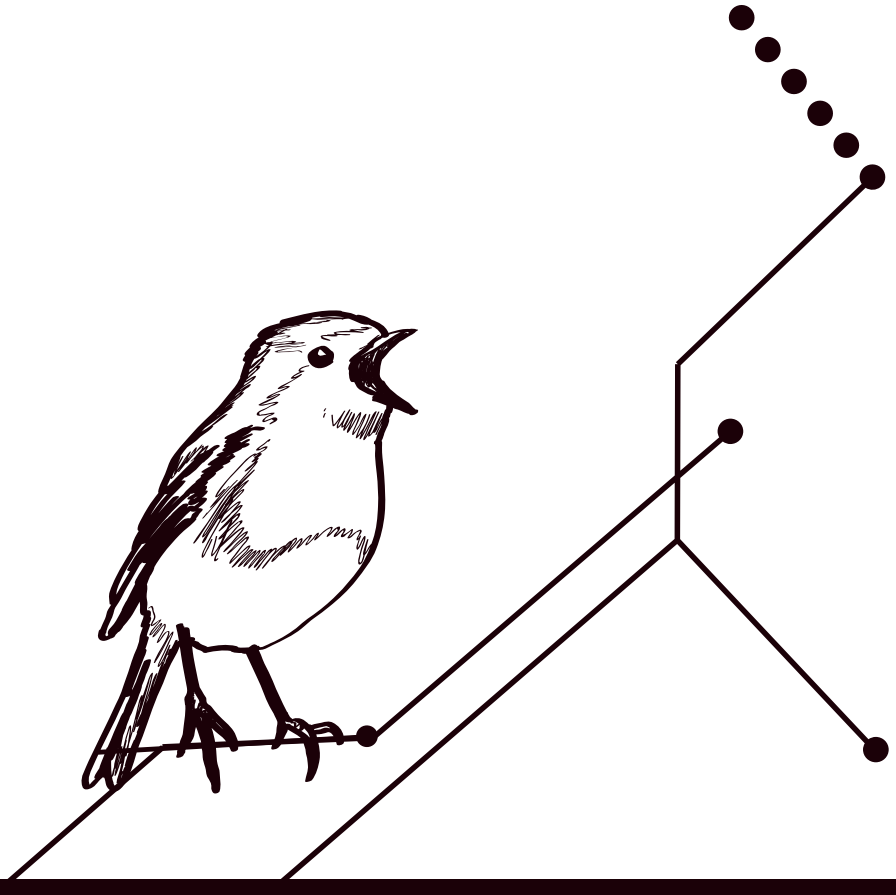


To date, no internationally binding agreement specific to gene drives exists to regulate the research and release of gene drive organisms. Neither do specific national or supranational laws exist. Nevertheless, Target Malaria could conduct the first release trials with gene drive mosquitoes as early as 2024.

Apart from the lack of specific international regulations, even adequate, scientifically based concepts and methods for the estimation, assessment and management of risks as well as for the monitoring of released GDO into the environment are missing so far. Neither does a central registry of all currently conducted research and development projects related to gene drives exist. There is also a lack of concepts and foundations for technology assessments that go beyond pure environmental risk assessment.

A societal discussion about the circumstances under which the release of a GDO might be justifiable, maybe even ethically required, or has to bee ruled out has not begun in earnest, neither at the national or international level.

Against this backdrop, it seems clear that the world community must take sufficient time to deal with this new global challenge. This is the prerequisite for building a consensus on how to deal with this technology, on how to assess the ecological, medical, ethical, cultural, scientific and international legal issues involved here and to make a decision on how to regulate this technology.



THAT'S WHY SAVE OUR SEEDS RECOMMENDS:

» A global moratorium on the release of gene drive organisms

At the 15th Conference of the Parties to the UN Convention on Biological Diversity (CBD), the European Union should advocate for a global moratorium on any environmental release of GDO. Even before that, the EU should clarify that such releases are prohibited under current EU legislation. The EU should also signal that it will take action with all available means against any release of GDO which could reach the territory of the EU.

In the view of Save Our Seeds, the following requirements are essential prerequisites for reaching an agreement on lifting the global moratorium, which should be considered on a case-by-case basis. Of course, it is in the nature of an open-ended decision-making process involving all stakeholders that such criteria may change in the course of the discussion. Whether this moratorium should be converted into a permanent and general ban, or whether the release of gene drive organisms is justified or even required in individual cases, also depends on the criteria to be developed.

Requirements for retrievability and controllability of gene drive organisms

The prerequisite for any release of GDO should be a sufficiently verified method for their removal from nature. In addition, a temporal and spatial controllability and thus a possibility to limit their effect and spread in nature should be mandatory before any release can be considered.

