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Driving Harm, Reversing Precaution?

An Analysis of the Additional Voluntary Guidance Materials on Risk Assessment of LMOs Containing Engineered Gene Drives

by Eva Sirinathsinghji

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Third World Network

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Chapter 1

Introduction

THE research and development of living modified organisms (LMOs) containing engineered gene drives (EGD-LMOs) is controversial. Their conceptual and biological novelties (Simon et al., 2018) present an array of biosafety, socioeconomic, ethical, cultural and biosecurity concerns.

Unlike other LMO strategies, EGD-LMOs are designed to spread and persist into wild populations, which may include spread to non-target species. Impacts on biodiversity have, to date, been considered an unintended effect of LMO releases, with risk assessment methods aimed at assessing such a risk. The explicit intention of EGD-LMOs to alter biodiversity heightens the risks and uncertainties associated with them, challenging the ability to perform robust and reliable risk assessments (Bauer-Panskus et al., 2020; Rabitz et al., 2023; Sirinathsinghji, 2020).

Compounding these concerns is the inability to recall or reverse a gene drive release if the technology goes awry. There are also implications of potential uncontrolled spread of EGD-LMOs. These include challenges to the ability to obtain free, prior and informed consent from potentially affected communities, and to control transboundary movements. These concerns have prompted calls for a moratorium on any EGD-LMO release, at least until there is appropriate precautionary oversight (CSS et al., 2019; SOS, 2025).

EGD-LMOs have been discussed under the Convention on Biological Diversity (CBD) and its Cartagena Protocol on Biosafety that sets international regulations on LMOs, for several years. In 2024, Parties to the Cartagena Protocol welcomed additional voluntary guidance materials on risk assessment of EGD-LMOs,[1] at their 11th meeting (CP-MOP11).

However, the guidance materials have adopted an approach that narrows the risk assessment framing and scope, while minimising data requirements for assessing risks. Moreover, the approach fails to sufficiently address the central risks and uncertainties associated with EGD-LMOs – their uncontrolled spread and persistence. There are also doubts about whether the guidance materials align with the precautionary approach, as well as with specific aspects of the Protocol's Annex III on risk assessment.

Nonetheless, the approach used by the guidance materials is being proposed for future guidance materials, despite these concerns. Crucially, fundamental questions remain as to the extent to which the guidance materials can assist decision-makers in protecting biodiversity, as well as peoples' right to a clean and healthy environment, and to health, in the face of highly experimental technologies such as gene drives.

[1] Additional voluntary guidance materials to support case-by-case risk assessments of living modified organisms containing engineered gene drives. CBD Biosafety Technical Series 7, https://bch.cbd.int/protocol/cpb_technicalseries.shtml#bst7

Chapter 2

Discussions on Risk Assessment of EGD-LMOs Under the CBD and Cartagena Protocol on Biosafety

IN paragraph 9 of decision 14/19, Parties to the CBD in 2018 recognised that specific guidance on EGD-LMOs may be useful due to their potential adverse effects. The decision also sets out precautionary conditions that should be met before any consideration of introducing such organisms into the environment, including for experimental releases and research and development purposes, given the uncertainties.

Subsequently, an Ad Hoc Technical Expert Group (AHTEG) on Risk Assessment established under the Cartagena Protocol concluded that there was a need for further guidance material on EGD-LMOs, due to the fundamental challenges they pose to current risk assessment methodologies (AHTEG on Risk Assessment, 2020).

This conclusion is based on the novel risks and uncertainties posed by EGD-LMOs, including intentional spread and persistence. EGD-LMOs are also described as moving the "lab to the field" (Simon et al., 2018) due to the inclusion of genetic engineering processes in every generation following environmental release, with the AHTEG noting that there are increased uncertainties and potential for next-generation effects – including on evolutionary potential and accumulation of off-target effects in populations. Without the availability of foolproof mitigation methods or the ability to recall EGD-LMOs, risk assessment needs to be comprehensive in tackling such risks and uncertainties.

In 2022, Parties to the Cartagena Protocol agreed to develop guidance materials on risk assessment of EGD-LMOs and established a new AHTEG on Risk Assessment to carry out this task. They further specified that the materials should have a specific focus on engineered gene drive mosquitoes, under the presumption that mosquito applications are currently the most advanced. Guidance materials were developed by the AHTEG with two main substantive elements: a novel general methodology for EGD-LMO assessment, and boxes elaborating on the specific risks of gene drive mosquitoes.

The guidance materials were discussed at the CBD's Subsidiary Body on Scientific, Technical and Technological Advice (SBSTTA) in May 2024. At CP-MOP11, Parties decided to welcome, but not endorse, the guidance materials and invited Parties and other relevant organisations and stakeholders to make use of them.

