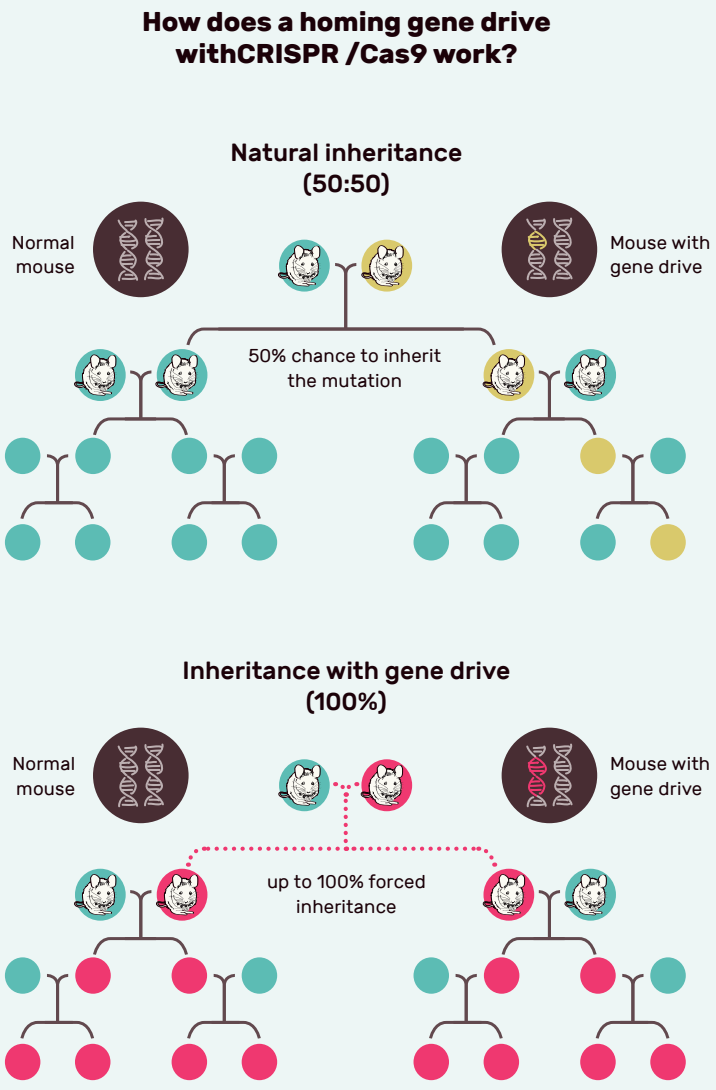
GENETIC ENGINEERING OF WILD SPECIES WITH GENE DRIVES

Gene drive technology is enabled by new genetic engineering tools such as CRISPR/Cas9. Gene drives are designed to genetically modify, replace or eradicate wild populations or entire species. So far the technology works in mosquitos, mice, flies, yeast and nematodes. But in principle it could be used to genetically modify any sexually reproducing organism. Gene drive organisms (GDO) are meant to mate with their wild relatives and spread their engineered genes to 100% of their offspring. This forced inheritance pattern circumvents nature's normal rules of inheritance. It triggers a genetic chain reaction in which the genetic engineering tool CRISPR/Cas9 and sometimes an additional new gene are passed on from generation to generation. Genetic changes induced by a gene drive can lead to sterility or the change of sex ratio of their descendants, leading to a crash in their population. It has not been proven yet that gene drives would work in nature as predicted by lab experiments. First environmental field trials are planned in Africa in the near future.

Proposed applications: Eradication of invasive species -- Eradication of agricultural pests - Eradication or modification of disease transmitting insects or animals -- Dual use as bioweapons for military purposes.

Remodeled rules of inheritance



Unassessed Risks

Invasiveness & uncontrollable, cross-border spread[i]: GDO will spread in any ecosystems they can survive in, likely beyond national borders – which could give rise to conflict.

Irreversibility & persistence over generations[ii]: GDO will persist and spread in the environment over generations. GDO cannot be recalled. The gene drive will spread irreversibly in nature; eventually causing changes to ecosystems. These effects may not be reversed. The genetic makeup of natural populations cannot be restored to its original state.

