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The need for horizon scanning and technology assessment to address the evolving nature of genetic engineering

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Introduction

The governance and regulation of advancing life and agricultural sciences is lagging behind technical innovations and our evolving understanding of the science underpinning genetic engineering technologies. Such technologies, mainly in the form of transgenic techniques, were first commercialized nearly three decades ago, though few traits have reached the market. With advances in science and technology, the field is attempting to explore new genetic engineering techniques that can expand the scope, applicability and depth of intervention.

New genetic engineering techniques, however, are evolving beyond the current scope of legal definitions, risk governance and consent mechanisms, with interventions increasingly moving towards ecosystem-wide projects for crop, human health and climate or biodiversity conservation interventions (Greiter et al., 2022; Heinemann, 2019; Sirinathsinghji, 2019). Such advances at the technical level are raising novel biosafety risks that urgently warrant updated assessment methodologies and regulations to address significant biosafety knowledge gaps and increasing levels of uncertainty about how these technologies will impact biodiversity and human health.

Moreover, thorough scrutiny of their potential limitations to alleviate the societal problems they are purported to address, and which existing living modified organisms (LMOs) have not been able to combat, is also needed. Indeed, many of the original concerns raised about LMO commercialization have been borne out, including efficacy problems and unintended agronomic and ecological effects resulting in repeated crop failures and economic damage, particularly for smallholder farmers (for example, see ENSSER, 2021; Kranthi & Stone, 2020; Luna & Dowd-Uribe, 2020; Wilson, 2021). While new technologies are being developed to address the problems that first-generation LMOs failed to solve, proponents are again hyping up the potential benefits and making blanket claims about safety.

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In this context, it is imperative that horizon scanning and technology assessment are fully operationalized to protect biodiversity and human health from the new genetic engineering technologies, including synthetic biology, that are yet to be fully understood, and currently difficult, if not impossible, to control, reverse or recall from the environment following release.

Discussions under the CBD

Parties to the Convention on Biological Diversity (CBD) already have obligations under Article 7 to identify and monitor processes and activities that have or are likely to have significant adverse impacts on the conservation and sustainable use of biological diversity, and to monitor their effects. They also have obligations under Article 14 to assess the impacts of projects, programmes and policies that are likely to have significant adverse effects on biological diversity. These treaty obligations can be operationalized through horizon scanning and monitoring, and technology assessment, respectively.

Horizon scanning is understood as a means to scan the literature and existing research, including applications in the pipeline, for future developments, to identify and track new developments, as well as anticipate potential adverse effects. This will also provide the information necessary for the adaptation of risk assessment and risk management methodologies that might be needed in light of the evolving nature of genetic engineering (Greiter et al., 2022).

Technology assessment is a well-established approach that embeds risk assessment in a broader societal perspective (Greiter et al., 2022). This is important, as technologies do not just have environmental or human health impacts, but also socioeconomic, cultural and ethical implications. In the context of the CBD and its Cartagena Protocol on Biosafety, where the role of indigenous peoples and local communities (IPLCs) in stewarding biodiversity, and the value of biodiversity to them, are explicitly recognized, these aspects are of particular importance.

In the discussions on synthetic biology, CBD Parties already agreed in 2018 in Decision 14/19 that "broad and regular horizon scanning, monitoring and assessing of the most recent technological developments is needed for reviewing new information regarding the potential positive and potential negative impacts of synthetic biology vis-à-vis the three objectives of the Convention and those of the Cartagena Protocol and Nagoya Protocol".

Current negotiations under the synthetic biology agenda item are about establishing the horizon scanning, monitoring and assessment process, including whether or not a multidisciplinary expert group should be established to perform the tasks, and all this is still to be agreed upon.

At the same time, CBD Parties are currently negotiating the post-2020 Global Biodiversity Framework (GBF), which is meant to address the CBD's implementation to 2030, as expressed in goals and targets. The current Target 17 and Target 19.2 contain text proposals for technology horizon scanning, monitoring and assessment, and these should be supported in order to ensure that the GBF is fit for purpose, allowing for the rapid and fast-paced developments of new genetic engineering technologies to be reviewed, and their potential adverse effects anticipated, monitored and assessed.