The decision to welcome the guidance materials was a compromise between Parties that wanted to endorse the guidance materials, and other Parties that wanted to merely acknowledge them. The latter had some concerns about whether the materials were precautionary enough to deal with the risks and uncertainties associated with EGD-LMOs. Several civil society organisations had also raised potential conflict-of-interest concerns related to how the guidance materials were developed (see box).

Potential conflicts of interest

In the course of the AHTEG proceedings, concerns were raised by civil society members of the AHTEG over potential conflicts of interest. This involved an individual member of the AHTEG who was affiliated with an entity that was considered one of, if not the, leading gene drive projects globally. This member belonged to an academic organisation and was not affiliated with a Party. These circumstances and interest could lead one to reasonably believe that the individual's objectivity in carrying out duties and responsibilities for the AHTEG may be in question, and that an unfair advantage may be created for that individual or the entity.

Concerns were further raised with regard to the failure of this individual to disclose this situation. Decision 14/33, which contains the procedure for avoiding or managing conflicts of interest in expert groups, states: "Each expert is expected to disclose any situations, financial or otherwise, that might be perceived as affecting the objectivity and independence of the contribution that the expert makes and thus affect the outcome of the work of the expert group."

Of significance is that this individual played an active role in the AHTEG. The individual was given a lead role in drafting the zero draft of one of the two main sections of the guidance, focusing specifically on risk assessment with regard to EGD-LMO mosquitoes. Moreover, this individual was the only participant to make a presentation to the other AHTEG members, on the "plausible pathways to potential harm" approach.

It is important to note, however, that due to the concerns raised by civil society, the mosquito section was later substantially modified by a new co-lead from a Party, which resulted in increased inclusion of risks and uncertainties surrounding mosquito applications. The methodological approach presented was however eventually adopted in the guidance materials despite divergence of views among experts as to its suitability, with limited to no discussions allowing for careful analysis of the implications.

This case was highlighted at discussions of the CBD's Subsidiary Body on Implementation. It has also, in part, led to amendments to the interest disclosure form contained in the appendix to the procedure for avoiding or managing conflicts of interest in expert groups, as well as mechanisms for enhancing the application of the procedure.

Chapter 3

The "Pathways to Harm" Approach and Its Industry Links

THE guidance materials for EGD-LMOs introduce a risk assessment methodology known as "pathways to harm" to identify risk, which is to be applied within a broader problem formulation approach. Problem formulation is used in some risk assessment frameworks to combine the process of establishing the context and scope of the risk assessment with the identification of potential adverse effects associated with the modifications of the LMO. In the Cartagena Protocol's Guidance on risk assessment of LMOs,[2] establishing the context and scope is part of the planning phase of the risk assessment, while the identification of potential adverse effects associated with the modifications is described as Step 1 of the risk assessment process.

Problem formulation refers to the initial planning stages of a risk assessment process, which determine the scope or limit of what is tested. Problem formulation can be a broad, precautionary and inclusive approach that includes public participation and "needs assessment" to frame the risk assessment (e.g., Hilbeck et al., 2004; Nelson et al., 2004).

[2] Guidance on Risk Assessment of Living Modified Organisms and Monitoring in the Context of Risk Assessment. UNEP/CBD/BS/COP-MOP/8/8/Add.1. https://www.cbd.int/doc/meetings/bs/mop-08/official/bs-mop-08-08-add1-en.pdf

Problem formulation should not be conflated with the specific "pathways to harm" approach. The new guidance materials, however, conflate the two, and state, for example (p. 7): *"The present additional voluntary guidance materials* ***introduce problem formulation*** *as the first step of risk assessment; this approach is being widely applied by governments and relevant international organizations (e.g. CCA, 2023; EFSA GMO Panel, 2020; European Union, 2018; NASEM, 2016; OECD, 2023; WHO, 2021). The testing of the risk hypotheses of the* ***plausible pathways to harm*** *would be performed in the subsequent risk assessment steps consistent with paragraph 8 of annex III to the Protocol, as outlined in Figure 1"* (emphases added).

The approach adopted in the guidance materials – using problem formulation to devise risk hypotheses by identifying "plausible pathways to harm" – is narrow, potentially undermining the precautionary approach embedded within the Cartagena Protocol. This is because the "pathways to harm" approach as spelt out in the guidance materials is used to generate *select* risk hypotheses for testing, in what industry describes as "plausible pathways to harm". Selective harms are chosen for analysis, based on *intended* design aims and function of the introduced trait(s).

As such, the approach as utilised in the guidance materials requires that a causal chain of events is constructed during problem formulation, where there is proven scientific evidence for each event. This "pathway to harm" thus needs to be known for harm to be accepted, therefore requiring proving harm, rather than risk.

This is a shift away from the unbiased characterisation of LMOs that is the basis of risk assessment under the Cartagena Protocol, where the aim is to detect any potential changes to the LMO that may have adverse impacts on biodiversity, irrespective of what has been chosen as relevant or an important harm to assess.