A global process for decision-making on the release of gene drive organisms

Due to the international nature of the potential consequences of the release of GDO, international standards and procedures for decision-making are also required for their approval. Crucial to this is the inclusion and equal participation of all potentially affected parties. This refers first to states, but also specifically to indigenous peoples and local communities as defined in UN Declaration 61/295 on the Rights of Indigenous Peoples and Declaration 73/165 on the Rights of Small Farmers and Other Rural Workers. The basis of such decisions must be their effective participation under the full implementation of the principle of free prior informed consent.

An integrated system of assessment, evaluation and management of risks from gene drive organisms to the environment and health

Given their invasive nature and inability to control, recall or reverse GDO in nature, risk assessment and modelling cannot be undertaken with existing concepts and methods established for genetically modified organisms. Before any release of GDO can be considered, internationally agreed procedures and guidelines must first be developed for how the environmental risks posed by GDO are to be uniformly recorded and assessed. Guidance on risk assessment should fully operationalize the precautionary principle, must seek to obtain the free, prior and informed consent of potentially affected indigenous peoples and local communities. Furthermore, monitoring and identification procedures would need to be established to document and track the spread and behavior of GDO in different ecosystems. In this context, the international community should commit to developing and maintaining contingency plans.

» Concepts for international, participatory technology assessments for gene drive organisms

A comprehensive, anticipatory technology assessment, ensuring the effective participation of all potentially affected states as well as indigenous peoples and local communities should go beyond the purely scientific investigation of ecological and health aspects. It should lay the foundation for discussing ethical questions, socio-economic and cultural and societal consequences, challenges and appropriate decision-making processes. This exercise should include, among other things, the evaluation of the root causes of the problem this technology aims to address, its goals and an assessment whether these root causes could better be addressed by other means. Additional effort should be put in assessing the costs and benefits for specific groups in society.

» Binding and specific global rules for liability and redress for damage caused by gene drive organisms

Both during a global moratorium on the release of gene drive organisms into nature and in the event of a justified lifting of a moratorium, there should be specific and internationally binding rules for liability and redress. They should be able to address unintentional or illegal releases of gene drive organisms and resulting damage.

» Mandatory global reporting of gene drive organism research in contained systems and uniform safety standards for gene drive research

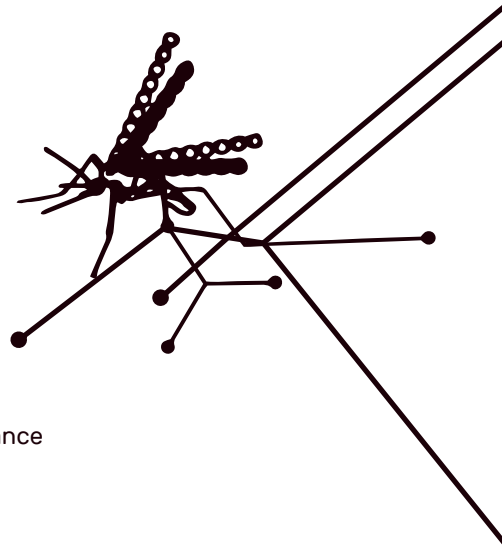
Because even individual, unintentionally released GDO could spread uncontrollably, both temporally and territorially, high safety standards for handling GDO adapted to the respective organisms are of global importance and urgency. An essential prerequisite for adequate safety measures is a central registry of all gene drive research and related field trials, which should include a precise description of the organisms, the gene drive constructs, and the goals pursued with them.

» A ban on the development of gene drive organisms with potential for military use

In addition to the already existing ban on the use of biological weapons by the UN Biological Weapons Convention, a prerequisite for research on gene drives should be the proof that the GDO developed in the process have no potential to be misused as weapons.

LIST OF ABBREVIATIONS

AfD:	Alternative für Deutschland / Alternative for Germany
AHTEG:	Ad Hoc Technical Expert Group
AMK:	Konferenz der Agrarminister*innen / Conference of Agriculture Ministers
BfN:	Bundesamt für Naturschutz / German Federal Agency for Nature Conservation
BMBF:	Bundesministerium für Bildung und Forschung / Federal Ministry of Education and Research
BWC:	Bioweapons Convention
Cas:	CRISPR-associated
CBD:	Convention on Biological Diversity
CDU:	Christlich Demokratische Union Deutschlands / Christian Democratic Union of Germany
CEO:	Corporate European Observatory
COP:	Conference of the Parties
CRISPR:	Clustered Regularly Interspaced Short Palindromic Repeats
DARPA:	Defense Advanced Research Project Agency
DNA:	Deoxyribonucleic acid
EFSA:	European Food Safety Authority
EGE:	European Group on Ethics in Science and new Technologies
EU:	Europäische Union
FDP:	Freie Demokratische Partei / Free Democratic Party
GBIRd:	Genetic Biocontrol of Invasive Rodents
GDO:	Gene Drive Organismus
GenTG:	Gentechnikgesetz / Genetic Engineering Act
GenTSV:	Gentechnik-Sicherheitsverordnung / Genetic Engineering Safety Ordinance
GVO:	Genetically modified organism
HCB:	Haut Conseil des Biotechnologies
IUCN:	International Union for Conservation of Nature
LMO:	Living modified organism
MOP:	Meeting of the Parties
MX:	Meeting of Experts
NGO:	Non Governmental Organisation
PBT:	Persistant Bioaccumulative Toxic
PMEM:	Post Market Environmental Monitoring
POP:	Persistant Organic Pollutant
REACH:	EU Regulation on Registration, Evaluation, Authorisation, and Restriction of Chemicals
SBSTTA:	Subsidiary Body on Scientific, Technical and Technological Advice
SDGD:	Sex Distorter Gene Drive
SPD:	Sozialdemokratische Partei Deutschlands /Social Democratic Party of Germany
TAB:	Büro für Technikfolgen-Abschätzung beim Deutschen Bundestag / Office of Technology Assessment at the German Bundestag
UN:	United Nations
USA:	United States of America
VPVB:	Very persistent very bioaccumulative
WHO:	World Health Organization
ZKBS:	Zentrale Kommission für die Biologische Sicherheit / Central Commission for Biological Safety