Error-prone mechanisms and unintended genetic effects[iii]: The active genetic engineering tool CRISPR/Cas9 built into GDO can have unintended genetic effects and create unwanted mutations or resistances.

Gene Drive transfer to non-target species[iv]: Gene drives could be transferred to and further spread in related species.

Hurdles to modelling - unpredictable effects[v]: Effects of GDO in their population dynamics and ecosystems are highly unpredictable due to the complexity of natural systems, their unlimited spread and the persistence of GDO in nature over many generations.

Serious damage to food webs and biodiversity[vi]: Suppressing, eradicating or genetically modifying entire wild populations or species has the potential for severe and irreversible negative effects on food webs and biodiversity. This could also negatively impact organic farming, peasant farming practices and food security.

Potential for conflict and hostile use[vii]: The US military research institute DARPA is one of the main sponsors of Gene Drive research, mainly to counteract the possible use of Gene Drives for military or hostile purposes. The UN Bioweapons Convention therefore studied the technology's potential to spark conflict and to be used as biological weapons.

Risky research[viii] and insufficent regulation[ix]: The debate on EU and international level on the regulation of gene drive technology is still in its infancy. Up to now this new technology lacks specific, binding national, EU and international regulation, as existing GMO regulations are insufficient for GDOs. The UN Convention on Biological Diversity (CBD) with its Cartagena Protocol is the appropriate forum to develop and agree on globally binding rules.

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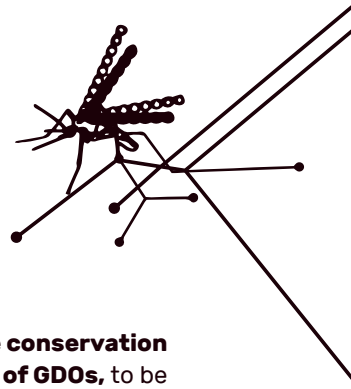

Policy recommendations

A global moratorium on the release of gene drive organisms

In order to enforce the precautionary principle enshrined in EU and international nature conservation regulatons, the European Union should advocate for a global moratorium on all releases of GDOs, to be adopted at the 15th Conference of the Parties (COP) to the UN Convention on Biological Diversity (CBD). The EU should also clarify that releases even in other regions of the world would be incompatible with its current EU GMO legislation (Directive 2001/18/EC). The EU should also signal, that it would therefore take action with all available means against any gene drive organism released, which could reach the territory of the Union in the short or long term.

Essential preconditions for the lifting a global moratorium:

Retrievability and controllability of gene drive organisms. The prerequisite for any release of GDOs should be a sufficiently verified method for their removal from nature. In addition, a temporal and spatial controllability and possibility for confinement should be proven to work.

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 a necessary prerequisite 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 full implementation of the principle of free prior and informed consent.

An integrated system of assessment, evaluation and management of risks posed by gene drive organisms to the environment and human, animal and plant 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 detection 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 of international inclusive, 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 & civil society should go beyond the purely scientific investigation of ecological and health aspects. It should lay the foundation for discussing ethical questions, social, 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 into 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 also be able to address unintentional or illegal releases of gene drive organisms and resulting damage.

Mandatory global reporting of gene drive 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 GDOs developed in the process have no potential to be misused as weapons.

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[i] **Invasiveness & uncontrollable, cross-border spread**
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- Kosicki M, Tomberg K, Bradley A (2018). Repair of double-strand breaks induced by CRISPR-Cas9 leads to large deletions and complex rearrangements. Nat Biotechnol 36:765

[iv] **Gene Drive transfer to non-target species**
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[v] **Impossible modelling - unpredictable effects**
- TWN Biosafety Briefing, Sirinathsinghji, Eva (2020): Risk Assessment Challenges of Synthetic Gene Drive Organisms
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- Benedict, M. Q. et al (2018). Recommendations for Laboratory Containment and Management of Gene Drive Systems in Arthropods. Vector borne and zoontic diseases. 18 (1)

[ix] **Insufficent regulation**
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STOP GENE DRIVES