It also adds significant weight to *who* is determining and selecting the risk hypotheses, which should be independently determined, and not influenced or conducted by LMO developers themselves. Yet, developers are publishing extensive protocols and example pathways, and their publications are repeatedly referenced in the guidance materials.

The approach is, in fact, a method long proposed by Syngenta, CropLife and others (Anderson et al., 2021; Raybould, 2006; Raybould & Macdonald, 2018; Raybould et al., 2019; Wolt et al., 2010) for LMO crops. It is consistent with decades-old, as well as continued, industry publications that promote "streamlining" (Anderson et al., 2021), "modernising" (e.g., Anderson et al., 2021; Koch et al., 2025) or, more clearly, "minimising" data and risk assessment requirements (Raybould, 2006), so as to be able to hasten regulatory approvals and eventual commercialisation of LMOs. As stated in the first industry publication on problem formulation: *"To reduce environmental risk, the objective of problem formulation should be to identify the minimum quantity of data needed for risk assessment to demonstrate the safety of a GM crop"* (Raybould, 2006).

More recently, the lead gene drive developer, Target Malaria, has also begun advocating for implementing the "pathways to harm" approach for gene drive mosquitoes (Connolly et al., 2023). LM potato developers are also advocating for the approach as part of a harmonised global risk assessment framework, for what they consider "low-risk" LMO technologies (Koch et al., 2025). Such papers notably evade discussions on the Cartagena Protocol.

With novel technologies such as EGD-LMOs, uncertainties regarding risks are increased. Risk assessments should therefore cast the net widely, broadening the scope for capturing observations to identify all potential risks, rather than narrowing the framing and scope of risk assessments. How the approach in the guidance materials does the latter is described in the next chapter.

Chapter 4

How the "Pathways to Harm" Approach Reverses Precaution

"Pathways to harm" select what risks to identify or ignore

ANY approach under the Cartagena Protocol should forward a framing of risk assessment that is broad enough to be in line with the Protocol's objectives, i.e., to ensure an adequate level of protection from the possible adverse effects of LMOs on the conservation and sustainable use of biodiversity, taking also into account risks to human health.

However, the approach as elaborated in the recent guidance materials narrows the framing and scope of risk assessment in numerous ways. It proposes a selective approach to identifying and assessing risk and potential harms. It is openly promoted by industry as a hypothesis-driven, or policy-driven (e.g., Raybould & Macdonald, 2018), rather than data-driven, approach. In contrast, the Protocol's approach aims to detect any potential harm through *unbiased* observational analysis that characterises the LMO and its effects, so as to inform decision-making.

The main architect of the "pathways to harm" version describes industry's problem formulation approach as follows:

"While lack of bias in testing a hypothesis is a virtue in risk assessment, as in all basic and applied science, lack of bias in selecting the hypotheses to be tested is a grave weakness: we should be strongly biased toward hypotheses that help decision-making and realization of policy objectives. Without this bias, policy may be formulated in response to trivial

differences, perhaps influenced by ill-informed indignation that a GM crop, unsurprisingly, differs from a non-GM comparator in some respect. ***It is this very lack of bias that we believe makes science-led risk assessment vastly less effective than the policy-led alternative****"* (Raybould & MacDonald, 2018) (emphasis added).

The rationale put forward is that the "pathways to harm" improve poor problem formulation by providing specific risk hypotheses that can avoid the production of data that may be unclear or uncertain to risk assessors. As stated by Raybould (2006), with regard to poor problem formulation, *"the introduction of beneficial products may be delayed, and environmental risk increased, because poor problem formulation results in production of data in the absence of a risk hypothesis"*.

Such a method also gets around addressing "unknown unknowns" (Wynne, 1992; Böschen et al., 2006; Böschen, 2009), for example an unpredicted, unintended effect that may be detected by an unbiased approach to characterising and testing of an LMO. **By focusing on select risks associated only with intended changes, unintended novel characteristics can potentially be ignored and thus left undetected.**

This method may be particularly vulnerable to the undue influence of developers who may wish to mould risk assessments in favour of selecting preferred pathways that may determine what harms become visible, or not, to risk assessors. Developers are already publishing their own "pathways to harm" risk assessment recommendations (Connolly et al., 2021), some of which were put forward for inclusion in the guidance materials, but were rejected by the AHTEG due to a divergence of opinions.

Selective characterisation narrows risk assessment considerations

The selective characterisation described above potentially skirts some of the steps and points to consider that are laid out in Annex III of the Cartagena Protocol, including the first risk assessment

step identified in paragraph 8: *"(a) An identification of any novel genotypic and phenotypic characteristics associated with the living modified organism that may have adverse effects on biological diversity in the likely potential receiving environment, taking also into account risks to human health."* And, in paragraph 9(e): *"Identity of the living modified organism, and the differences between the biological characteristics of the living modified organism and those of the recipient organism or parental organisms."*

As described in Annex III, characterisation is clearly not restricted to assessing intended changes and introduced traits only, but is broad enough to capture unintended changes such as the risks associated with the genetic engineering process itself, or unanticipated interactions of introduced traits within the target organism. **For a novel technology such as engineered gene drives, it is not sufficient to rely on known characteristics to assess risks.** A precautionary approach necessitates broad and unbiased assessments that are able to detect and identify novel characteristics that may not be intended or expected.