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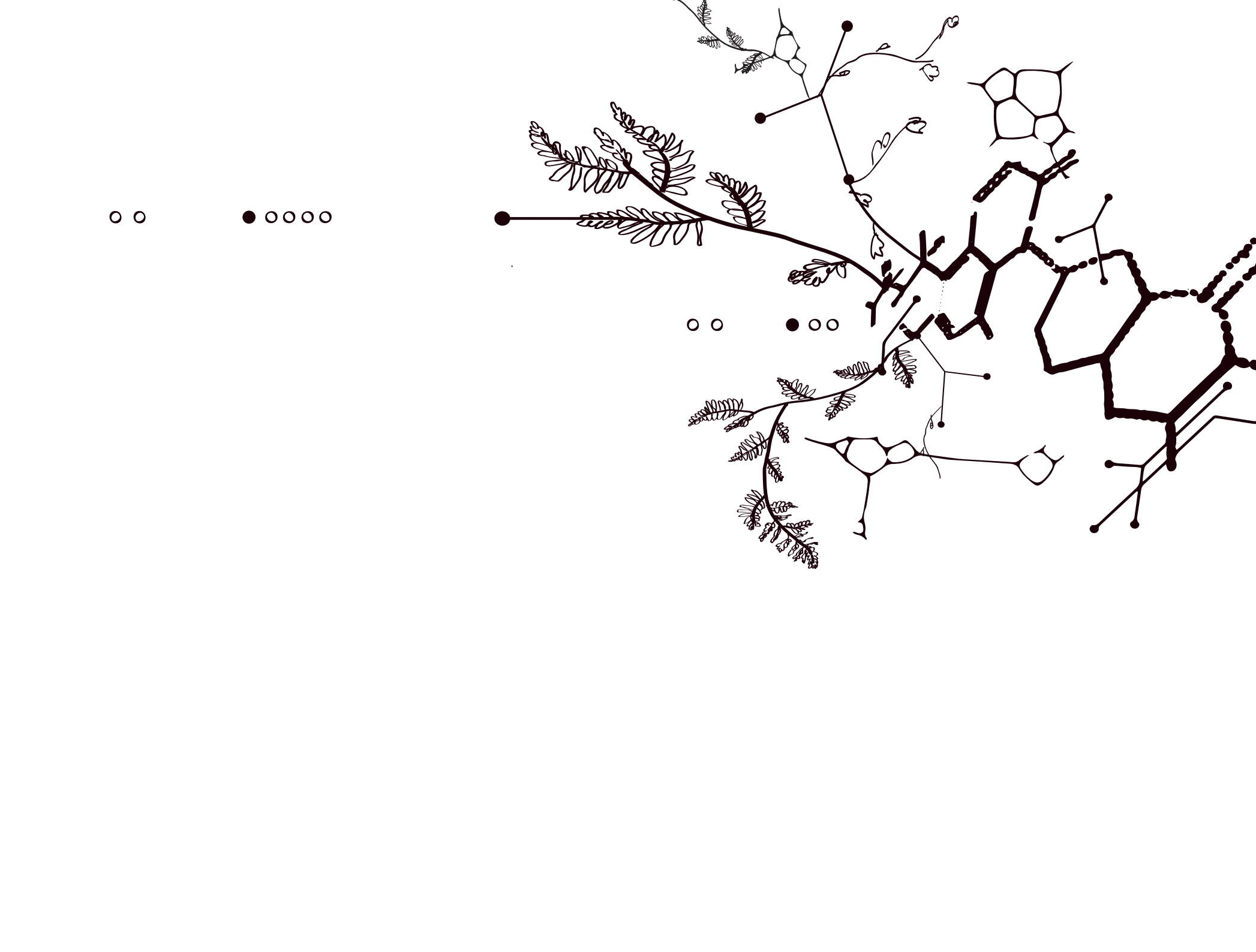

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