In addition, text calling for access to and transfer of technology should be coupled with the notion of technology horizon scanning, monitoring and assessment, so that any technology that is transferred is subject to this process. This will help ensure that only those technologies that are appropriate, socially acceptable and environmentally sound are accessed and transferred.

This paper provides some examples of new developments in genetic engineering – gene drives, genetically engineered viruses and RNA interference – to demonstrate why horizon scanning and technology assessment are urgently needed.

Gene drive technologies

Gene drive technologies are a form of genetic engineering designed to skew inheritance of the engineered trait such that most, if not all, offspring will inherit the trait, with the aim of rapidly "driving" it through a population. Various applications have been proposed, with the most advanced and promoted being gene drive mosquitoes that aim to reduce vector-borne disease burden, such as malaria or dengue fever. The Target Malaria project aims to use gene drives to eliminate mosquito populations (population suppression) by spreading infertility or gender-bias traits, while other projects aim to alter transmission (population modification) of disease pathogens to humans. Agricultural applications such as the elimination of pests, as well as conservation applications such as the elimination of invasive species, are also envisaged (CSS et al., 2019).

Various molecular mechanisms are being deployed to achieve the driving characteristic, the most common being the use of genome editing technologies such as CRISPR systems. These are incorporated into the gene drive organism in order to carry out genetic engineering "live" inside wild organisms, "cutting and pasting" transgenic DNA at each generation for perpetuity. Described as transferring the laboratory to the field (Simon et al., 2018), rather than the genetic engineering being performed in the laboratory where, in theory, it can be assessed for biosafety concerns, the continuing engineering process means that any unintended effect cannot be ruled out prior to release.

Unintended effects at the molecular level have been widely documented with genome editing techniques such as those deployed for gene drives. These include on-target and off-target effects, novel protein production and cellular impacts (e.g., see Agapito-Tenfen et al., 2018; Biswas et al., 2020; Brunner et al., 2019; GeneWatch UK, 2021; Ihry et al., 2018; Kawall, 2019; Norris et al., 2020; Ono et al., 2019; Skryabin et al., 2020; Tuladhar et al., 2019), with next-generation effects (Zhang et al., 2018). These unintended effects may continue to occur or accumulate following release, and spread with unknown consequences with regard to their interaction with the environment, pathogens or humans who may be exposed to gene drive organisms and any pathogen within them. The evolutionary impacts of such next-generation effects are completely unknown, and raise novel challenges to risk assessment methodologies, as concluded by the Cartagena Protocol on Biosafety's Ad Hoc Technical Expert Group (AHTEG) on Risk Assessment and Risk Management (AHTEG, 2020).

Unlike existing LMOs, gene drives are designed to spread and persist. The ecological consequences of this are unknown, for example any potential impacts on the target organism's wider food webs, or non-target organisms that are connected via gene flow to the target organism itself. Ecological effects may take decades to become visible, and are notoriously difficult to study. Using gene drives to remove invasive species can have unexpected detrimental effects if functional roles within ecosystems have been embedded (Lim & Traavik, 2007; Sirinathsinghji, 2020). Such interventions also introduce the risk that they may spread to the target organism within its native range, with potentially serious ecological harm.

Discussions around disease applications have also not given sufficient consideration to potential negative impacts on disease epidemiology. How any unintended or intended effect may impact on disease transmission is unknown and difficult to assess prior to release (Beisel & Boëte, 2013; Sirinathsinghji, 2020). For example, how the modifications may alter disease transmission, or pathogenicity of the target (or non-target) pathogen, particularly with population modification drives that will exert pressure on the pathogens to evolve around the modified trait. Most crucially, such risks, as partially acknowledged by developers (James et al., 2020), cannot be comprehensively assessed in the lab. Moreover, the capacity for vectors to transmit disease is mediated by wider environmental factors, e.g., bacterial symbionts in mosquitoes. How the genetic engineering process impacts on these factors is highly uncertain. Further, whether gene drives will positively impact disease epidemiology, even if they are capable of reducing mosquito numbers, is still questionable.