Specific to EGD-LMOs, for example, this would include the expected level of "driving" efficiency of the gene drive constructs, which determines the extent of spread and persistence – key information for EGD-LMO risk assessment. Also important would be the potential for off-target effects to continuously arise in EGD-LMOs and their offspring following release, due to active and continuous genome editing processes in the EGD-LMOs.

Genetic backgrounds and abiotic factors have been shown to mediate CRISPR-Cas systems, raising questions regarding the ability to test for, or predict, how the environment may mediate gene drive behaviour and unintended effects post release, as the drive moves across wild populations and receiving environments. Additional complexities such as the interplay between transgenes and their genetic background have also been shown to have unintended impacts (e.g., see Bauer-Panskus et al., 2020). A release of a gene drive into a wild population raises the issue that new EGD-LMOs are being generated as the drive moves through a wild, genetically diverse species.

How such considerations are taken on board remains unaddressed in the guidance materials, beyond the use of modelling, which would require yet-to-be-acquired knowledge of the genetic diversity of all target species connected by gene flow. This would include, for example, sibling mosquito species, and how all those genetic backgrounds may impact the EGD-LMO.

Nonetheless, due to a divergence of opinions within the AHTEG, elements of paragraph 8(a) of Annex III are included in relation to mosquito applications only, including, for example, gene drive conversion rates to determine potential spread, transboundary movement, or unintended spread from a trial site. Also included as a point to consider is the genetic diversity of the unmodified organism, which is relevant to gene drives that are designed to move through wild populations that are genetically diverse. However, these more precautionary considerations are not reflected in the general sections of the guidance materials, and may not be included in any future proposals to adapt the approach to other categories of LMOs.

A more precautionary approach would incorporate the broader characterisation considerations that are included in the mosquito sections of the guidance materials, as part of the initial stages of risk assessment. This would help ensure alignment with the Cartagena Protocol, rather than narrowing characterisation to strictly those factors considered relevant to a selected pathway to harm.

Reduction in number of pathways deemed "plausible" for testing

The Guidance on Risk Assessment of Living Modified Organisms and Monitoring in the Context of Risk Assessment[3] was developed under the Cartagena Protocol to assist Parties in implementing their

[3] Guidance on Risk Assessment of Living Modified Organisms and Monitoring in the Context of Risk Assessment. UNEP/CBD/BS/COP-MOP/8/8/Add.1. https://www.cbd.int/doc/meetings/bs/mop-08/official/bs-mop-08-08-add1-en.pdf

risk assessment obligations. The Guidance includes a Roadmap which provides direction on how to conduct a risk assessment in line with the Protocol's Article 15 and Annex III.

The Roadmap has five steps that expand on Annex III. Step 2 lays out assessment considerations for determining the *likelihood* of an identified hazard occurring, which would include exposure assessments. Step 3 is conducted to *identify or characterise* a particular hazard, which is an evaluation of the consequences of the adverse effect.

These two steps can be conducted iteratively and independently of each other, such that even if the likelihood of a hazard occurring is low (step 2), but step 3 identifies that the impact/consequence of the identified hazard is high, then the overall risk is considered high. Similarly, even if a hazard consequence/impact is low, but the likelihood of that hazard occurring is high, then risk is considered to be high.

In contrast, the "pathways to harm" approach conflates these two iterative steps of the risk assessment into a linear process. **If one step of the pathway is deemed as having a low likelihood of occurring, instead of considering that a risk may still be high because of potentially high consequences, it instead causes the entire pathway to harm to be considered equally unlikely.** As stated in the guidance materials (p. 21): *"A particularly useful feature of this analysis is that it decisively determines with sufficient confidence whether a critical step is highly unlikely or not. If one step in the pathway is highly unlikely this would cause the entire pathway to harm to be equally unlikely."*

Proof of harm, rather than identifying risk

The precautionary approach states that when there is reasonable suspicion of harm, lack of scientific certainty must not be used to postpone preventative action, placing the burden of proof on the innovator to demonstrate safety. If there is uncertainty or lack of knowledge over risks of harm, precaution takes precedence and action should be taken to prevent the harm.

However, the "pathways to harm" approach requires the risk assessor to provide proof of harm instead of identifying risk, undermining a layer of precautionary decision-making that is designed to address any such identified risks. **The methodology is based on a causal chain of events necessary for harm to occur. The default assumption is that no risk exists because no harm pathway has been identified, until proven otherwise.** This tends to increase the likelihood of failing to demonstrate harm, due to limited empirical data on harm pathways. Consequently, the approach significantly differs from common environmental risk assessment practices, which emphasise testing and measures to prevent or mitigate risks to biodiversity and human health.

