ISAAA POLICY BRIEFS

Risk Assessment for Gene Drive Organisms

ISAAA Inc. and the Outreach Network for Gene Drive Research

Introduction

Gene drive approaches offer the potential to develop new tools to address important conservation and public health challenges that have not been successfully solved by current methods alone, such as invasive alien species and vector-borne diseases.

Gene drive is a genetic phenomenon that occurs in nature and causes a selected trait to spread rapidly through a species via sexual reproduction over generations, potentially becoming increasingly common within a specific species. Gene drive systems are being developed in the laboratory to replicate this natural phenomenon in order to help tackle major challenges such as malaria. In this way, a desired change is passed on to up to 100% of offspring, rather than at the more usual rate of 50%. This technology is currently under research, and the risks and benefits of each potential application are being thoroughly investigated.

What is a risk assessment?

Risk assessments can be carried out at many different points during the development of a gene drive organism. Risk assessments can take place at key research stages, such as before starting small-scale outdoor evaluations or for final regulatory evaluation before a technology is put forward for use.

A risk assessment aims to identify potential pathways to harm that could lead to adverse health or environmental impacts. It evaluates the likelihood and magnitude of such potential harm occurring and highlights any further elements of uncertainty. This process then informs possible risk management activities, which aim to identify and implement suitable measures that can eliminate or mitigate risks.

Key Concepts for Risk Assessment

The risk assessment methodology applied can vary, but experts will always evaluate:

HAZARD
Anything that could cause potential damage, harm, or adverse effects on something or someone

+

EXPOSURE
The extent to which something or someone is subjected to that hazard

=

RISK
The chance — high or low — that something or someone will be harmed by a hazard

Every risk assessment has different steps

Risk assessment starts with hazard identification, commonly referred to as the "what-can-go-wrong" step. Often, this will involve engagement with stakeholders, including local communities where research may take place or where the technology may be used. Engaging stakeholders to assess their experience is an important step in ensuring the hazard identification is thorough, as the perception of hazard can vary according to values and individual experience. The assessors will then verify which of the perceived or assumed hazards are in fact likely at this stage. Afterwards, they will evaluate the probability of exposure and the consequences (or severity) of such hazard. They want to respond to questions such as "how likely is it to happen?" and "would it be a problem?". With this information, the assessors should be able to adequately characterize the risks. If the risks are significant, it is then time to decide whether and which measures can be taken to manage or minimize the risks. Once mitigation measures are defined, the risk assessment can be repeated to determine whether remaining risks are acceptable.

The risk associated with any gene drive research, in particular for field evaluation, must be assessed on a case-by-case basis. Risks and benefits associated with each gene drive approach will primarily depend on the type of modification made, the species it is applied to, and the ecosystem and geography where the organism with the drive system will be used, rather than on the gene drive mechanism itself. The assessment of risk might change as new evidence from testing or the scientific literature emerges, thus a risk assessment should be regarded as a living document.

There are many different types of gene drive constructs, for many different uses and contexts. Therefore, gene drive risk assessment must be science-based and consistent with the principle of case-by-case assessment.

Risk assessments are typically undertaken both by the 'applicants' and national authorities, separately. For example, a project or team developing a product and applying for a permission to do research in containment, undertake field trials, or commercialize their work must assess the potential risks and benefits of such a product. National authorities can conduct additional risk assessments to feed into their decision process about whether to allow a new technology to be researched and developed. It is worth noting that risk assessment results are not the only decision-factor – national authorities might also consider socio-economic, cultural, or environmental factors, as well as the country's priorities.

Who oversees gene drive research?

Gene drive research is ultimately regulated at the national level. Research organizations must comply with national regulatory frameworks that determine what research can occur and how. To ensure they are suitable to new developments and conditions, national authorities can choose to create different or additional requirements for gene drive research other than the ones that already exist for other research on genetically modified organisms.

Research in physical containment	Research outside of physical containment
• Often under permits issued by governments to the institution to cover a range of research allowed to take place for a certain time period.	• Permits requested on a case-by-case basis for each research project or experiment.
• Permits outline research terms and conditions. Individual permits are not required for each experiment.	• A risk assessment will be needed as part of a request for a permit.
• Usually overseen by a biosafety committee or board. Some research will need additional notification to governments.	• Authorities can also conduct their own risk assessments, based on the information provided by the developer.
• Without an institution-wide permit, the research team will need to request case-by-case permission from national authorities. Risk assessment islikely to be required as part of the request.	

Are we ready to assess the risks and benefits from gene drive technologies?

Many countries have drafted their own frameworks for carrying out risk assessments of genetically modified organisms. These regulations are often based on international guidelines, such as the Cartagena Protocol. For countries that may be in the process of creating national regulatory frameworks or reviewing them to check their adequacy for evaluating new technologies, international guidance is also helpful.

Examples of International Guidelines

- The Cartagena Protocol on Biosafety to the Convention on Biological Diversity (CBD) aims to ensure the safe handling, transport and use of living modified organisms (LMOs). Since gene drive organisms are considered LMOs by the CBD Decision 14/19, the principles and methodologies used for the risk assessment under the Protocol are considered broadly adequate to assess the potential risks of gene drive applications.
- The WHO recently reviewed its Guidance Framework for Testing of Genetically Modified Mosquitoes to contribute to the decision-making process of countries interested in the potential use of genetically modified mosquitoes to control vector-borne diseases. WHO addresses specific challenges associated with such research and development, considering issues related to ethics, safety, affordability and effectiveness.
- The US National Academy of Sciences, Engineering and Medicine (NASEM) has recommended that ecological risk assessments could be used as a framework for gene drive risk assessment. It also acknowledges that gene drive organisms could require a more complex risk assessment process, warranting further research.
- The European Food Safety Authority (EFSA) recognizes that its existing guidelines to assess genetically modified animals are adequate for evaluating risks associated with gene drive modified insects, but further work is needed in areas such as molecular characterization.
- The Australian Office of the Gene Technology Regulator (OGTR) issued guidance on the topic of gene drive research saying their national biosafety regulation are broadly sufficient to assess gene drive organisms. They recommendoperating on a case-by-case basis for reviewsin order to decide if any additional measures are needed.

Policy recommendations

- Risk assessment processes must be science-based and consistent with the principle of case-by-case assessment, as there are many different types of gene drive constructs, for many different uses and contexts.
- Risk assessment should be inclusive by allowing a broad range of stakeholders to voice their concerns and contribute to the process.
- National authorities should turn to existing international risk assessment guidelines for LMOs to create and review their national frameworks, as they are broadly adequate for gene drive organisms.
- Many countries already have strong regulatory frameworks but investments in building biosafety expertise are needed to increase other countries' ability to take part in and benefit from innovative research.

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