Finally, gene drives are currently irreversible, and there are no existing strategies to recall, reverse or mitigate a gene drive release. While there are proposals to release mitigating drive systems in response to

a gene drive going awry, these only add uncertainty and complexity, with research recently demonstrating unintended genetic effects with some techniques in laboratory flies (Xu et al., 2020). How different genetic elements interact once multiple systems are released into the environment, with continued development of novel gene drive systems, adds yet more uncertainty and complexity that warrant horizon scanning to continually monitor such developments. New developments are also taking place in bacterial systems with applications for addressing antibiotic resistance and bacterial infections, by taking advantage of the natural processes of horizontal gene transfer in bacteria. These developments have thus far garnered little attention but require further monitoring.

Technology assessment that incorporates not only biosafety, but also suitability, ethical and political considerations, is needed. Issues around consent, particularly in obtaining the free, prior and informed consent of potentially affected IPLCs, are critical and part of the broader discussions around gene drives. Social, political and commercial determinants of disease need to be taken into account when weighing up potential costs and benefits of gene drive applications. A narrow focus on vector control may risk marginalizing key health determinants such as strengthening healthcare systems, access to treatments, poverty alleviation and wider sanitation interventions, which should be incorporated into the technology assessment discussions.

Genetically engineered viruses

Efforts are underway to genetically engineer viruses for a wide range of agricultural and health applications (Greiter et al., 2022; Lentzos et al., 2022; Reeves et al., 2018). The use of viruses represents some of the most recent and aggressive environmental engineering applications under development. Genetically engineered viruses that are able to spread in the environment raise a number of challenges for current risk assessment and consent protocols.

Viruses can potentially spread rapidly, infect numerous host species, and rapidly evolve to alter characteristics such as increased transmissibility, or to find new host species. How an accurate assessment can be made prior to release, when such next-generation effects are predicted, is a fundamental challenge. Applications are wide and include using viruses to deliver genome edited machinery to plant species, termed “horizontal environmental genetic alteration agents” (HEGAAs), the use of viruses as self-spreading vaccines in the wild, and the use of viruses themselves to alter plant traits.

In the agriculture sphere, the US Defence Advanced Research Projects Agency (DARPA) is funding the Insect Allies HEGAA project. This project plans to use insects as vectors to deliver genetically engineered viruses directly to crop fields to modify those crops, potentially by delivering genome editing machinery to crops (Sirinathsinghji, 2019). The stated goals are to protect US crop systems from potential natural and engineered threats. However, the project appears to go beyond modifying the US food system, as it is working also on crops that are staples in developing countries, such as cassava and cowpea. While the project claims the aim is to create transient alterations that are not heritable, the viruses being used have been shown to infect germ cells, and thus generate heritable modifications.

Self-spreading vaccines are also being funded, including a DARPA project aimed at developing viral vaccines for use in rodents in order to prevent spill-over of the Lassa fever virus to people (Lentzos et al., 2022). This type of application raises additional challenges around consent and who makes the decision to release them, considering the potential for spread, including transboundary spread. Academic research projects are also working on the use of mosquitoes to spread viral vaccines. While these “flying vaccinators” were being envisaged for people (Shinzawa et al., 2022), obvious issues regarding the inability to control exposure may mean that any application of this type may focus on livestock.

Such developments exemplify the vast range of applications being developed and the critical need for horizon scanning and technology assessment. With viruses displaying such a high degree of complexity and lack of knowledge surrounding them, as well as the potential for global spread, urgent horizon

scanning and technology assessment are needed. This will help ensure that such applications do not slip through the regulatory net without thorough analysis, assessment and societal discussion.

RNA interference technologies

RNA interference (RNAi) technologies are now being developed as external products that can be used in various applications from pesticide sprays, to animal feed additives, to post-harvest food preservation products (Heinemann & Walker, 2019). Distinct from already commercialized LMO crops that carry transgenes that encode for RNAi molecules, synthetic RNAi molecules are being developed for direct application to organisms.