Moreover, null assumptions are easily baked into a pathway, and if the pathway is rejected, these can potentially omit a risk. This flaw becomes evident in the publication by Raybould (2006), which advocates for discounting the potential that Bt crops targeting Lepidopteran pests could also impact other insect orders such as Coleoptera. Coleoptera impact was rejected based on assumptions on the mode of action of Bt toxicity. The "pathways to harm" approach then dismisses all other potential modes of toxicity that may occur, and fails to pick up on any unknown risks. For example, if it is assumed that an introduced toxin works by a particular mode of action such as binding to a particular receptor to induce toxicity, the pathway can be dismissed if a non-target organism is shown not to have this receptor. This then dismisses all other potential modes of toxicity that may occur and fails to pick up on any unknown risks.

By this logic, a "pathway to harm" would not be required to assess for potential unintended impacts on Coleopteran pests. However, since this study was published, impacts of Bt toxins intended to target Lepidoptera have indeed been linked to toxicity to Coleoptera, highlighting the limitation of this hypothesis-driven approach and its reliance on assumptions and a certain degree of hubris (see Hilbeck & Otto, 2015). Moreover, only a reported 17% of Cry toxins have been tested with species from more than one or two insect orders, challenging claims of Cry toxin specificity (Van Frankenhuyzen, 2013).

This narrow approach therefore does not sufficiently incorporate knowledge gaps and uncertainties. **The high level of uncertainties associated with gene drive technologies, given the design for uncontrolled spread into wild ecosystems, warrants an unbiased, open process to observe and capture all potential risks.** Further work is needed to incorporate knowledge gaps, unknowns and uncertainties in this regard.

Focus on intended changes and behaviours downplays unintended changes

Another important way in which the "pathways to harm" approach narrows the framing and scope of risk assessment is that it focuses risk assessment on *intended* changes and behaviours, while ignoring potential *unintended* changes.

This is exemplified by publications by the lead gene drive developers (e.g., Connolly et al., 2021) whereby toxicological assessment is largely limited to assessing the toxicity of the transgene product and not the organism as a whole. Such an approach, by not considering the whole LMO, fails to incorporate potential unintended effects of the genetic engineering process, such as unintended changes to the genetic background, or interactions between the target organism and the transgene. As experienced with first-generation LMOs, unexpected effects on fitness have been documented when crossed onto other genetic backgrounds, e.g., rice to weedy relatives or with oilseed rape outcrossing to conventional varieties (reviewed by Bauer-Panskus et al., 2020). Assessments of how the genome may impact the behaviour of the gene drive construct are crucial, as such impacts could mediate its basic functions, including the extent of spread and persistence.

Focusing on the transgene product – either a gene or a protein – rather than the entire organism or population, avoids assessing the risks related to the scale of releases and the commercialisation of gene-drive organisms outdoors or in natural ecosystems. This conceptual shift reduces data requirements and deems unintended changes irrelevant and thus risks their remaining

undetected. Rather than casting the net widely to be able to detect any potential unintended effects that may have implications for biodiversity and human health, this approach explicitly narrows data requirements. It also implicitly rules out the ability to assess any inherent risks arising from the process of genetic engineering. At a molecular level, such a reductionist approach would mean focusing on the introduced gene and trait, while disregarding the LMO as a whole.

By importing these conceptual ideas, the guidance materials thus largely ignore the possibility that the genetic engineering process may lead to unintended effects, e.g., off-target effects, resistance mechanisms, changeable gene drive conversion rates – that will impact degree of spread – across genetically diverse species, amongst other aspects. This also means that non-lethal effects could increase the invasiveness potential of organisms that now contain transgenes in wild populations.

At the behavioural, phenotypic level, questions include how a gene drive design may hold up to its design aims, e.g., of suppressing target population numbers, and via what molecular mechanisms. How these factors would change as the drive moves through genetically diverse populations where genetic backgrounds or even abiotic factors may alter gene drive activity means that the organism as a whole also needs to be considered. In order to assess the whole organism, pathways would need to be devised accordingly, but the guidance materials provide little direction in this regard.

The guidance materials thus largely fail to address the central risks and uncertainties of EGD-LMOs such as gene flow to non-target organisms, unanticipated effects and interactions, and unintended spread beyond target sites. These are some of the most controversial aspects of EGD-LMOs, and raise particular concerns with regard to transboundary movement. However, the methodology proposed and examples given are largely based on standard LMO assessment methods that do not necessarily address the specific risks.

The unintended effects of the genetic engineering process, along with the rise of increasingly complex LMOs such as EGD-LMOs, have prompted consistent calls to update risk assessment processes in order to assist in identifying potential intended and unintended changes (Benevenuto et al., 2023; Heinemann et al., 2011; Kawall et al., 2020; Zanon Agapito-Tenfen et al., 2021). This is especially relevant where adequate comparators may be lacking, as is the case with EGD-LMOs.