RNAi is a naturally occurring cellular process that functions as a gene regulatory system to turn genes off (and sometimes on) in cells. By hijacking the process, scientists can activate this process in organisms by using synthetic interfering RNA molecules that are sequence-specific to a target gene, which then go on to block translation of a gene into a protein, e.g., one that is essential for survival, and thus exerting insecticidal activity, in the case of pesticide sprays.

The process of RNAi is incompletely understood, with developers claiming that the effects of RNAi, and the traits exerted, are transient and not passed down to the next generation. However, there is well-established evidence that RNAi effects can indeed be inherited, via multiple mechanisms, with developers themselves filing patents for the offspring of organisms exposed to RNAi products. As such, exposing organisms – both the target as well as all the unknown non-target organisms – to foliar RNA sprays has been described as environmental engineering that involves, rather than the release of LMOs, the release of a product that can produce LMOs upon exposure. Such a process is uncontrolled, as well as potentially exposing entire agroecosystems.

There are significant risks and knowledge gaps about this technology and its potential impacts on biodiversity. RNAi is associated with unintended off-target effects where it can silence genes other than the target, and also in non-target organisms, as has already been documented for RNAi-expressing LMO crops (Baum et al., 2007). Significant knowledge gaps remain in our ability to answer fundamental questions such as which species could be exposed, what their genome sequences are, or how similar the genomes of non-target organisms are to those of target organisms. While some species of RNAs are well known to be unstable, double-stranded RNAs (dsRNAs) have been shown to survive mammalian digestion and may exert effects on organisms, including people, who consume them. Moreover, synthetic RNAi products are being developed to be more stable and persistent in the environment with, for example, the use of nanoparticles, in order to improve efficacy.

Their development is raising controversy over how they may be regulated, with organisms modified by RNAi technologies potentially being excluded from being defined as an LMO. Despite a lack of regulation, products appear to be heading for market, including pesticide sprays, products that confer gender bias in seafood, animal feed additives to target seafood and bee pathogens. Horizon scanning and technology assessment are therefore urgently needed to keep abreast of a technology whose commercial development has overtaken any assessment of potential risk.

Conclusion

Genetic engineering technologies and their applications are rapidly evolving. They are, however, being framed by proponents as safe, necessary or even as falling outside of LMO definitions, in various attempts to avoid the scrutiny required to protect against potential risks to biodiversity. Emerging techniques such as genome editing that are being applied to crops, gene drive technologies, genetically engineered viruses, HEGAAs and more, pose a plethora of risks and unintended effects, which are already notably acknowledged in biomedical fields (Burgio & Teboul, 2020; Ledford, 2020; National Academy of Medicine (U.S.) et al., 2020).

Nonetheless, proponents are intending to release these technologies into the environment, with explicit intent to increase the scale and levels of intervention beyond agroecosystems, directly into wild species and ecosystems. Reduction of genetic diversity, even at the level of a single gene, can impact food webs and ecosystems, such that even without unintended effects of the genetic engineering process itself, the impacts of altering genes in open settings are unpredictable, with potential adverse effects (Barbour et al., 2022). Genetic changes by human activity can bypass the processes of evolution for their establishment and spread in nature (Heinemann et al., 2021), raising new levels of uncertainty and risk. Moreover, this will occur in the context of fundamental knowledge gaps around how such interventions will interact with complex, wild ecosystems.

Gene drives, RNAi and genetically engineered viruses are just a few examples of some technologies on the horizon or already reaching markets. More applications, including of synthetic biology, and new genetic technologies are in the pipeline.

It is imperative that there is:

(1) horizon scanning so that regulators and policy makers can keep abreast of the science, have information relevant for risk assessment and risk management, and thus be adequately prepared for whatever technologies are approaching; and

(2) technology assessment so that these new technologies can be robustly assessed, not just for their environmental and human health impacts, but also for their social, cultural and ethical implications.

The CBD, as the near-universal legally binding treaty governing biodiversity, must therefore include and operationalize horizon scanning and technology assessment, including in its post-2020 Global Biodiversity Framework.

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