New techniques such as "omics" profiling that can provide broader in-depth analyses at increasing efficiency and lower cost offer an opportunity to advance risk assessment methods, rather than limit them to concepts largely devised for LMO crop traits developed decades ago. However, Raybould and Macdonald (2018) argue against the addition of profiling as a means to assist in the characterisation of new LMOs, claiming that it would lead to policymaking that is based on *"spurious statistically significant differences, between the LMO and its comparator, rather than careful deliberation about delivering agreed societal objectives"*, which *"should be discouraged"*.

In order to capture unintended effects, a narrow application of the "pathways to harm" approach, such as detailed in the guidance materials, would not suffice. **Incorporation of additional assessments such as genotypic and phenotypic characterisation, as well as more specificity on how to address the risks identified, would bring a more precautionary approach to the current methodology. Assessing the organism as a whole, rather than the introduced trait alone, would also reduce the chances of potential risks remaining undetected.**

Reduced need for laboratory empirical testing

The overall approach of problem formulation based on "pathways to harm" minimises data requirements and empirical testing. This is exemplified by the first industry paper advocating for this approach (Raybould, 2006): *"To reduce environmental risk, the objective of problem formulation should be to identify the minimum*

quantity of data needed for risk assessment to demonstrate the safety of a GM crop."

The paper further states: *"Conservatism in study requirements leads to bloated regulatory dossiers that raise the cost of complying with regulations and act as a barrier to market for small companies and public sector institutions. Even in large companies, the cost of regulation is a significant disincentive to product development."* And further, that *"collection of irrelevant data can increase public unease about GM crops (Johnson et al., 2007), and so lead to inconsistent or highly conservative decisions by regulators".*

The inclusion of a tiered-testing method in the guidance materials further favours a minimised laboratory empirical testing approach that is not sufficiently precautionary for EGD-LMOs. The approach, as laid out in the guidance materials, specifies that initial conservative tests be done at lower tiers where a likelihood of detecting harm is thought to be high, and if no effects are found at this level, then more realistic testing is not performed. This approach is more easily applied to toxicity testing of known toxins. How this is to be adapted to the risks of gene drives, which are not based on exposure to toxins, needs to be further clarified.

Moreover, the "pathways to harm" approach promotes the use of already existing data over the generation of new laboratory data dedicated to filling in gaps to case-by-case risk assessment. This means that data from previous risk assessments, or product development data, for example, could be used instead.

Chapter 5

Central Risks of Gene Drives Remain Unaddressed

AS a whole, the guidance materials are not sufficiently geared towards EGD-LMOs. This is exemplified by the singular example of a "pathway to harm" included within the guidance materials (p. 22) that is far better suited to first-generation LMO crops. Indeed, the method was developed with such crops in mind, prior to the development of EGD-LMOs.

The example pathway to harm focuses on potential toxicity of the introduced trait, a risk more relevant to LMO crops such as those producing insecticidal, toxic proteins. To date, EGD-LMOs are not introducing known toxins into organisms, and thus the potential toxicity of the introduced trait, while of relevance, is not one of the central risks. Using this example regrettably sets a framing that minimises the novelties of EGD-LMOs, such as intentional spread and persistence, that have been the source of concern due to their biosafety and regulatory implications. This chapter briefly highlights some of the key risks of EGD-LMOs, which the guidance materials do not address sufficiently.

Ecosystem-wide effects

What is central to EGD-LMOs is their design aim for spread and persistence, their intended use for potentially eradicating or altering entire populations of species, and also for mediating crucial public health risks. There is still a lack of guidance on how to adequately assess and address long-term impacts such as

eradication of a layer of a food web, scalability issues, evolutionary potential and ecosystem-wide effects.

The guidance materials also fail to take into account the issue of the spread of gene drives into genetically diverse populations, with potential next-generation impacts. This was an issue that was recognised by the earlier AHTEG as a characteristic that is challenging for current risk assessment methodologies (AHTEG on Risk Assessment, 2020). This lack of spatio-temporal controllability raises significant uncertainties that are not easily assessed or controlled for in laboratory settings prior to release.

Spread and persistence

The guidance materials do, however, acknowledge the inevitable spread of self-sustaining EGD-LMOs, e.g., via gene flow to non-target organisms or unintended spread of the EGD-LMO beyond target areas.

Nonetheless, they propose using an existing methodology – phased trial releases, going from smaller to larger field trials – to assess risks empirically. This methodology was previously highlighted as being a challenge to risk assessment of EGD-LMOs (AHTEG on Risk Assessment, 2020), as their release into the environment, whether in small or large field trials, poses risks because of their propensity to spread and persist. Yet, this fundamental problem remains unaddressed.

Moreover, evidence suggests that localised drives may behave like self-sustaining drives (e.g., split drives behaving as shadow drives (Kandul et al., 2020)), including due to ecological and spatial factors (Novel and Exceptional Technology and Research Advisory Committee, 2020), yet these issues were also not explicitly raised as risk considerations. Their relevance in informing on potential future releases of self-sustaining drives is also limited, considering it is exactly this aim of unlimited spread and persistence for population- or species-wide modification that is central to the risks and uncertainties associated with EGD-LMOs.

In addition, it is now widely expected from modelling studies that EGD-LMOs that aim to suppress populations may instead lead to cyclical population crashes and rebound effects ("chasing" dynamics) (Champer et al., 2021). This means that any field trial may require long-term measures to prevent escape beyond the target area. It also has vital implications for applications that aim to target invasive species which may lead to spread of the EGD-LMO back to the native range of the target organism. As invasive species are not a focus of the guidance materials, such risks remain unaddressed.

Gene flow

Gene flow can be considered a harm in and of itself with biosafety, socioeconomic and ethical implications. It is not only a step to harm, as envisaged in the "pathway to harm" approach. Gene flow risks contaminating the gene pool of populations, with implications for the conservation of biodiversity. Gene flow from LMOs has always been considered a risk to prevent, not an explicit design intention. It also raises specific risk considerations, including with direct implications for human health with regard to mosquito applications.

In a tacit acknowledgement of the inevitability of gene flow to non-target organisms with EGD-LMOs, lead developers have proposed redefining target organisms as all species connected via gene flow, such that gene flow from one species of malaria-carrying mosquito to a different species of non-malaria-carrying mosquito would not be considered a harm. This is because the non-malaria-carrying mosquito would be redefined as a target organism, as part of a "target species complex" (Connolly et al., 2023).

The risks of unintended gene flow would not however be sufficiently addressed by simply flipping the definition of "non-target" organisms to "target" organisms. Such an attempt to reframe non-target organisms was not accepted by the AHTEG. However, the guidance materials do point readers towards

Connolly et al. (2023) that states, *"vertical gene transfer of the transgene via hybridization amongst species of the* An. gambiae *complex was considered to be an intended effect and not a harm itself, because spread of the gene drive transgene to all species of the* An. gambiae *complex is an expected outcome"*.

A recent paper in PNAS (Boëte, 2025) raises concerns that such an approach could create a *"risky trend in vector control"*, via *"reframing collateral impacts as intentional outcomes, narrowing, rather than broadening, the scope of ecological and regulatory considerations"*. Indeed, species within a complex are ecologically diverse, and may play different and critical roles in ecosystems. As such, *"[t]he assumption that modifying an entire species complex will yield only beneficial outcomes is scientifically misleading, overly reductive, and ecologically risky"*. Hybridisation also opens the door to evolutionary uncertainty. As the paper elaborates, *"Hybrid species created as a result of gene drives could have unpredictable ecological traits that make them more invasive, harder to control, or lead to negative epidemiological consequences. This is not just theoretical, but highlighted by the hybridization between* Culex pipiens *and* Culex quinquefasciatus *mosquitoes on Madera. This hybridization may have promoted a more opportunistic feeding behavior, thus contributing to the human transmission of zoonotic arboviruses such as West Nile Virus."*

Boëte (2025) makes clear that any risk assessment that focuses on one single species within a complex would fall short of capturing the range of potential impacts of gene drive releases: *"Researchers must therefore make sure to incorporate risk assessments that take into account the effects on numerous species and make a concerted effort to understand the downstream effects."*

The guidance materials therefore fail to address the risks of gene flow of EGD-LMOs sufficiently, but these need to be considered carefully by decision-makers.

Chapter 6

Remaining Gaps and Shortfalls in the Guidance Materials

Lack of consensus amongst experts

EVIDENT also in the guidance materials is a divergence of expert views. For example, risks and uncertainties are well captured within the sections specific to mosquitoes, but the methodology introduced does not give concrete guidance on how to address those points. Unfortunately, calls from civil society to subject the guidance to an independent review and further work to iron out limitations and inconsistencies were not heeded.

Nonetheless, some crucial aspects of risks are now captured in the guidance materials. For example, key human health risks such as potential increased pathogenicity of the target pathogen, increased disease transmission, evolution of resistance, or the potential to interrupt conventional mosquito control, are included. Guidance is lacking, however, on how to address these complex risks, and the uncertainties associated with them. Indeed, certain risks such as the evolution of pathogen resistance to a gene drive are not easily detectable or assessable prior to release.

Failure to adequately provide guidance on addressing uncertainties

With regard to addressing uncertainties, there is an over-reliance in the guidance materials on modelling. The limitations and uncertainties associated with modelling itself are not sufficiently expanded upon. This means that the guidance materials are

not well-placed to facilitate a judgement on whether or not uncertainties have been sufficiently addressed.

Fundamentally, the accuracy of a model cannot easily be validated without field empirical testing, i.e., an environmental release of an EGD-LMO, which itself raises a conundrum. This issue was previously acknowledged by the earlier AHTEG in 2020, but is not fully addressed in the guidance materials. Any unintended effects not predicted by modelling would not be accounted for until evidence of damage has already occurred. As a result, there remain serious concerns about a self-spreading technology that cannot be recalled following release. A major limitation is the lack of knowledge that is needed to feed into a model for it to be able to predict accurate scenarios.

An alternative means to address uncertainties is the incorporation of "cut-off criteria", i.e., when a risk assessment cannot provide the required certainty needed for going ahead with environmental release (Bauer-Panskus et al., 2020). In this regard, the guidance materials could be complemented by applying cut-off criteria to: (i) situations when a risk assessment cannot be finalised; (ii) describing in detail the conceptual and practical challenges of implementing the methodological steps; and (iii) difficulties in operationalising protection goals due to knowledge gaps in defining and identifying assessment endpoints.

An industry-favoured approach

The incorporation into the guidance materials of a narrow problem formulation approach based on "pathways to harm" fits into a wider context of industry attempts to promote the adoption of this approach globally, in the name of regulatory harmonisation.

A limited number of countries have now adopted this approach for assessing first-generation LMOs. For example, Paraguay adopted it following a Memorandum of Understanding between its National Agricultural and Forestry Commission and the International Life Science Institute (ILSI) Research Foundation

for capacity building on risk assessment. ILSI has been regularly funded by different private industry groups including CropLife International, Monsanto, Bayer, BASF, Dow and Pioneer Hi-Bred, which have interests in LMO development, and have been promoting a problem formulation approach to gene drives in Africa (Boëte, 2018).

This resulted in a speeding up of regulatory approvals of LMOs in the country (Benítez Candia et al., 2020): *"The national regulatory authorities in Paraguay incorporated the problem formulation approach to environmental risk assessment into their regulatory processes, leading to an improvement in the regulatory system, which could be shown by the implementation of more timely decisions on the use of new GE [genetically engineered] crop varieties for commercial release. In this regard, 'the time for decision making by the national regulatory authority was reduced from 2 years to 3 months' (McLean and Roberts, 2015). Between June 2013 and February 2014, seven GE events were approved."*

The interests of industry in reducing data requirements for regulatory approvals are unfortunately reflected in the guidance materials. This approach may work to facilitate approvals for environmental release of EGD-LMOs, without the requisite robust risk assessment that is required by the Cartagena Protocol on Biosafety.

Chapter 7

Conclusions

THE welcoming of these guidance materials by Parties to the Cartagena Protocol should not set a precedent for further guidance materials for other LMOs based on this approach. At the same time, there should be a serious attempt to independently review and update the guidance materials in order to address their limitations, increase scientific rigour, and remove any lingering questions over the integrity of the guidance materials, due to the potential conflicts of interest involved in their development (see box above).

The guidance materials, while providing a resource for decision-makers on certain aspects of potential risks with regard to EGD-LMO mosquito applications, regrettably fall short in providing a sufficiently robust method for tackling the most controversial characteristics of EGD-LMOs. Their complexity poses enormous challenges to the ability to assess the full range of potential impacts on biodiversity. Moreover, with gene drive technologies also being applied to public health, an additional layer of complexity is introduced, including direct impacts on disease epidemiology and people's well-being.

The lack of guidance on applications outside of mosquito control is a significant further limitation. Two papers have been recently published showing the development of EGD-LMO plants (Liu et al., 2024; Oberhofer et al., 2024). Plant (and other species) applications have specific risks that have not been considered in the guidance materials.

At the national level, decision-makers may require applying additional layers of assessment, in line with a precautionary approach, rather than narrowly applying the approach as set out in the general guidance section. Mechanisms such as "cut-off criteria" may need to be also used to acknowledge when there is insufficient knowledge to be able to finalise a risk assessment, and thus when the precautionary approach should be applied and EGD-LMOs not released.

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LIVING modified organisms containing engineered gene drives (EGD-LMOs) are designed to spread genetic modifications through wild populations and persist – a novel technology that brings with it fresh biosafety challenges. In light of these concerns, a set of guidance materials to support risk assessment of EGD-LMOs has been drawn up by a group of experts and welcomed by Parties to the Cartagena Protocol on Biosafety.

However, the guidance materials advocate a narrow approach under which only what are identified as "plausible pathways to harm" are selected for assessment. This methodology fails to sufficiently address the central risks of gene drives arising from their very design objective – spread and persistence.

Instead of being limited in scope, risk assessment should cast the net widely to capture all potential harms of EGD-LMOs. Only then will it align with the precautionary principle that is enshrined in the Cartagena Protocol and that will ensure adequate protection from the possible adverse effects of this controversial technology on biodiversity and human health.

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